Synthesis and Use of 2*H*-Azirin-3-amines as Dipeptide Synthons

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The synthesis of the new 2*H*-azirin-3-amines ('3-amino-2*H*-azirines') **11**, **20**, **28**, and **33** as dipeptide synthons is described. The reactions of the starting amides with *Lawesson* reagent gave the corresponding thioamides, and consecutive treatment with $COCl_2$, 1,4-diazabicyclo[2.2.2]octane (DABCO), and NaN_3 led to the desired products. It is shown that these 2*H*-azirin-3-amines can conveniently be used as building blocks of the dipeptides Aib-(Me)Axx (Axx = alanine, valine), Aib-Homoproline, and Iva-Pro in the synthesis of several model peptides. However, some limitations apply for the synthesis of such 2*H*-azirin-3-amines. The starting material for the azirine synthesis, the corresponding thioamides, cannot generally be synthesized, and the 2*H*-azirin-3-amines could not be obtained in all cases from the thioamides prepared.

Introduction. – In the last few years, we have shown in extensive studies that 2*H*-azirin-3-amines ('3-amino-2*H*-azirines') are versatile synthons for α,α-disubstituted glycines (α,α-disubstituted α-amino acids) in peptide synthesis. One procedure for the introduction of such amino acids into peptides is the so-called 'azirine/oxazolone method' [1], which was developed as a convenient preparative access to such peptides. This strategy has been employed in the synthesis of linear oligopeptides [2–8], endothiopeptides [9–10], cyclic peptides [11–14], and cyclic depsipeptides [14–17] containing α,α-disubstituted glycines.

Peptides that contain α,α-disubstituted α-amino acids are considerably restricted in their conformational freedom, *i.e.*, secondary structures such as β-turns, and α- or 3_{10}-helices are stabilized or induced (*cf.* [18], and refs. cit. therein). Two of these amino acids, Aib (α-aminoisobutyric acid) and Iva (isovaline), are characteristic members of the peptaibols, an important family of natural peptide antibiotics that show bactericidal and hemolytic activity [19][20]. Due to the severe steric hindrance, the synthesis of related peptides is difficult [21–23].

Some years ago, 2*H*-azirin-3-amines became available that are enantiomerically pure, such as the (*S*)-isovaline (Iva) synthon **1** [24] and the (*S*)-2-(methyl)phenylalanine (Phe(Me)) synthon **2** [4]. They have been used to synthesize stereochemically pure peptides. Furthermore, the first three representatives of a novel class of 2*H*-azirin-3-amines, namely methyl (*S*)-*N*-(2,2-dimethyl-2*H*-azirin-3-yl)prolinate (**3**) [25], methyl (*S*)-*N*-(1-aza-6-oxaspiro[2.5]oct-1-en-2-yl)prolinate (**4**) [6], and (2*S*,4*R*)-4-(benzyloxy)-*N*-(2,2-dimethyl-2*H*-azirin-3-yl)prolinate (**5**) [8], have been prepared and found to be suitable as dipeptide synthons for the sequences Aib-Pro, 4-aminotetrahydropyran-4-carboxylic acid-Pro, and Aib-Hyp[2]). These synthons have been successfully used

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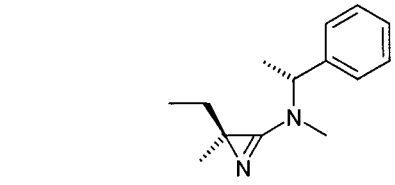
[1]) Part of the Ph. D. thesis of *R. A. B.*, Universität Zürich, 2001.

[2]) Hyp = (4*S*,4*R*)-4-hydroxyproline.



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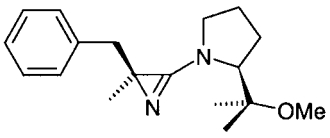

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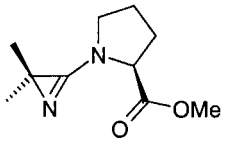

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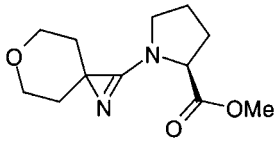

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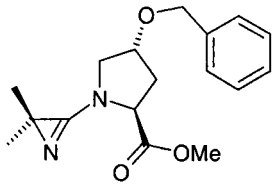

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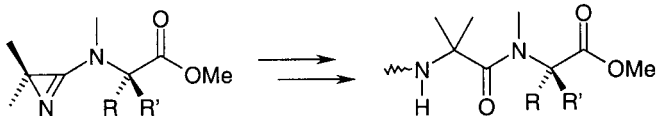
in the syntheses of *Trichovirin* I *1B* and I *4A* [7], an analogue of the C-terminal nonapeptide of *Trichovirin* I *1B* [6], and model peptides.

On the basis of these findings, we postulated that further dipeptide synthons for the sequence 'α,α-disubstituted α-amino acid-(homo)proline' or 'α,α-disubstituted α-amino acid-*N*-methylated amino acid' should be preparatively available [26]. In the present paper, we describe the attempts to prepare such 2*H*-azirin-3-amines with the aim of showing how far this principle can be generalized. Their applicability in peptide synthesis is demonstrated in the preparation of several model peptides.

Results and Discussion. – 1. *Synthesis of a Racemic Aib-(Me)Ala Synthon.* First of all, we intended to replace the amino acid proline in the synthon **3** by *N*-methylated glycine ((Me)Gly), alanine ((Me)Ala), valine ((Me)Val)[3]), α,α-dimethyl glycine ((Me)Aib), and phenylalanine ((Me)Phe) with the aim of obtaining 2*H*-azirin-3-amines of type **A** (*Scheme 1*) as synthons for dipeptides of type **B**.

Scheme 1



A **B**

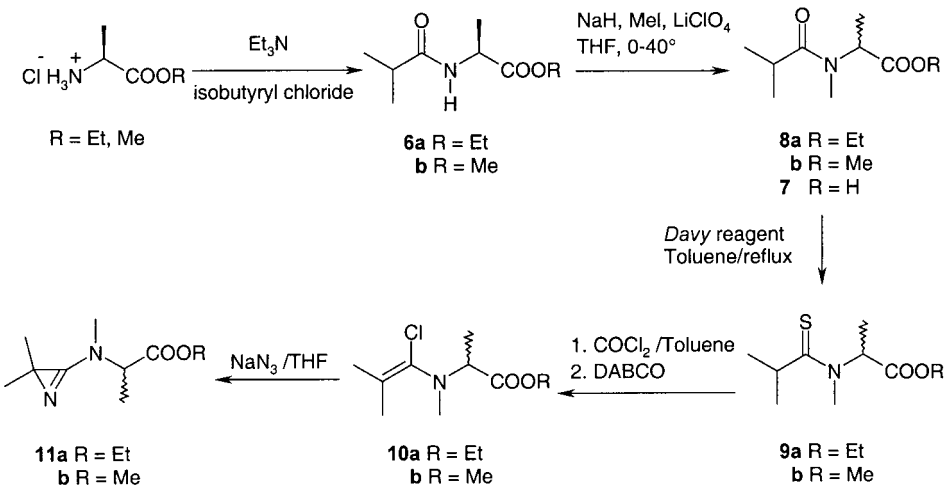
In a first approach (*Scheme 2*), the synthesis started from methyl/ethyl alaninate hydrochloride, which was treated with isobutyryl chloride in the presence of Et_3N (*Schotten-Baumann* conditions) to form methyl/ethyl (*S*)-*N*-(2-methylpropanoyl)alaninate (**6**) in 92/90% yield. *N*-Methylation with NaH/MeI in the presence of $LiClO_4$ (suppression of *O*-methylation) [27][4]) gave racemized methyl/ethyl (*S/R*)-*N*-methyl-

[3]) Taken in part from the Diploma thesis of *R. A. B.*, Universität Zürich, 1997.

[4]) After longer reaction times at 60°, the corresponding acid **7** was isolated. A possible mechanism is the halolyses described by *Eschenmoser* and co-workers [27].

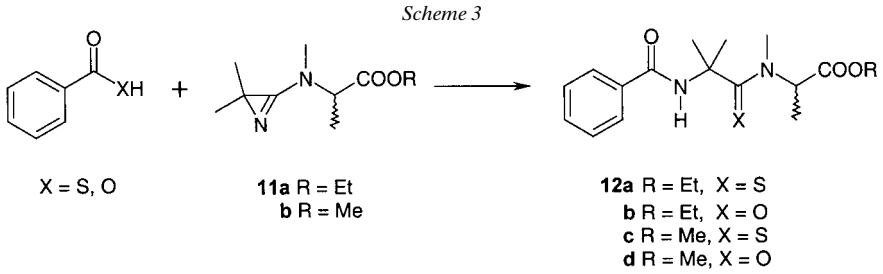
N-(2-methylpropanoyl)alaninate (**8**) in 58/79% yield. Thionation with a *Davy* reagent in refluxing toluene led to methyl/ethyl (*S/R*)-*N*-methyl-*N*-[2-(methyl)thiopropanoyl]-alaninate (**9**) in 71/70% yield. In analogy to the procedure described in [25][7], the reactions of **9** in CH_2Cl_2 with a solution of $COCl_2$ in toluene in the presence of catalytic amounts of DMF led to the chloroenamines **10**. Evaporation of the solvent, dissolution of the residue in THF, addition of 1,4-diazabicyclo[2.2.2]octane (DABCO), filtration, and treatment of the solution with NaN_3 for 5 h gave methyl/ethyl (*S/R*)-*N*-(2,2-dimethyl-2*H*-azirin-3-yl)-*N*-methylalaninate (**11)** in 39/52% yield.

Scheme 2



Reactions of **11** *with PhCOSH and PhCOOH.* For the chemical characterization of the 2*H*-azirin-3-amines **11**, reactions with PhCOSH and PhCOOH were performed in CH_2Cl_2 at 0° → r.t. (*Scheme 3*). In the case of **11b**, the *N*-benzoyl endothiodipeptide **12c** and *N*-benzoyl dipeptide **12d** were obtained in 56–60% yield after 17 h and chromatographic workup. When the reactions with **11a** were carried out for 1 h, the yield of the *N*-benzoyl endothiodipeptide **12a** was within the same range. However, the yield of **12b** remained lower (44%), thus indicating the slower coupling reaction with PhCOOH.

Scheme 3



Reactions of **11** *with Amino Acids.* With the aim of testing the utility of **11** as a dipeptide synthon, the reactions of the *N*-protected amino acids **13** (Boc-Trp-OH, Boc-Val-OH, and Z-Phe-OH, resp.) with 1.0–1.1 equiv. of **11** were carried out in CH_2Cl_2 or Et_2O at r.t. for 1–22 h (*Scheme 4* and *Table 1*). Chromatographic purification gave the tripeptides **14** in 55–70% yield. However, ^{1}H-NMR spectra showed the doubling of some signals (ratio 1:1), *i.e.*, completely racemized **11** had been used.

Scheme 4

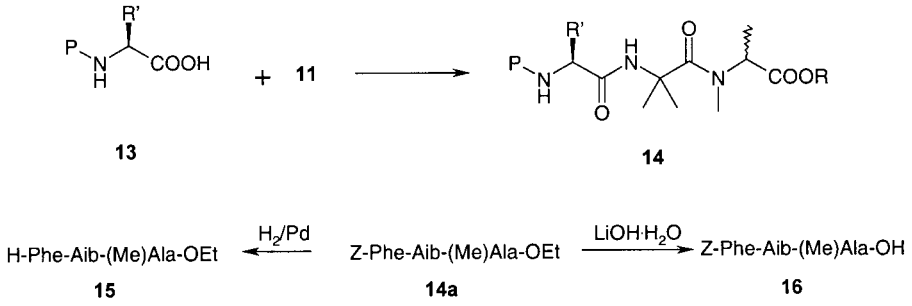


Table 1. *Synthesis of Tripeptides* **14**

13	Azirine	P	R′	Tripeptide	Yield [%]
a	**11a**	Z	$PhCH_2$	Z-Phe-Aib-(Me)Ala-OEt [5]) (**14a**)	70
b	**11b**	Boc	Me_2CH	Boc-Val-Aib-(Me)Ala-OMe (**14b**)	50
c	**11b**	Boc	Indolyl-CH_2	Boc-Trp-Aib-(Me)Ala-OMe (**14c**)	55

The racemization must have taken place during the *N*-methylation. In *N*-monosubstituted amino acids, the NH group is more acidic than the α-CH group, thus protecting the latter against ionization. A free acid group provides the same effect [28]. In an *N*,*N*-disubstituted amino acid ester, none of these effects play a role, and the α-CH group will be deprotonated more readily.

With the aim of showing the general use of **11** as a dipeptide synthon in peptide synthesis, **14a**[5]) was selectively deprotected. The Z-protecting group was removed by catalytic hydrogenation in the presence of Pd/C to yield H-Phe-Aib-(Me)Ala-OEt (**15**) in 71% yield. The ethyl ester group of **14a** was saponified with $LiOH \cdot H_2O$, yielding Z-Phe-Aib-(Me)Ala-OH (**16**) in 67% yield. These N- or C-terminal deprotected tripeptides can be further used in standard peptide chemistry.

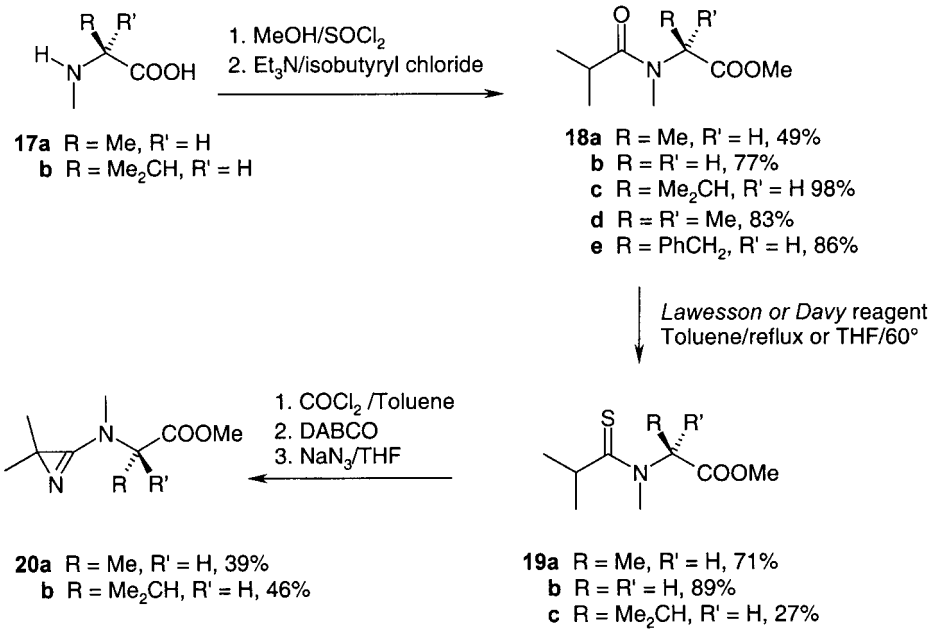
2. *General Synthesis of Aib-(Me)Axx Synthons.* Treatment of α,α-dimethyl glycine (Aib) with isobutyryl chloride in the presence of Et_3N led to methyl *N*-(2-methylpropanoyl)-2,2-dimethylglycinate in 75% yield. The *N*-methylation (NaH/MeI in the presence of $LiClO_4$) failed in this case. An analogous case has already been reported in [29]. Therefore, other methods for the introduction of the *N*-Me group had

[5]) Z-Phe-Aib-(Me)Ala-OMe (**14d**) was also prepared in 70% yield.

to be found, as *N*-Me amino acid esters are commercially not readily available. Two strategies were feasible: *1*) Synthesis of *N*-Me amino acid methyl esters. Various methods are known, *e.g.*, direct methylation [30], reductive amination [31], preparation of oxazolidinones, and their subsequent transformation to the *N*-Me derivatives [32] (*cf.* [3], and refs. cit. therein), and the use of immonium ions in *Diels-Alder*/*retro-Diels-Alder* sequences [34]. *2*) Esterification of commercially available *N*-Me amino acids, which narrows the range of available amino acids but is synthetically more straightforward and was, therefore, chosen.

As depicted in *Scheme 5*, the *N*-methyl-L-amino acids H-(Me)Ala-OMe and H-(Me)Val-OMe (**17a**, **b**) were converted to their methyl esters by treatment with $SOCl_2$ in MeOH. The *N*-Me amino acid methyl esters of glycine[6]), alanine, valine[6]), α,α-dimethyl glycine[7]) (Aib), and phenylalanine[6]) were transformed to the 'amides' **18**, which should be converted to the corresponding 'thioamides' **19** by treatment with *Lawesson* or *Davy* reagent in refluxing toluene, and further to the 2*H*-azirin-3-amines **20** by the usual three-step reaction.

Scheme 5



In the case of *N*-methylalanine (R = Me, R′ = H), azirine **20a** was obtained in 39% yield as a 2:1 mixture of enantiomers[8]) due to partial racemization during the

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6) Commercially available.

7) For a description of the synthesis, *vide infra*.

8) Ratio of the diastereoisomers of Z-Phe-Aib-(Me)Ala-OMe. Rotamers could be excluded on the basis of EXCY-NMR experiments.

conversion of the amino acid into the methyl ester (for an explanation, *vide infra*)[9]) [35][36].

Starting with methyl sarcosinate (H-Sar-OMe)[10]), methyl *N*-methyl-*N*-(2-methylpropanoyl)glycinate (**18b**), and methyl *N*-methyl-*N*-[2-(methyl)thiopropanoyl]glycinate (**19b**) were obtained in good yields. However, the synthesis of the azirine failed. Control experiments showed that the reactions with $COCl_2$ and DABCO led to the chloro-enamine intermediate[11]). However, after addition of NaN_3, only a small amount of a rapidly decomposing substance was obtained, possibly the expected azidoenamine (^{1}H-NMR, MS).

Starting with H-(Me)Val-OMe, H-(Me)Aib-OMe, and H-(Me)Phe-OMe (*Scheme 5*) **18b**, **d**, and **e** were obtained in 98, 83, and 86% yield, respectively. Unfortunately, neither the reaction with *Lawesson* nor with *Davy* reagent in refluxing toluene led to the corresponding 'thioamides' of type **19**. We assume the steric hindrance of the side chains to be the main obstacle [37][12]). However, when THF instead of toluene was used for the thionation reaction with *Lawesson* reagent, methyl (*S*)-*N*-methyl-*N*-(2-methylthiopropanoyl)valinate (**19c**) was obtained, albeit in only 27% yield[13]). According to the standard procedure for azirine synthesis, methyl (*S*)-*N*-(2,2-dimethyl-2*H*-azirin-3-yl)-*N*-methylvalinate (**20b**) was obtained in 46% yield in optically active form.

Reactions of **20b** *with Amino Acids and Syntheses of Model Peptides.* With the aim of testing the usefulness of **20b** as a dipeptide synthon, the reactions of Z-Phe-OH (**13a**), Fmoc-Val-OH (**13d**), and Fmoc-Phe-Gly-OH (**13e**) with 1 equiv. of **20b** were carried out at room temperature (*Scheme 6* and *Table 2*). After stirring overnight, the expected tri- and tetrapeptides **22** and **23** were obtained in good-to-very-good yields.

The general applicability of the dipeptide synthon **20b** in peptide synthesis, was established by the preparation of the tetrapeptides Fmoc-Val-Aib-(Me)Val-Ala-OMe (**24**) and Boc-Ala-Val-Aib-(Me)Val-OMe (**25**, *Scheme 7*). Hydrolysis of the methyl ester **22a** with $LiOH \cdot H_2O$ led quantitatively to Z-Phe-Aib-(Me)Val-OH, which was coupled without further purification to H-Ala-OMe · HCl with the coupling reagent *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) in

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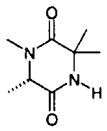
[9]) It was shown that this azirine is stable for several months at 4°. However, when stored for years, the formation of 1,3,3,6-tetramethylpiperazine-2,5-dione (**21**) was detected, which can be explained by the hydrolysis of **20a** and subsequent cyclization. It is known that *N*-Me amino acid containing dipeptides are prone to cyclize to diketopiperazines [35][36].



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[10]) Sar = *N*-methylglycine.

[11]) Hydrolysis of the intermediate yielded **18b**.

[12]) We also tried to synthesize the azirines from the 'amides' **18** instead of the more reactive 'thioamides' **19** with condensed $COCl_2$ according to the procedure of *Wipf* [37]. Usually, lower yields are to be expected when using this method, and in the cases of **18d** (R = R′ = Me) and **18c** (R = Me_2CH, R′ = H) no azirines could be isolated.

[13]) This method failed for the thionation of **18d**.

Scheme 6

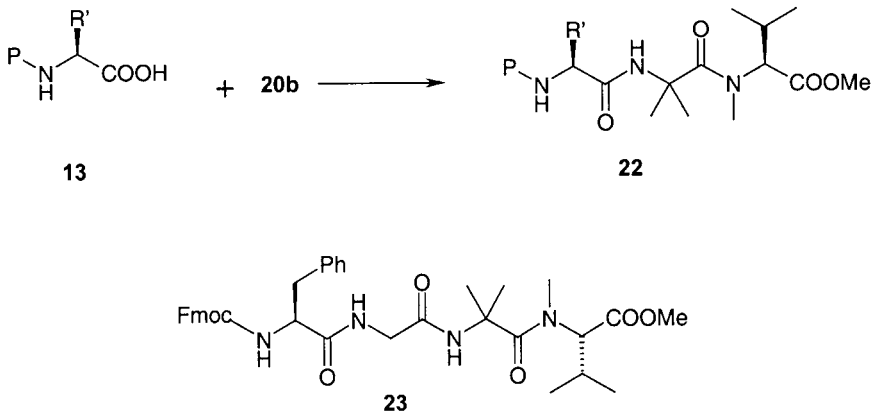
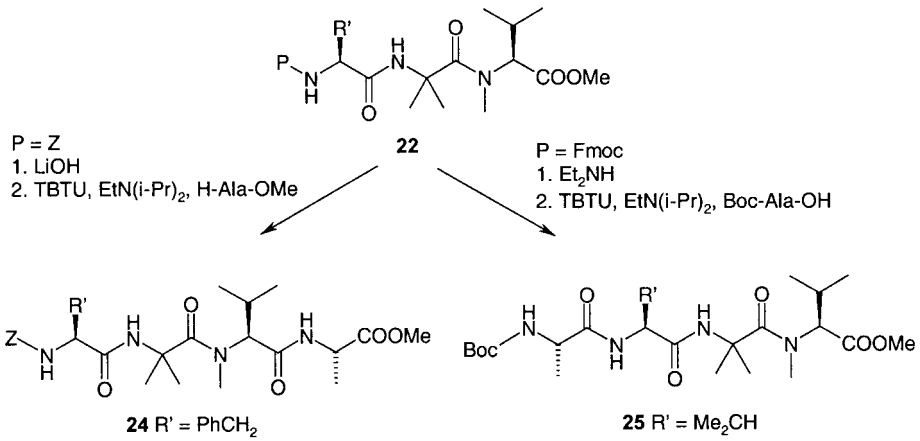


Table 2. *Synthesis of Peptides* **22** *and* **23**

13	P	R′	Product	Yield [%]
a	Z	$PhCH_2$	Z-Phe-Aib-(Me)Val-OMe (**22a**)	83
d	Fmoc	Me_2CH	Fmoc-Val-Aib-(Me)Val-OMe (**22b**)	83
e	Fmoc-Phe	H	Fmoc-Phe-Gly-Aib-(Me)Val-OMe (**23**)	67

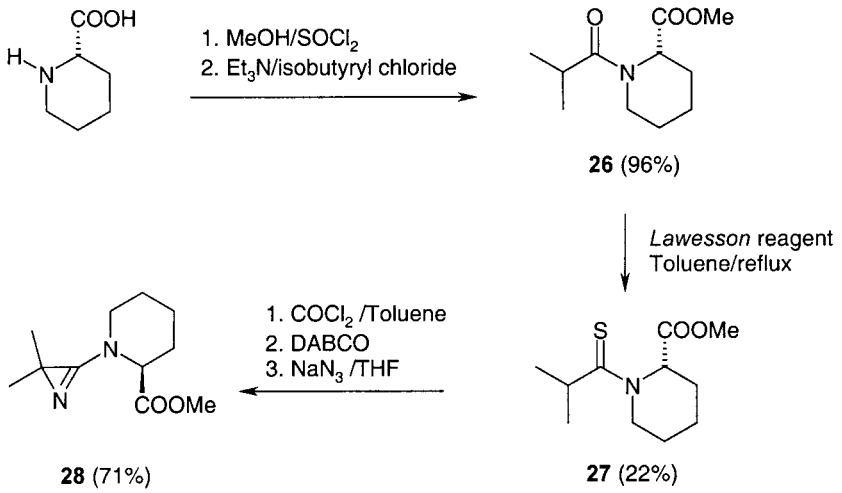
MeCN in the presence of 1-hydroxybenzotriazole (HOBt) and $EtN(i\text{-}Pr)_2$. After chromatographic workup, the tetrapeptide **24** was obtained in 72% yield. Removal of the Fmoc group of **22b** with Et_2NH gave crude H-Val-Aib-(Me)Val-OMe, which was coupled without further purification to Boc-Ala-OH (TBTU, HOBt, $EtN(i\text{-}Pr)_2$). After chromatographic workup, the tetrapeptide **25** was obtained in 73% yield.

Scheme 7



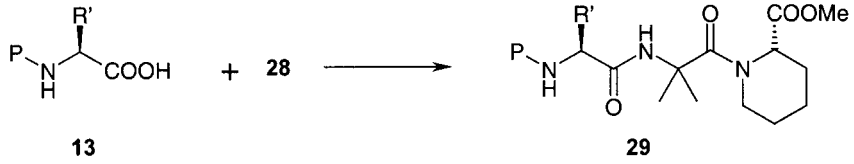
3. *Synthesis of an Aib-Homoproline Synthon.* As depicted in *Scheme 8*, (*S*)-picoleinic acid[14]) was converted to methyl (*S*)-*N*-(2-methylpropanoyl)homoprolinate (**26**), which was then converted by thionation with *Lawesson* reagent in refluxing toluene to methyl (*S*)-*N*-(2-methylpropanethioyl)homoprolinate (**27**). Treatment of a solution of the latter in CH_2Cl_2 and catalytic amounts of DMF with a solution of $COCl_2$ in toluene, DABCO, and NaN_3 led within one day to methyl (*S*)-*N*-(2,2-dimethyl-2*H*-azirin-3-yl)homoprolinate (**28**) in 71% yield.

Scheme 8



Reactions of **28** *with Amino Acids.* The dipeptide synthon **28** was coupled with Z-Phe-OH (**13a**), Fmoc-Val-OH (**13d**), and Boc-Ala-OH (**13f**), leading to the corresponding tripeptides **29** in good yields. All reactions were carried out in CH_2Cl_2 with 1 equiv. of **28** and stirring for 15–24 h at room temperature (*Scheme 9* and *Table 3*).

Scheme 9



Tripeptide **29c** was crystallized from a mixture of CH_2Cl_2/Et_2O/MeOH/hexane and the structure was established by X-ray crystallography (*Fig. 1*). The crystals are enantiomerically pure, however the absolute configuration of the molecule has not been determined. The enantiomer used in the refinement was based on the known (*S*)-configurations at C(2) and C(8)[15]).

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[14]) Experiments were also carried out with D/L-picoleinic acid, leading to similar results.

[15]) Arbitrary numbering used in *Fig. 1*.

Table 3. *Synthesis of Tripeptides* **29**

13	Azirine	P	R′	Tripeptide	Yield [%]
a	*rac*-**28**	Z	$PhCH_2$	Z-Phe-Aib-Homoproline-OMe (**29a**) [a])	87
d	**28**	Fmoc	Me_2CH	Fmoc-Val-Aib-Homoproline-OMe (**29b**)	91
f	**28**	Boc	Me	Boc-Ala-Aib-Homoproline-OMe (**29c**)	83

[a]) 1 : 1 Mixture of diastereoisomers.

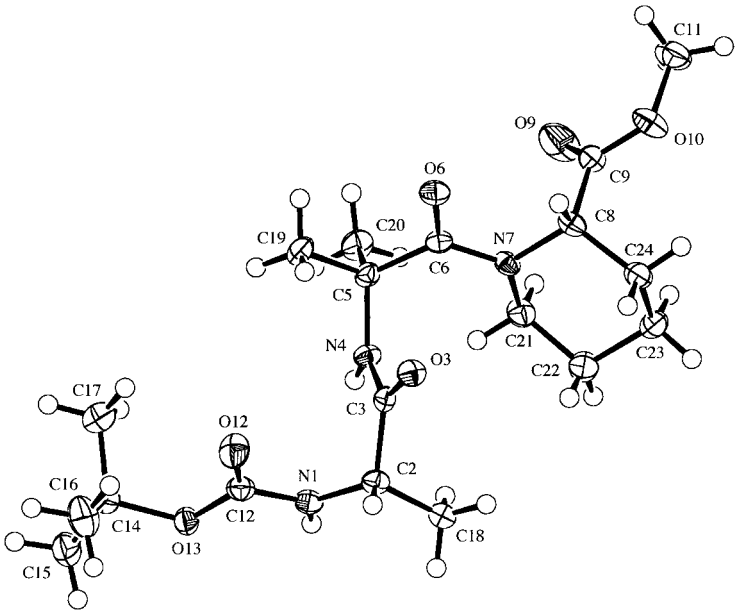
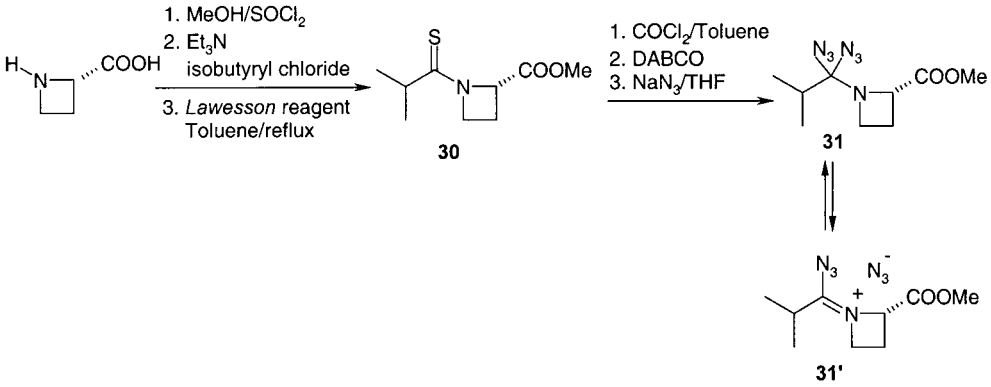


Fig. 1. *ORTEP Plot of the molecular structure of* **29c** (with 50% probability ellipsoids, H-atoms with arbitrary displacement parameters for clarity; arbitrary numbering of the atoms)

4. *Attempted Synthesis of an Aib-Norproline Synthon.* As shown in *Scheme 10*, (*S*)-azetidine-2-carboxylic acid was converted to methyl (*S*)-*N*-(2-methylpropanoyl)norprolinate, which was thionated with *Lawesson* reagent in refluxing toluene to give methyl (*S*)-*N*-(2-methylpropanethioyl)norprolinate (**30**) in 93% yield. Consecutive treatment of the latter in CH_2Cl_2 containing catalytic amounts of DMF with $COCl_2$ in toluene, DABCO, and NaN_3 in THF for 2 days did not lead to the expected azirine but yielded a compound with a molecular formula corresponding to **31** in 67% yield. The proposed structure of the geminal diazide is in agreement with most of the obtained spectra (^{1}H-NMR, IR, MS, EA), but not with the ^{13}C-NMR, which, in addition to the signal for *C*OOMe at 169.5 ppm, shows a second *singlet* at 159.4 ppm, which could correspond to C(1′) in **31′**.

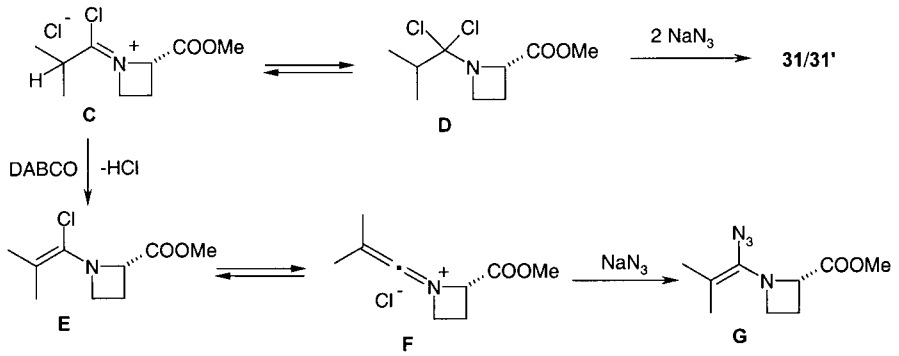
The unexpected formation of the geminal diazide **31** can be explained by the mechanism depicted in *Scheme 11*. Treatment of **30** with $COCl_2$ leads to the formation

Scheme 10



of chloriminium chloride **C**. Addition of a second chloride ion gives the geminal dichloride **D**, thus revealing the high ring strain of the exocyclic double bond of the four-membered ring. On treatment with NaN_3, the Cl-atoms of **D** are substituted by N_3^- to give **31**. The usual reaction pathway *via* the base-catalyzed deprotonation of **C** to give the α-chloroenamine **E**, which, in the next step, reacts *via* the ketiminium salt **F** to give the α-azidoenamine **G** and the azirine, can, therefore, not take place.

Scheme 11



5. *Synthesis of an Iva-Pro Synthon*. Several peptaibols, *e.g.*, emerimicin III and IV [38][39][16]), contain the dipeptide segment Iva-Hyp. Therefore, the corresponding (2*H*-azirin-3-yl)prolinate is an attractive building block in the synthesis of analogs of this class of conformationally restricted, biologically active peptides (*cf.* [36]). Such a synthon should be accessible by the methodology described above. The following synthesis led to a diastereoisomeric mixture[17]) of the analogous Iva-Pro synthon (containing (*S*/*R*)-Iva [38])[18]).

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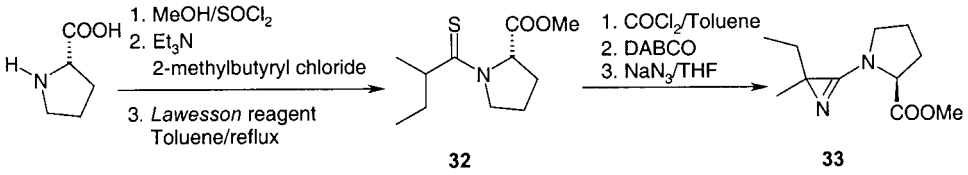
16) In the natural emerimicin III and IV, Iva has the (*R*)-configuration.

17) The ratio of the diastereoisomers was 58 : 42 according to HPLC.

18) The absolute configuration of Iva has only a minimal effect on the solution conformation and the biological activity [38].

As depicted in *Scheme 12*, (*S*)-proline was converted into methyl (*S*)-*N*-(2-methylbutanoyl)prolinate (94% yield) according to the usual protocol. Thionation with *Lawesson* reagent in refluxing toluene led to methyl (*S*)-*N*-(2-methylbutanethioyl)-prolinate (**32**) in 70% yield. Standard reactions with the latter led to methyl (*S*)-*N*-(2-ethyl-2-methyl-2*H*-azirin-3-yl)prolinate (**33**, mixture of diastereoisomers) in 50% yield.

Scheme 12



Reaction of **33** *with Amino and Peptide Acids.* The dipeptide synthon **33** was reacted with 1 equiv. of Z-Phe-OH (**13a**), Fmoc-Val-OH (**13d**), and Fmoc-Phe-Gly-OH (**13e**), respectively, at room temperature. After stirring for one night, the expected tri- and tetrapeptides **34** and **35** were obtained in good-to-very-good yields (*Scheme 13* and *Table 4*).

Scheme 13

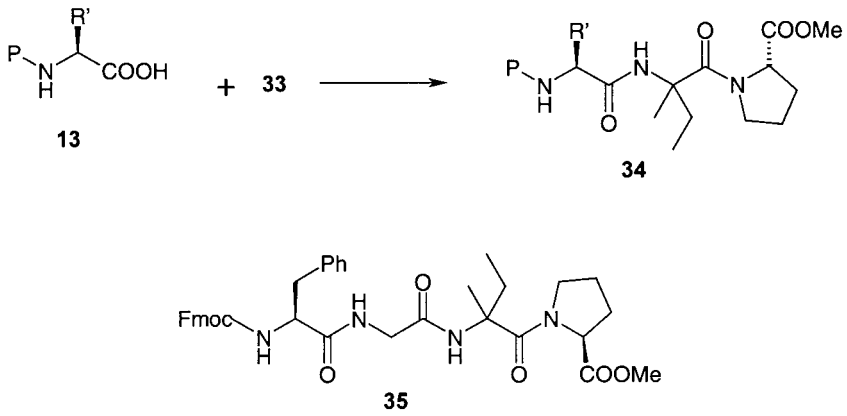


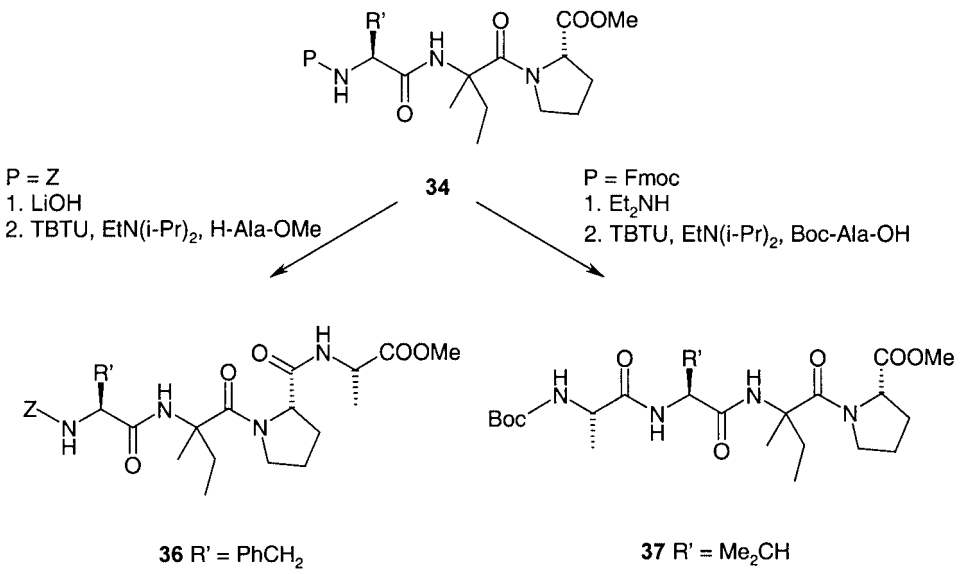
Table 4. *Synthesis of Peptides* **34** *and* **35**

13	P	R′	Product	Yield [%]
a	Z	$PhCH_2$	Z-Phe-Iva-Pro-OMe (**34a**)	91
b	Fmoc	Me_2CH	Fmoc-Val-Iva-Pro-OMe (**34b**)	90
c	Fmoc-Phe	H	Fmoc-Phe-Gly-Iva-Pro-OMe (**35**)	99

Hydrolysis of **34a** with $LiOH \cdot H_2O$ led quantitatively to Z-Phe-Iva-Pro-OH, which was coupled without further purification with H-Ala-OMe · HCl (TBTU, HOBt, in MeCN). After chromatographic workup, the tetrapeptide **36** was obtained in 82%

yield. Treatment of **34b** with Et_2NH led to crude H-Val-Iva-Pro-OMe, which was coupled with Boc-Ala-OH (TBTU, HOBt, in MeCN). Chromatographic workup gave the tetrapeptide **37** in 97% yield (*Scheme 14*).

Scheme 14



The comparison of the yields of the thionation reaction with *Lawesson* reagent in the *Table 5* reveals the tendency that 'amides' that cannot enolize readily are more reactive towards thionation. Due to the high strain of an exocyclic double bond of a four-membered ring, this is particularly the case for norproline. On the other hand, for the azirine synthesis the trend is reversed.

Table 5. *Comparison of the Yields of Thionation and Azirine Formation*

	Norproline	Proline [25]	Homoproline
'Thioamide' [%]	93	60	22
Azirine [%]	0	52	71

In conclusion, we have shown that the 2*H*-azirin-3-amines **11**, **20**, **28**, and **33** can be used conveniently as dipeptide synthons for the sequences Aib-(Me)Ala, Aib-(Me)Val, Aib-Homoproline, and Iva-Pro in the 'azirine/oxazolone method'. After the coupling with amino or peptide acids, which proceeds in good yields, the peptide chain can be elongated at the N- or C-terminus by standard peptide chemistry.

A serious limitation of the general applicability of the method is the synthesis of the necessary starting materials, *i.e.*, the corresponding 'thioamides', which was not possible for all desired cases. However, it can be emphasized that, once these are obtained, the preparation of the 2*H*-azirin-3-amines proceeds smoothly.

We thank the analytical units of our institute for spectra and analyses, especially Dr. *G. Hopp-Rentsch*, Ms. *N. Walch*, and Mr. *S. Jurt* for NMR spectra, Dr. *L. Bigler* and Mr. *N. Bild* for mass spectra, and Dr. *A. Linden* for the crystal-structure determination. Financial support by the *Swiss National Science Foundation*, *F. Hoffmann-La Roche AG*, Basel, and the *Stiftung für wissenschaftliche Forschung an der Universität Zürich* is gratefully acknowledged.

Experimental Part

1. *General.* Solvents were purified by standard procedures. TLC: *Merck 60* F_{254} SiO_2-coated glass plates, 0.25 mm. Column chromatography (CC): *Merck 60* 230–400 mesh SiO_2. M.p.: *Büchi B-540*. IR: *Perkin-Elmer 1600-FTIR* spectrometer, KBr or $CHCl_3$; in cm^{-1}. NMR: *Bruker ARX-300* spectrometer (^1H: 300 MHz, ^{13}C: 75.5 MHz); in $CDCl_3$; chemical shifts δ [ppm] refer to residual $CHCl_3$ (7.27 ppm, ^1H) and to $CDCl_3$ (77.0 ppm, ^{13}C); *J* in Hz. MS: *Finnigan MAT SSQ-700* (CI) and *Finnigan MAT TSQ-700* (ESI) spectrometers; *m/z* (rel.%).

General Procedure A (*GP A*). Under cooling with liquid N_2, $SOCl_2$ (1–1.1 equiv.) was added to MeOH keeping the temp. below 5°. To this soln., the amino acid (1 equiv.) was added, and the mixture was heated under reflux for 1 h. Excess MeOH was evaporated.

General Procedure B (*GP B*). To a soln. of the sticky pale yellow residue of the above experiment (*GP A*) or the commercially available amino acid ester in CH_2Cl_2 and Et_3N (3 equiv.), isobutyryl chloride (1 equiv.) was added at 0°. The mixture was stirred at r.t. for several h, the solvent was evaporated, and the residue was dissolved in Et_2O. Then, H_2O was added until the precipitated $Et_3N \cdot HCl$ dissolved. Extraction with Et_2O, drying ($MgSO_4$), and evaporation of the solvent yielded the 'amide'.

General Procedure C (*GP C*). To a soln. of the 'amide' in abs. toluene or abs. toluene/pyridine was added *Lawesson* or *Davy* reagent (synthesis according to the procedure in [40]; 1.0–1.1 equiv.), and the mixture was heated to 90°–reflux temp. for 0.5–22 h. After cooling to r.t. and evaporation, the crude 'thioamide' was purified by CC (SiO_2).

General Procedure D (*GP D*). To a stirred soln. of the 'thioamide' in abs. CH_2Cl_2 and 2–3 drops of DMF, cooled to 0°, was added a soln. of $COCl_2$ (2M in toluene, 3–5 equiv.). The mixture was stirred at 0° → r.t. for 1 h, the solvent was evaporated, the residue was dissolved in abs. THF, and 1,4-diazabicyclo[2.2.2]octane (DABCO, 1 equiv.) was added. After stirring for 20 min at r.t., the mixture was filtered under N_2, and the residue was washed with abs. THF. The pale yellow soln. was directly used in the subsequent reaction.

General Procedure E (*GP E*). To the soln. from the above experiment (*GP D*) was added NaN_3 (3 equiv.), the mixture was stirred at r.t. for up to several days, filtered though a *Celite* pad, washed with Et_2O, and the solvent was evaporated. The crude product was purified by CC (SiO_2).

General Procedure F (*GP F*). To a soln. of *N*-protected amino acid or peptide acid in the given solvent was added the 2*H*-azirin-3-amine (1.0–1.1 equiv.), and the mixture was stirred at r.t. After completion of the reaction (TLC), the soln. was concentrated *in vacuo*, and the residue was purified by CC (SiO_2).

General Procedure G (*GP G*). To a soln. of terminal-*C*- and terminal-*N*-protected peptide in THF/MeOH/H_2O 3:1:1, $LiOH \cdot H_2O$ (3 equiv.) was added. The mixture was stirred until completion of the reaction (TLC), transferred to a separatory funnel, diluted with 5% $KHSO_4$ soln., and extracted with CH_2Cl_2 (3×). The combined org. phase was dried ($MgSO_4$) and concentrated *in vacuo*.

General Procedure H (*GP H*). To a soln. of *N*-protected amino acid or *N*-protected peptide, $EtN(i\text{-}Pr)_2$ or Et_3N (3 equiv.), and *O*-(benzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU, 1.05 equiv.) in MeCN was added 1.1 equiv. of amino acid ester or peptide ester. The mixture was stirred at r.t., until the starting material was completely consumed (TLC). Then, the soln. was concentrated *in vacuo* and the crude product purified by CC (SiO_2).

2. *Synthesis of Ethyl (*R/S*)*-N-*(2,2-Dimethyl-2*H*-azirin-3-yl)*-N-*methylalaninate* (**11a**). 2.1. *Ethyl (*S*)*-N-*(2-Methylpropanoyl)alaninate* (**6a**). According to the *GP B*, with ethyl (*S*)-alaninate hydrochloride (19.91 g, 129.61 mmol) in abs. CH_2Cl_2 (800 ml), Et_3N (54.2 ml, 388.84 mmol), and isobutyryl chloride (13.45 ml, 129.61 mmol); reaction time: 1 h. Evaporation yielded 21.80 g (90%) of **6a**. Colorless solid. M.p. 45–47°. IR (KBr): 3305*s*, 3080*m*, 2966*s*, 2934*s*, 2874*w*, 2799*w*, 1728*s*, 1643*s*, 1548*s*, 1469*s*, 1387*m*, 1373*s*, 1340*s*, 1256*s*, 1226*s*, 1116*s*, 1099*s*, 1054*m*, 1020*w*, 933*m*, 879*w*, 759*w*. ^1H-NMR: 5.98 (br. *s*, NH); 4.60–4.55 (*m*, CH(α)(Ala)); 4.20 (*q*, *J* = 7.1, $MeCH_2O$); 2.38 (*sept.*, *J* = 7.0, Me_2CH); 1.40 (*d*, *J* = 7.2, Me(Ala)); 1.28 (*t*, *J* = 7.1, $MeCH_2O$); 1.17 (*d*, *J* = 7.0, Me_2CH). ^{13}C-NMR: 176.4, 173.4 (2*s*, 2 CO); 61.5 (*t*, $MeCH_2O$); 47.9 (*d*, CH(α)(Ala)); 35.5 (*d*, Me_2CH); 19.5, 19.4 (2*q*, Me_2CH); 18.6 (*q*, Me(Ala)); 14.0 (*q*, $MeCH_2O$). EI-MS: 187 (8, $M^{+\cdot}$), 116 (9), 114 (48), 71 (17), 70 (6), 44 (100), 43 (32). Anal. calc. for $C_9H_{17}NO_3$ (187.23): C 57.74, H 9.15, N 7.48; found: C 58.30, H 9.15, N 7.40.

2.2. *Ethyl (*R/S*)*-N-*Methyl*-N-*(2-methylpropanoyl)alaninate* (**8a**). To a soln. of **6a** (8.63 g, 46.08 mmol) and $LiClO_4$ (5.39 g, 50.69 mmol) in abs. THF (400 ml) was added NaH (2.21 g, 55.29 mmol, washed with hexane) at 0°. The mixture was stirred for 30 min, then MeI (4.31 ml, 69.12 mmol) was added at 0°. After stirring for 3 h at r.t. and 2 h at 40°, the mixture was poured onto ice and extracted with CH_2Cl_2. The org. phase was washed with brine and dried ($MgSO_4$) to yield 8.56 g (92%) of crude **8a**. CC (Et_2O/hexane 1:1) gave 6.49 g (70%) of **8a** as a colorless oil, as well as 0.9 g (10%) of **6a**. Yield calc. regarding consumed **6a**: 79%. IR (neat): 2980*s*, 2940*s*, 2870*m*, 1740*s*, 1650*s*, 1470*s*, 1410*s*, 1390*m*, 1370*m*, 1310*s*, 1280*s*, 1210*s*, 1180*s*, 1090*s*, 1040*m*, 930*w*, 890*w*, 860*w*, 750*w*. ^{1}H-NMR: 5.22 (*q*, *J* = 7.3, CH(α)(Ala)); 4.21–4.11 (*m*, MeCH_2O); 2.98 (*s*, MeN); 2.85–2.79 (*m*, Me_2CH); 1.38 (*d*, *J* = 7.3, Me(Ala)); 1.25 (*t*, *J* = 7.1, *Me*CH_2O); 1.15, 1.13 (2*d*, *J* = 4.4, Me_2CH). ^{13}C-NMR: 177.3, 172.1 (2*s*, 2 CO); 61.0 (*t*, Me*C*H_2O); 52.2 (*d*, CH(α)(Ala)); 31.4 (*q*, MeN); 30.5 (*d*, Me_2CH); 19.0 (*q*, Me_2CH); 14.4 (*q*, Me(Ala)); 14.2 (*q*, *Me*CH_2O). CI-MS: 203 (10), 202 (100, $[M+H]^+$), 125 (5). Anal. calc. for $C_{10}H_{19}NO_3 \cdot 0.1\ H_2O$ (203.06): C 59.15, H 9.53, N 6.90; found: C 59.22, H 9.45, N 7.08.

2.3. *Ethyl (*R/S*)*-N-*Methyl*-N-*(2-methylpropanethioyl)alaninate* (**9a**). According to the *GP C*, with **8a** (4.25 g, 21.12 mmol) in abs. toluene/pyridine 1:1 (150 ml) and *Davy* reagent [41] (4.61 g, 10.56 mmol); reaction time: 17 h, temp. 100°. The residue was dissolved in Et_2O and washed twice with 1N aq. HCl soln., 1N aq. NaOH soln., and 1N aq. HCl soln. Drying ($MgSO_4$), evaporation, and CC (Et_2O/hexane 3:1) yielded 2.27 g (50%) of **9a** as a yellow oil, as well as 1.22 g (29%) of **8a**. Yield calc. regarding consumed material: 70%. IR (neat): 2980*s*, 2940*m*, 1740*s*, 1480*s*, 1440*s*, 1410*s*, 1380*m*, 1280*s*, 1210*s*, 1140*m*, 1110*s* 1090*s*, 1010*s*, 980*w*, 860*w*. ^{1}H-NMR: 6.65 (*q*, *J* = 7.2, CH(α)(Ala)); 4.25–4.15 (*m*, MeCH_2O); 3.20 (*s*, MeN); 3.23-3.14 (*m*, Me_2CH); 1.48 (*d*, *J* = 7.3, Me(Ala)); 1.35–1.24 (*m*, *Me*CH_2O, Me_2CH). ^{13}C-NMR: 213.2 (*s*, CS); 170.7 (*s*, CO); 61.4 (*t*, MeCH_2O); 59.4 (*d*, CH(α)(Ala)); 37.0 (*d*, Me_2CH); 34.7 (*q*, MeN); 22.9, 22.8 (2*q*, Me_2CH); 14.2 (*q*, Me(Ala)); 14.0 (*q*, *Me*CH_2O). CI-MS: 219 (8), 218 (78, $[M+H]^+$), 187 (10), 186 (100).

2.4. *Ethyl (*R/S*)*-N-*(1-Chloro-2-methylprop-1-enyl)*-N-*methylalaninate* (**10a**). According to the *GP D*, with **9a** (1.13 g, 5.20 mmol) in abs. CH_2Cl_2 (15 ml), 2 drops of DMF, 2N $COCl_2$ soln. (3.25 ml, 6.5 mmol), abs. THF (15 ml), and DABCO (0.59 g, 5.20 mmol).

2.5. *Ethyl (*R/S*)*-N-*(2,2-Dimethyl-*2H-*azirin-3-yl)*-N-*methylalaninate* (**11a**). According to the *GP E*, with NaN_3 (1.01 g, 15.60 mmol); reaction time: 5 h. The residue was dissolved in AcOEt, washed with sat. aq. $NaHCO_3$ soln. and brine. Drying ($MgSO_4$), evaporation, and CC (AcOEt) yielded 0.54 g (52%) of **11a** as an oil, as well as 0.32 g (28%) of **8a**. IR (neat): 1980*m*, 1940*m*, 1770*s* (azirine C=N), 1740*s*, 1640*w*, 1470*m*, 1450*m*, 1370*m*, 1300*m*, 1200*s*, 1100*s*, 1020*m*, 860*w*. ^{1}H-NMR: 4.20 (*q*, *J* = 7.1, MeCH_2O); 4.05 (br. *s*, CH(α)(Ala)); 3.00 (*s*, MeN); 1.52 (*d*, *J* = 7.4, Me(Ala)); 1.34, 1.33 (2*s*, Me_2C); 1.27 (*t*, *J* = 7.1, *Me*CH_2O). ^{13}C-NMR: 171.5 (*s*, CO); 61.4 (*t*, Me*C*H_2O); 59.2 (*d*, CH(α)(Ala)); 33.1 (*q*, MeN); 25.2 (*q*, Me_2C); 15.6 (*q*, Me(Ala)); 14.2 (*q*, *Me*CH_2O). The signals for C(2′) and C(3′) could not be localized. CI-MS (NH_3): 200 (11), 199 (100, $[M+H]^+$), 172 (4). Anal. calc. for $C_{10}H_{18}N_2O_2 \cdot 0.33\ H_2O$ (204.27): C 58.80, H 9.24, N 13.71; found: C 58.86, H 9.09, N 13.77.

3. *Reactions of* **11a** *with PhCOSH, PhCOOH, and Z-Phe-OH.* 3.1. *Ethyl (*R/S*)*-N-*[2-(Benzoylamino)-2-methylpropanethioyl]*-N-*methylalaninate* (**12a**). According to the *GP F*, with PhCOSH (0.12 ml, 1.05 mmol) in abs. Et_2O (5 ml), **11a** (230 mg, 1.16 mmol) in abs. Et_2O (5 ml); reaction time: 1 h. CC (hexane/AcOEt 2:1) yielded 0.21 g (60%) of **12a**. Colorless oil, which solidified under h.v. IR ($CHCl_3$): 3240*w*, 3000*s*, 1730*s*, 1650*s*, 1580*w*, 1510*s*, 1480*s*, 1380*s*, 1300*m*, 1230*m*, 1100*s*, 1090*s*, 1040*w*, 1020*w*, 880*w*. ^{1}H-NMR: 8.50 (br. *s*, NH); 7.84 (*d*, *J* = 7.5, 2 arom. H); 7.50–7.32 (*m*, 3 arom. H); 6.48–5.52 (*m*, CH(α)(Ala)); 4.25–4.07 (*m*, MeCH_2O); 3.34 (*s*, MeN); 1.93, 1.91 (2*s*, 2 Me(Aib)); 1.52 (*d*, *J* = 7.1, Me(Ala)); 1.25 (*t*, *J* = 7.1, *Me*CH_2O). ^{13}C-NMR: 208.8 (*s*, CS); 172.5, 160.1 (2*s*, 2 CO); 133.7 (*s*, 1 arom. C); 131.3, 128.4, 126.9 (3*d*, 5 arom. C); 63.1 (*s*, C(α)(Aib)); 61.4 (*t*, Me*C*H_2O); 52.2 (*d*, CH(α)(Ala)); 30.5 (*q*, MeN); 27.4 (*q*, 2 Me(Aib)); 19.0 (*q*, Me(Ala)); 14.1 (*q*, *Me*CH_2O). CI-MS (NH_3): 337 (2, $[M+H]^+$), 322 (24), 293 (5), 292 (16), 291 (100), 204 (5), 202 (26), 188 (27), 145 (6), 130 (12). Anal. calc. for $C_{17}H_{24}N_2O_3S \cdot 0.25\ H_2O$ (340.94): C 59.89, H 7.24, N 8.21; found: C 59.85, H 7.06, N 8.06.

3.2. *Ethyl (*R/S*)*-N-*[2-(Benzoylamino)-2-methylpropanethioyl]*-N-*methylalaninate* (**12b**). According to the *GP F*, with PhCOOH (32 mg, 0.26 mmol) in abs. CH_2Cl_2 (4 ml), **11a** (57 mg, 0.29 mmol) in abs. CH_2Cl_2 (4 ml); reaction time: 1 h. CC (hexane/AcOEt 2:1) yielded 30 mg (44%) of **12b**. Colorless oil, which solidified under h.v. IR (KBr): 3300*s*, 3000*s*, 1760*s*, 1650*s*, 1620*s*, 1580*m*, 1530*s*, 1490*s*, 1400*s*, 1300*s*, 1220*s*, 1120*s*, 1090*s*, 1030*m*, 1020*w*, 940*w*, 870*w*, 800*w*, 780*w*, 750*m*, 720*s*, 700*s*. ^{1}H-NMR: 7.80 (*d*, *J* = 6.7, 2 arom. H); 7.55 (br. *s*, NH); 7.49–7.39 (*m*, 3 arom. H); 5.29 (*q*, *J* = 7.1, CH(α)(Ala)); 4.20–4.11 (*m*, MeCH_2O); 3.08 (br. *s*, MeN); 1.80 (*s*, 2 Me(Aib)); 1.44 (*d*, *J* = 7.2, Me(Ala)); 1.25 (*t*, *J* = 7.1, *Me*CH_2O). ^{13}C-NMR: 173.6, 171.9, 165.6 (3*s*, 3 CO); 134.8 (*s*, 1 arom. C); 131.3, 128.4, 126.8 (3*d*, 5 arom. C); 61.2 (*t*, MeCH_2O); 57.5 (*s*, C(α)(Aib)); 55.5 (*d*, CH(α)(Ala)); 30.4 (*q*, MeN); 24.5 (*q*, 2 Me(Aib)); 19.0 (*q,* Me(Ala)); 14.2 (*q*, *Me*CH_2O). ESI-MS: 343 ($[M+Na]^+$). Anal. calc. for $C_{17}H_{24}N_2O_4 \cdot 0.33\ H_2O$ (326.40): C 62.56, H 7.62, N 8.58; found: C 62.50, H 7.65, N 8.45.

3.3. *Ethyl* N-*[(Benzyloxy)carbonyl]-(*S*)-phenylalanyl-dimethylglycyl-(*R/S*)*-N-*methylalaninate* (Z-Phe-Aib-(Me)Ala-OEt; **14a**). According to the *GP F*, with Z-Phe-OH (**13a**, 0.43 g, 1.42 mmol) in Et_2O (5 ml), **11a** (310 mg, 0.56 mmol) in Et_2O (5 ml); reaction time: 1 h. CC (hexane/AcOEt 1:1) gave 500 mg (70%) of **14a**. Colorless foam. ^{1}H-NMR (epimers): 7.34–7.18 (*m*, 10 arom. H); 6.82, 5.33 (2br. *s*, 2 NH); 5.08 (br. *s*, PhC*H*$_2$(Z)); 4.90 (*q*, *J* = 7.0, CH(α)(Ala)); 4.36 (*t*, *J* = 6.8, CH(α)(Phe)); 4.17–4.12 (*m*, MeC*H*$_2$O); 3.11–3.03 (*m*, CH_2(Phe)); 2.86, 2.83 (2*s*, 1:1, MeN); 1.48, 1.47 (2*s*, 2 Me(Aib)); 1.36 (*d*, *J* = 7.2, Me(Ala)); 1.24 (*t*, *J* = 7.0, *Me*CH$_2$O). ^{13}C-NMR (epimers): 173.6, 172.4, 170.0 (3*s*, 3 CO); 156.2 (*s*, CO(carbamate)); 136.6, 136.3 (2*s*, 2 arom. C); 129.4, 128.5, 128.1, 127.8, 126.8 (5*d*, 10 arom. C); 66.8 (*t*, PhCH$_2$(Z)); 60.5 (*t*, MeCH$_2$O); 56.8 (*s*, C(α)(Aib)); 56.4, 55.2 (2*d*, CH(α)(Ala), CH(α)(Phe)); 38.2 (*t*, CH_2(Phe)); 32.7, 31.8 (2*q*, MeN); 25.5, 25.2, 24.6 (3*q*, 2 Me(Aib), *Me*CH$_2$O); 14.1 (*q*, Me(Ala)). CI-MS: 498 (19, $[M+H]^+$), 453 (27), 452 (100), 344 (31), 132 (22).

3.4. *Deprotection*. 3.4.1. *Ethyl (*S*)-Phenylalanyl-dimethylglycyl-(*R/S*)*-N-*methylalaninate* (H-Phe-Aib-(Me)Ala-OEt; **15**). To a soln. of **14a** (162 mg, 0.34 mmol) in MeOH (10 ml) was added Pd/C, and the resulting mixture was stirred under H_2 for 14 h at r.t. Filtration through a *Celite* pad, evaporation of the filtrate, and CC (AcOEt/MeOH 20:1) yielded 83 mg (71%) of **15**. Yellow oil. IR ($CHCl_3$): 3320*w*, 3000*s*, 1730*s*, 1680*s*, 1630*s*, 1500*s*, 1470*s*, 1450*s*, 1400*s*, 1380*m*, 1300*m*, 1220*s*, 1090*s*, 1040*w*, 1020*w*, 910*w*. ^{1}H-NMR (epimers): 7.99 (br. *s*, NH); 7.32–7.21 (*m*, 5 arom. H); 5.05–4.98 (*m*, CH(α)(Ala)); 4.20–4.11 (*m*, MeC*H*$_2$O); 3.38 (*t*, *J* = 7.1, CH(α)(Phe)); 2.98 (br. *s*, MeN); 2.83 (*s*, NH_2); 2.38–2.31, 2.08–2.02 (2*m*, CH_2(Phe)); 1.60 (*s*, 2 Me(Aib)); 1.35 (*d*, *J* = 7.1, Me(Ala)); 1.25 (*t*, *J* = 7.1, *Me*CH$_2$). CI-MS: 727 (64, $[2M+H]^+$), 365 (20), 364 (100, $[M+H]^+$), 233 (6), 132 (38), 100 (10).

3.4.2. N-*[(Benzyloxy)carbonyl]-(*S*)-phenylalanyl-dimethylglycyl-(*R/S*)*-N-*methylalanine* (Z-Phe-Aib-(Me)Ala-OH; **16**). According to the *GP G*, with **14a** (288 mg, 0.58 mmol) in THF/MeOH/H_2O (3:1:1), LiOH·H_2O (97 mg, 2.32 mmol). Reaction time: 20 h. Evaporation led to 236 mg (87%) of crude Z-Phe-Aib-(Me)Ala-OH. CC (AcOEt with a gradient to AcOEt/MeOH 20:1) gave 183 mg (67%) of **16**. Colorless foam. IR ($CHCl_3$): 3430*w*, 3340*w*, 2980*s*, 1740*s*, 1720*s*, 1690*s*, 1680*s*, 1630*s*, 1500*s*, 1390*s*, 1370*s*, 1160*s*, 1090*s*, 1040*w*, 1020*w*, 920*w*, 870*w*. ^{1}H-NMR (epimers): 7.78 (br. *s*, OH); 7.37–7.21 (*m*, 10 arom. H); 6.88 (br. *s*, NH); 6.10–6.03 (br. *d*, *J* = 8.4, NH)); 5.04 (br. *s*, PhC*H*$_2$(Z)); 4.67 (*s*, CH(α)(Ala)); 4.43 (*t*, *J* = 7.2, CH(α)(Phe)); 3.08–2.98 (*m*, CH_2(Phe)); 2.78, 2.74 (2*s*, ratio 1:1, MeN); 1.58–1.31 (*m*, Me(Ala), 2 Me(Aib)). CI-MS: 470 (3, $[M+H]^+$), 435 (15), 434 (60), 368 (21), 367 (100), 300 (18), 174 (13), 108 (9), 104 (67).

4. *Synthesis of Methyl (*R/S*)-*N*-(2,2-Dimethyl-2*H*-azirin-3-yl)-*N*-methylalaninate* (**11b**). 4.1. *Methyl (*S*)-*N*-(2-Methylpropanoyl)alaninate* (**6b**). According to the *GP B*, with methyl (*S*)-alaninate hydrochloride (24.76 g, 177.39 mmol) in abs. CH_2Cl_2 (800 ml), Et_3N (74.2 ml, 532.17 mmol), and isobutyryl chloride (18.4 ml, 177.39 mmol); reaction time: 1 h. Evaporation yielded 28.24 g (92%) of **6b**. Colorless solid. M.p. 53–55°. IR (KBr): 3280*s*, 3080*m*, 3000*s*, 2960*s*, 1740*s*, 1640*s*, 1550*s*, 1440*s*, 1370*s*, 1330*s*, 1260*s*, 1220*s*, 1120*s*, 1090*m*, 1050*m*, 990*w*, 930*w*, 700*m*. ^{1}H-NMR: 6.07 (br. *s*, NH); 4.62–4.57 (*m*, CH(α)(Ala)); 3.75 (*s*, MeO); 2.40 (*sept.*, *J* = 6.9, Me_2CH); 1.40 (*d*, *J* = 7.2, Me(Ala)); 1.16 (*d*, *J* = 6.9, *Me*$_2$CH). ^{13}C-NMR: 176.5, 173.8 (2*s*, 2 CO); 52.4 (*q*, MeO); 47.8 (*d*, CH(α)(Ala)); 35.4 (*d*, Me_2CH); 19.5, 19.4 (2*q*, *Me*$_2$CH); 18.5 (*q*, Me(Ala)). CI-MS: 364 (13, $[2M+NH_4]^+$), 347 (9, $[2M+H]^+$), 277 (7), 192 (8), 191 (100), 174 (34, $[M+H]^+$).

4.2. *Methyl (*R/S*)-*N*-Methyl-*N*-(2-methylpropanoyl)alaninate* (**8b**). To a soln. of **6b** (9.20 g, 53.15 mmol) and $LiClO_4$ (6.24 g, 58.46 mmol) in abs. THF (400 ml) was added NaH (2.55 g, 63.78 mmol, washed with hexane) at 0°. The mixture was stirred for 30 min, then MeI (5.00 ml, 79.72 mmol) was added at 0°. After stirring for 3 h at r.t. and 2 h at 40°, the mixture was poured onto ice and extracted with CH_2Cl_2. The org. phases were washed with brine and dried ($MgSO_4$) to yield 7.46 g (75%) of crude **8b**. CC (Et_2O/hexane 1:1) gave 5.78 g (58%) of **8b**. Colorless oil. IR (neat): 2980*s*, 1740*s*, 1640*s*, 1460*m*, 1410*m*, 1310*m*, 1270*m*, 1210*s*, 1170*m*, 1090*s*, 980*w*, 750*w*. ^{1}H-NMR: 5.20 (*q*, *J* = 7.4, CH(α)(Ala)); 3.70 (*s*, MeO); 3.00 (*s*, MeN); 2.89–2.80 (*m*, Me_2CH); 1.39 (*d*, *J* = 7.4, Me(Ala)); 1.17 (*d*, *J* = 7.0, *Me*$_2$CH). ^{13}C-NMR: 177.3, 173.7 (2*s*, 2 CO); 52.1 (*q*, MeO); 52.0 (*d*, CH(α)(Ala)); 31.5 (*q*, MeN); 30.1 (*d*, Me_2CH); 19.1, 19.0 (2*q*, *Me*$_2$CH); 14.5 (*q*, Me(Ala)). CI-MS: 375 (11, $[2M+H]^+$), 245 (6), 189 (10), 188 (100, $[M+H]^+$). Anal. calc. for $C_9H_{17}NO_3 \cdot 0.5\ H_2O$ (189.04): C 57.18, H 9.17, N 7.41; found: C 57.20, H 9.08, N 7.50.

4.3. *(*R/S*)-*N*-Methyl-*N*-(2-methylpropanoyl)alanine* (**7**). When the same mixture as described above was heated to 60° for longer reaction times, the acid **7** could also be isolated from the reaction mixture. IR (KBr): 2976*s*, 2943*s*, 2881*s*, 2594*m*, 1730*s*, 1635*s*, 1485*s*, 1460*m*, 1420*m*, 1368*w*, 1351*w*, 1305*m*, 1284*m*, 1207*s*, 1180*s*, 1126*m*, 1097*s*, 1015*w*, 938*m*, 815*w*, 774*w*, 752*m*, 727*w*. ^{1}H-NMR (conformers): 10.3 (br. *s*, OH); 5.17, 4.68 (2*q*, *J* = 7.3, CH(α)(Ala)); 3.02, 2.86 (2*s*, MeN); 2.88–2.79 (*m*, Me_2CH); 1.49, 1.42 (2*d*, *J* = 7.3, Me(Ala)); 1.14, 1.13 (2*d*, *J* = 6.7, *Me*$_2$CH). ^{13}C-NMR (conformers): 178.1, 175.8 (2*s*, 2 CO); 54.7, 52.5 (2*d*, CH(α)(Ala)); 31.6 (*q*, MeN);

30.3 (*d*, Me_2CH); 18.8, 18.7 (2*q*, Me_2CH); 15.6, 14.1 (2*q*, Me(Ala)). ESI-MS: 423 (30), 401 (30), 369 (15, $[2M+Na]^+$), 196 (100, $[M+Na]^+$), 174 (15, $[M+H]^+$).

4.4. *Methyl (*R/S*)*-N-*Methyl*-N-*(2-methylpropanethioyl)alaninate* (**9b**). According to the *GP C*, with **8b** (4.38 g, 23.39 mmol) in abs. toluene/pyridine 1:1 (120 ml) and *Davy* reagent [41] (6.13 g, 14.04 mmol); reaction time: 22 h, temp. 100°. The residue was dissolved in Et_2O and washed twice with 1N aq. HCl soln., 1N aq. NaOH soln., and 1N aq. HCl soln. Drying ($MgSO_4$), evaporation, and CC (Et_2O/hexane 3:1) yielded 3.37 g (71%) of **9b**. Yellow oil. IR (neat): 2960*s*, 1740*s*, 1480*s*, 1450*s*, 1405*s*, 1380*s*, 1360*m*, 1270*s*, 1210*s*, 1140*m*, 1110*s*, 1090*s*, 1010*s*, 900*w*, 860*w*, 810*w*, 780*w*. ^{1}H-NMR: 6.68 (*q*, *J* = 7.2, CH(α)(Ala)); 3.74 (*s*, MeO); 3.20 (*s*, MeN); 3.23–3.14 (*m*, Me_2CH); 1.48 (*d*, *J* = 7.2, Me(Ala)); 1.28–1.23 (*m*, Me_2CH). ^{13}C-NMR: 213.3 (*s*, CS); 171.3 (*s*, CO); 59.2 (*d*, CH(α)(Ala)); 52.7 (*q*, MeO); 36.9 (*d*, Me_2CH); 34.6 (*q*, MeN); 22.6, 22.9 (2*q*, Me_2CH); 14.0 (*q*, Me(Ala)). CI-MS: 205 (11), 204 (100, $[M+H]^+$), 172 (43), 170 (15). Anal. calc. for $C_9H_{17}NO_2S \cdot 0.1\ H_2O$ (205.09): C 52.71, H 8.45, N 6.83, S 15.63; found: C 52.73, H 7.90, N 6.95, S 15.62.

4.5. *Methyl (*R/S*)*-N-*(1-Chloro-2-methylprop-1-enyl)*-N-*methylalaninate* (**10b**). According to the *GP D*, with **9b** (2.98 g, 14.66 mmol) in abs. CH_2Cl_2 (50 ml), 3 drops of DMF, 2N $COCl_2$ soln. (9.2 ml, 18.33 mmol), abs. THF (40 ml) and DABCO (1.65 g, 14.66 mmol).

4.6. *Methyl (*R/S*)*-N-*(2,2-Dimethyl-2*H*-azirin-3-yl)*-N-*methylalaninate* (**11b**). According to the *GP E*, with NaN_3 (2.86 g, 43.98 mmol); reaction time: 5 h. The residue was dissolved in AcOEt, washed with a sat. aq. $NaHCO_3$ soln. and brine. Drying ($MgSO_4$), evaporation, and CC (AcOEt) yielded 1.03 g (39%) of **11b**. Pale yellow oil. B.p. 90°/0.30 mbar. IR (neat): 2980*m*, 2940*m*, 1765*s* (azirine C=N), 1745*s*, 1645*s*, 1450*m*, 1370*m*, 1300*m*, 1210*s*, 1100*m*, 980*w*, 920*w*, 730*m*. ^{1}H-NMR: 4.05 (br. *s*, CH(α)(Ala)); 3.70 (*s*, MeO); 2.96 (*s*, MeN); 1.48 (*d*, *J* = 7.3, Me(Ala)); 1.29, 1.28 (2*s*, Me_2C). ^{13}C-NMR: 171.8 (*s*, CO); 58.8 (*d*, CH(α)(Ala)); 52.2 (*q*, MeO); 33.2 (*q*, MeN); 25.0 (*q*, Me_2C); 19.6 (*q*, Me(Ala)). The signals for C(2′) and C(3′) could not be assigned. CI-MS: 369 (24, $[2M+H]^+$), 281 (17), 186 (10), 185 (100, $[M+H]^+$), 158 (11).

5. *Reactions of* **11b** *with PhCOSH, PhCOOH and Amino Acids.* 5.1. *Methyl (*R/S*)*-N-*[2-(Benzoylamino)-2-methylpropanethioyl]*-N-*methylalaninate* (**12c**). According to the *GP F*, with PhCOSH (38 mg, 0.31 mmol) in abs. CH_2Cl_2 (2 ml), **11b** (63 mg, 0.34 mmol) in abs. CH_2Cl_2 (2 ml); reaction time: 17 h. CC (hexane/AcOEt 4:1) yielded 62 mg (60%) of **12c**. Colorless oil, which solidified under h.v. IR (KBr): 3340*s*, 3060*m*, 3000*m*, 2920*m*, 1740*s*, 1640*s*, 1580*m*, 1540*s*, 1470*s*, 1380*s*, 1340*s*, 1310*s*, 1220*s*, 1180*s*, 1110*s*, 1090*s*, 1040*s*, 870*m*, 720*m*. ^{1}H-NMR: 8.50 (br. *s*, NH); 7.88–7.84 (*m*, 2 arom. H); 7.52–7.40 (*m*, 3 arom. H); 6.35–5.60 (*m*, CH(α)(Ala)); 3.73 (*s*, MeO); 3.35 (*s*, MeN); 1.96, 1.93 (2*s*, 2 Me(Aib)); 1.56 (*d*, *J* = 7.1, Me(Ala)). ^{1}H-NMR ((D$_6$)DMSO, 373 K): 8.29 (br. *s*, NH); 7.88–7.81 (*m*, 2 arom. H); 7.53–7.41 (*m*, 3 arom. H); 6.12 (*q*, *J* = 7.0, CH(α)(Ala)); 3.62 (*s*, MeO); 3.25 (*s*, MeN); 1.79, 1.78 (2*s*, 2 Me(Aib)); 1.39 (*d*, *J* = 7.1, Me(Ala)). ^{13}C-NMR ((D$_6$)DMSO, 373 K): 207.6 (*s*, CS); 169.7, 164.5 (2*s*, 2 CO); 134.4 (*s*, 1 arom. C); 130.1, 127.3, 126.5 (3*d*, 5 arom. C); 60.8 (*d*, CH(α)(Ala)); 60.5 (*s*, C(α)(Aib)); 51.0 (*q*, MeO); 37.7 (*q*, MeN); 29.0, 28.5 (2*q*, 2 Me(Aib)); 13.4 (*q*, Me(Ala)). CI-MS (NH_3): 324 (8), 323 (43, $[M+H]^+$), 320 (6), 293 (5), 292 (17), 291 (100), 237 (6), 204 (5), 188 (7).

5.2. *Ethyl (*R/S*)*-N-*[2-(Benzoylamino)-2-methylpropanoyl]*-N-*methylalaninate* (**12d**). According to the *GP F*, with PhCOOH (40.6 mg, 0.294 mmol) in abs. CH_2Cl_2 (2 ml), **11b** (60 mg, 0.32 mmol) in abs. CH_2Cl_2 (2 ml); reaction time: 17 h. CC (hexane/AcOEt 2:1) yielded 58 mg (56%) of **12d**. Colorless oil, which solidified under h.v. IR ($CHCl_3$): 3360*w*, 3000*s*, 1790*w*, 1740*s*, 1660*s*, 1620*s*, 1580*m*, 1510*s*, 1480*s*, 1400*s*, 1280*m*, 1230*s*, 1090*s*, 1040*w*, 1020*w*, 1000*w*, 910*m*, 880*w*. ^{1}H-NMR: 7.81–7.77 (*m*, 2 arom. H); 7.54 (br. *s*, NH); 7.52–7.38 (*m*, 3 arom. H); 5.06–4.98 (*m*, CH(α)(Ala)); 3.70 (*s*, MeO); 3.08 (br. *s*, MeN); 1.77 (*s*, 2 Me(Aib)); 1.44 (*d*, *J* = 7.2, Me(Ala)). ^{13}C-NMR: 173.4, 172.1, 165.6 (3*s*, 3 CO); 134.7 (*s*, 1 arom. C); 131.4, 129.9, 126.8 (3*d*, 5 arom. C); 57.3 (*s*, C(α)(Aib)); 55.3 (*d*, CH(α)(Ala)); 52.2 (*q*, MeO); 30.4 (*q*, MeN); 24.7, 24.4 (2*q*, 2 Me(Aib)); 14.1 (*q*, Me(Ala)). CI-MS (NH_3): 630 (12, $[2M+NH_4]^+$), 425 (23), 424 (100), 324 (6, $[M+NH_4]^+$), 289 (21). Anal. calc. for $C_{16}H_{22}N_2O_4 \cdot 0.1\ H_2O$ (308.16): C 62.36, H 7.26, N 9.09; found: C 62.18, H 7.02, N 8.98.

5.3. *Methyl* N-*[(*tert-*Butoxy)carbonyl]-(*S*)-valyl-dimethylglycyl-(*R/S*)*-N-*methylalaninate* (Boc-Val-Aib-(Me)Ala-OMe; **14b**). According to the *GP F*, with Boc-Val-OH (**13b**; 60 mg, 0.28 mmol) in CH_2Cl_2 (2 ml), **11b** (51.6 mg, 0.28 mmol) in CH_2Cl_2 (2 ml); reaction time: 12 h. CC (AcOEt) gave 54 mg (50%) of **14b**. Colorless foam. IR ($CHCl_3$): 3420*m*, 3300*m*, 3000*s*, 1730*s*, 1720*s*, 1500*s*, 1450*s*, 1400*s*, 1320*s*, 1200*s*, 1080*s*, 1040*s*, 910*m*. ^{1}H-NMR (epimers): 7.06 (br. *s*, NH); 5.21, 5.18 (2*s*, NH); 5.05, 4.94 (2*s*, CH(α)(Ala)); 3.85–3.75 (*m*, CH(α)(Val)); 3.71, 3.70 (2*s*, MeO); 3.00 (br. *s*, MeN); 2.17–2.03 (*m*, CH(β)(Val)); 1.62, 1.60 (2*s*, 2 Me(Aib)); 1.43, 1.42 (2*s*, Me_3C); 1.41, 1.40 (2*d*, *J* = 7.3, Me(Ala)); 1.00–0.89 (*m*, 2 Me(Val)). ^{13}C-NMR (epimers): 174.6, 172.8, 172.0, 170.2 (4*s*, 3 CO); 155.9 (*s*, CO(carbamate)); 79.9 (*s*, Me_3C); 60.1 (*d*, CH(α)(Val)); 57.0 (*s*, C(α)(Aib)); 55.2 (*d*, CH(α)(Ala)); 52.1 (*q*, MeO); 32.9 (*q*, MeN); 31.0, 30.5 (2*d*, CH(β)(Val)); 28.2 (*q*, Me_3C); 24.7 (*q*, 2 Me(Aib)); 19.2, 17.9 (2*q*, 2 Me(Val)); 14.1 (*q*, Me(Ala)). CI-MS (NH_3): 419 (7, $[M+NH_4]^+$), 403 (21),

402 (100, $[M+H]^+$), 285 (17), 118 (24). Anal. calc. for $C_{19}H_{35}N_3O_6$ (401.50): C 56.84, H 8.79, N 10.47; found: C 56.93, H 8.82, N 10.44.

5.4. *Methyl* N-*[(*tert-*Butoxy)carbonyl]-(*S*)-tryptyl-dimethylglycyl-(*R/S*)*-N-*methylalaninate* (Boc-Trp-Aib-(Me)Ala-OMe; **14c**). According to the *GP F*, with Boc-Trp-OH (**13c**, 87 mg, 0.286 mmol) in CH_2Cl_2 (2 ml), **11b** (58 mg, 0.315 mmol) in CH_2Cl_2 (2 ml); reaction time: 22 h. CC (AcOEt) and (AcOEt/hexane 1:1) gave 76.9 mg (55%) of **14c**. Colorless foam. IR (KBr): 3320*s*, 2980*m*, 1740*s*, 1720*s*, 1670*s*, 1640*s*, 1500*s*, 1390*s*, 1360*s*, 1240*s*, 1160*s*, 1090*s*, 1020*m*, 920*w*, 850*s*, 740*m*. ^{1}H-NMR: 8.43 (br. *s*, NH); 7.68 (*d*, *J* = 7.7, C(4) of Trp); 7.38 (*d*, *J* = 7.7, C(7) of Trp); 6.52 (br. *s*, NH); 7.21 – 7.07 (*m*, 3 arom. H); 5.13 (br. *s*, NH); 4.97 – 4.88 (*m*, CH(α)(Ala)); 4.41 (*q*, *J* = 5.8, CH(α)(Trp)); 3.68 (*s*, MeO); 3.34 – 3.13 (*m*, CH_2(Trp)); 2.87, 2.84 (2*s*, MeN, epimers); 1.42 (*s*, *t*-Bu); 1.41 – 1.33 (*m*, 2 Me(Aib), Me(Ala)). ^{13}C-NMR: 172.7, 170.5 (2*s*, 3 CO); 155.7 (*s*, CO(carbamate)); 136.4, 127.3 (2*s*, 2 arom. C); 123.9, 122.1, 119.6, 118.6, 111.5 (5*d*, 5 arom. C); 109.9 (*s*, 1 arom. C); 80.2 (*s*, Me_3C); 56.8 (*s*, C(α)(Aib)); 55.2 (*d*, CH(α)(Ala)); 54.8 (*d*, CH(α)(Trp)); 52.2 (*q*, MeO); 32.8 (*q*, MeN); 28.3 (*q*, Me_3C); 27.9 (*t*, CH_2(Trp)); 25.2 (*q*, 2 Me(Aib)); 14.2 (*q*, Me(Ala)). ESI-MS: 527 (20, $[M+K]^+$), 511 (100, $[M+Na]^+$), 489 (30), 372 (40), 316 (20). Anal. calc. for $C_{25}H_{36}N_4O_6 \cdot 1\ H_2O$ (506.60): C 59.27, H 7.56, N 11.06; found: C 59.14, H 7.34, N 10.70.

6. *Attempted Synthesis of Methyl* N-*(2,2-Dimethyl-2*H*-azirin-3-yl)-2,2,*N*-trimethylglycinate*. 6.1. *Methyl* N-*(2-Methylpropanoyl)-2,2-dimethylglycinate*. According to the *GP B*, with Aib-OMe (998 mg, 8.8 mmol) in abs. CH_2Cl_2 (40 ml), Et_3N (2.12 ml, 29.4 mmol) and isobutyryl chloride (0.76 ml, 7.2 mmol); reaction time: 1.5 h, temp. r.t. $\rightarrow$ 35°. Evaporation yielded 1.37 g (75%) of methyl *N*-(2-methylpropanoyl)-2,2-dimethylglycinate. Colorless oil which solidified under h.v. IR (KBr): 3327*s*, 3186*w*, 2986*m*, 2952*m*, 2876*w*, 1741*s*, 1649*s*, 1539*s*, 1469*s*, 1438*m*, 1387*m*, 1364*m*, 1285*s*, 1244*s*, 1195*s*, 1150*s*, 1097*m*, 1024*m*, 1003*m*, 980*w*, 946*w*, 934*w*, 904*w*, 859*w*, 814*w*, 760*w*. ^{1}H-NMR: 5.99 (br. *s*, NH); 3.73 (*s*, MeO); 2.33 (*sept.*, *J* = 6.9, Me_2CH); 1.54 (*s*, 2 Me(Aib)); 1.13 (*d*, *J* = 6.9, Me_2CH). ^{13}C-NMR: 176.2, 175.2, 169.5 (3*s*, 3 CO); 56.1 (*s*, C(α)(Aib)); 52.5 (*q*, MeO); 35.5 (*d*, Me_2CH); 24.7 (*q*, 2 Me(Aib)); 19.3 (*q*, Me_2CH). CI-MS: 375 (7, $[2M+H]^+$), 305 (37), 245 (19), 189 (9), 188 (100, $[M+H]^+$). Anal. calc. for $C_9H_{17}NO_3 \cdot 0.1\ H_2O$ (189.04): C 57.18, H 9.18, N 7.41; found: C 57.24, H 9.10, N 7.40.

6.2. *Attempted N-Methylation*. To a soln. of methyl *N*-(2-methylpropanoyl)-2,2-dimethylglycinate (367 mg, 1.96 mmol) and $LiClO_4$ (230 mg, 2.16 mmol) in abs. THF/DMF 10:1 (10 ml) was added NaH (282 mg, 5.88 mmol; washed with hexane) at 0°. The mixture was stirred for 30 min, then MeI (0.98 ml, 15.7 mmol) was added at 0°. After stirring for 3 h at 30° and 18 h at 60°[19]), the mixture was poured onto ice and extracted with CH_2Cl_2. The org. phase was washed with brine and dried ($MgSO_4$) to yield 349 mg (95%) of the starting material; no *N*-methyl derivative was detected.

7. *Synthesis of Methyl (*S*)-*N-*(2,2-Dimethyl-2*H*-azirin-3-yl)-*N-*methylalaninate* (**20a**). 7.1. *Methyl (*S*)-*N-*methylalaninate*. According to the *GP A*, with $SOCl_2$ (1.19 ml, 16.30 mmol), MeOH (8.5 ml), and H-(Me)Ala-OH (1.68 g, 16.13 mmol). Yield: quant. Colorless oil. IR ($CDCl_3$): 2977*s*, 2702*s*, 2456*m*, 1753*s*, 1570*m*, 1459*m*, 1439*m*, 1386*w*, 1347*w*, 1308*w*, 1248*s*, 1106*m*, 1072*w*, 1045*w*, 1014*w*, 977*w*, 876*w*. ^{1}H-NMR (D_2O): 4.32 (*q*, *J* = 7.3, CH(α)(Ala)); 4.03 (*s*, MeO); 2.93 (*s*, MeN); 1.36 (*d*, *J* = 7.3, Me(Ala)). ^{13}C-NMR: 170.5 (*s*, CO); 56.2 (*d*, CH(α)(Ala)); 53.5 (*q*, MeO); 30.7 (*q*, MeN); 13.3 (*q*, Me(Ala). ESI-MS: 118 ($[M+H]^+$).

7.2. *Methyl (*S*)-*N-*Methyl-*N-*(2-methylpropanoyl)alaninate* (**18a**). According to the *GP B*, with H-(Me)Ala-OMe (0.56 g, 5.43 mmol) in abs. CH_2Cl_2 (50 ml), Et_3N (2.28 ml, 16.31 mmol), and isobutyryl chloride (0.56 ml, 5.38 mmol); reaction time: 2 h at 30°. Evaporation and CC (hexane/AcOEt 2:1) yielded 1.50 g (49%) of **18a**. Colorless oil. The spectroscopic data are identical with those of racemic **8b** (*vide supra 4.2*).

7.3. *Methyl (*S*)-*N-*Methyl-*N-*(2-methylpropanethioyl)alaninate* (**19a**). The thionation was carried out as described in *Sect. 4.4*. The spectroscopic data are identical with those of **9b** (*vide supra 4.4*).

7.4. *Methyl (*S*)-*N-*(2,2-Dimethyl-2*H*-azirin-3-yl)-*N-*methylalaninate* (**20a**). The reaction was carried out as described in *Sect. 4.6*. The spectroscopic data are identical with those of racemic **11b** (*vide supra 4.6*).

7.5. *1,3,3,6-Tetramethylpiperazine-2,5-dione* (**21**). When **20a** was stored for 3 years at 4°, the whole amount had cyclized to **21**. IR (KBr): 3204*m*, 3064*m*, 2989*m*, 2930*m*, 1679*s*, 1651*s*, 1521*m*, 1463*s*, 1406*s*, 1372*m*, 1316*m*, 1224*s*, 1199*s*, 1119*m*, 1040*m*, 998*w*, 885*w*, 847*m*, 767*m*, 701*w*. ^{1}H-NMR: 7.49 (br. *s*, NH); 3.93 (*q*, *J* = 7.0, MeC*H*); 2.98 (*s*, MeN); 1.55 (*d*, *J* = 7.0, *Me*CH); 1.51, 1.50 (2*s*, Me_2C). ^{13}C-NMR: 169.2, 168.5 (2*s*, 2 CO); 58.1 (*d*, Me*C*H); 55.9 (*s*, Me_2C); 32.4 (*q*, MeN); 29.9, 28.0 (2*q*, Me_2C); 18.4 (*q*, *Me*CH). CI-MS: 188 (100, $[M+NH_4]^+$), 171 (85, $[M+H]^+$). Anal. calc. for $C_8H_{14}N_2O_2$ (170.21): C 56.45, H 8.29, N 16.46; found: C 56.18, H 8.31, N 16.31.

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[19]) A number of similar reactions with different temp., reaction times, and ratio of reagents were also carried out. In none of the experiments was the desired product obtained.

7.6. *Reaction of* **20a** *with Z-Phe-OH: Methyl* N-*[(Benzyloxy)carbonyl]-(*S*)-phenylalanyl-dimethylglycyl-(*S*)-*N*-methylalaninate* (Z-Phe-Aib-(Me)Ala-OMe; **14d**). According to the *GP F*, with Z-Phe-OH (110 mg, 0.367 mmol) in CH_2Cl_2 (2 ml), **20a** (76 mg, 0.413 mmol) in CH_2Cl_2 (2 ml); reaction time: 17 h. CC (hexane/AcOEt 1:1) gave 124 mg (70%) of **14d**. Colorless foam. IR (KBr): 3300*s*, 3000*m*, 2940*m*, 1750*s*, 1660*s*, 1630*s*, 1530*s*, 1450*s*, 1400*s*, 1290*s*, 1240*s*, 1090*s*, 910*w*, 830*w*, 740*m*, 700*s*. ^{1}H-NMR (epimers): 7.42–7.21 (*m*, 10 arom. H); 6.72, 5.31 (2 br. *s*, 2 NH); 5.09 (br. *s*, PhCH_2(Z)); 4.91 (*q*, J = 7.2, CH(α)(Ala)); 4.35 (*t*, J = 6.9, CH(α)(Phe)); 3.96 (*s*, MeO); 3.08–2.98 (*m*, CH_2(Phe)); 2.86, 2.83 (2*s*, 2:1, MeN); 1.50, 1.46 (2*s*, 2 Me(Aib)); 1.36 (*d*, J = 7.2, Me(Ala)). ^{13}C-NMR (epimers): 172.5, 172.0, 169.2 (3*s*, 3 CO); 155.9 (*s*, CO(carbamate)); 136.3, 136.0 (2*s*, 2 arom. C); 129.3, 128.5, 128.4, 128.0, 127.9, 126.9 (6*d*, 10 arom. C); 66.9 (*t*, Ph*C*H_2(Z)); 57.0 (*s*, C(α)(Aib)); 56.3, 55.0, 54.9 (3*d*, CH(α)(Phe), CH(α)(Me)Ala)); 52.0 (*q*, MeO); 38.2 (*t*, CH_2(Phe)); 32.6 (*q*, MeN); 24.9, 24.7, 24.3 (3*q*, 2 Me(Aib)); 14.1 (*q*, Me(Ala)). ESI-MS: 522 ([M + K]$^+$), 506 ([M + Na]$^+$), 484 ([M + H]$^+$), 452 ([M – MeO]$^+$), 367 ([M – N(Me)CH(Me)CO_2Me]$^+$), 285. Anal. calc. for $C_{26}H_{33}N_3O_6 \cdot 0.33\ H_2O$ (489.57): C 63.79, H 6.93, N 8.58; found: C 63.89, H 6.72, N 8.48.

8. *Attempted Synthesis of Methyl* N-*(2,2-Dimethyl-2*H*-azirin-3-yl)*-N-*methyl-glycinate.* 8.1. *Methyl* N-*Methyl*-N-*(2-methylpropanoyl)glycinate* (**18b**). According to the *GP B*, with methyl sarcosinate hydrochloride (20.03 g, 143.5 mmol) in abs. CH_2Cl_2 (700 ml), Et_3N (80 ml, 574 mmol), and isobutyryl chloride (14.9 ml, 143.5 mmol); reaction time: 40 min at r.t. and 1.25 h under reflux). Evaporation yielded 18.24 g (77%) of **18b**. Colorless oil. Purity (GC): >96%. B.p. 100°/0.15 mbar. IR (neat): 3486*w*, 2972*s*, 2875*m*, 1751*s*, 1651*s*, 1480*s*, 1403*s*, 1364*s*, 1335*s*, 1280*s*, 1210*s*, 1120*s*, 1091*s*, 1011*m*, 983*m*, 941*m*, 890*w*, 843*w*, 754*m*, 705*m*. ^{1}H-NMR: 4.12 (*s*, CH_2(Gly)); 3.73 (*s*, MeO); 3.13 (*s*, MeN); 2.87 (*sept.*, J = 6.8, Me_2CH); 1.15 (*d*, J = 6.8, Me_2CH). ^{13}C-NMR: 177.8, 170.0 (2*s*, 2 CO); 52.0 (*q*, MeO); 49.5 (*t*, CH_2(Gly)); 36.4 (*q*, MeN); 30.2 (*d*, Me_2CH); 19.0 (*q*, Me_2CH). EI-MS: 174 (97, [M + H]$^+$), 173 (43, $M^{+\cdot}$), 142 (16), 114 (71), 104 (59), 102 (97), 86 (18), 84 (28), 72(14), 71 (100), 58 (68). Anal. calc. for $C_8H_{15}NO_3 \cdot 0.25\ H_2O$ (177.71): C 54.07, H 8.79, N 7.88; found: C 53.90, H 8.59, N 7.58.

8.2. *Methyl* N-*Methyl*-N-*(2-methylpropanethioyl)glycinate* (**19b**). According to the *GP C*, with **18b** (18.06 g, 104.27 mmol) in abs. toluene (200 ml) and *Lawesson* reagent (21.10 g, 52.13 mmol); reaction time: 1.5 h, temp. 90°. Then, another 0.1 equiv. of *Lawesson* reagent was added; reaction time: 1.5 h, temp. 90°. The residue was dissolved in Et_2O and washed twice with 1N aq. HCl soln., H_2O, sat. aq. $NaHCO_3$ soln., and once with brine. Drying ($MgSO_4$), evaporation, and CC (Et_2O) yielded 17.62 g (89%) of **19b**. Yellow oil. Purity (GC): >97%. IR (neat): 3479*w*, 2968*s*, 2098*w*, 1748*s*, 1652*w*, 1597*m*, 1494*s*, 1393*s*, 1360*s*, 1336*s*, 1294*s*, 1210*s*, 1090*s*, 995*s*, 933*w*, 914*w*, 890*w*, 873*m*, 840*w*, 804*w*, 718*m*. ^{1}H-NMR: 4.78 (*s*, CH_2(Gly)); 3.75 (*s*, MeO); 3.42 (*s*, MeN); 3.21 (*sept.*, J = 6.6, Me_2CH); 1.24 (*d*, J = 6.6, Me_2CH). ^{13}C-NMR: 213.4 (*s*, CS); 168.1 (*s*, CO); 57.0 (*t*, CH_2(Gly)); 52.1 (*q*, MeO); 40.3 (*q*, MeN); 36.7 (*d*, Me_2CH); 22.7 (*q*, Me_2CH). CI-MS: 192 (5), 191 (10), 190 (100, [M + H]$^+$), 189 (7, $M^{+\cdot}$), 156 (15). Anal. calc. for $C_8H_{15}NO_2S$ (189.27): C 50.77, H 7.99, N 7.40; found: C 50.97, H 7.73, N 7.27.

8.3. *Methyl* N-*(1-Azido-2-methylprop-1-enyl)*-N-*methylglycinate.* According to the *GP D*, with **19b** (1.59 g, 8.40 mmol) in abs. CH_2Cl_2 (20 ml), 2 drops of DMF, 2N $COCl_2$ soln. (5 ml, 10 mmol), abs. THF (20 ml), and DABCO (0.94 g, 8.40 mmol). The crude methyl *N*-(1-chloro-2-methylprop-1-enyl)-*N*-methylglycinate was treated with NaN_3 (2.18 g, 33.6 mmol) according to *GP E*; reaction time: 20 h. The residue was dissolved in AcOEt, washed with a sat. aq. $NaHCO_3$ soln. and brine. Drying ($MgSO_4$), evaporation, and CC (AcOEt, 2% Et_2N) yielded 20 mg (1.2%) of an oil that possibly is the azido-enamine. ^{1}H-NMR: 3.99 (br. *s*, CH_2(Gly)); 3.76 (*s*, MeO); 3.07 (*s*, MeN); 1.351, 1.349 (2*s*, Me_2C). ^{13}C-NMR: 168.9 (*s*, CO); 123.0, 116.7 (2*s*, C(1′), C(2′)); 52.1 (*q*, MeO); 49.4 (*t*, CH_2(Gly)); 40.8 (*q*, MeN); 24.7 (*q*, Me_2C). CI-MS: 224 (13), 223 (100), 172 (6), 171 (69, [M + H]$^+$), 144 (7).

9. *Synthesis of Methyl (*S*)-*N*-(2,2-Dimethyl-2*H*-azirin-3-yl)*-N-*methylvalinate* (**20b**). 9.1. *Methyl (*S*)-*N*-Methyl*-N-*(2-methylpropanoyl)valinate* (**18c**). According to the *GP B*, with (Me)Val-OMe·HCl (3.19 g, 17.60 mmol) in abs. CH_2Cl_2 (80 ml), Et_3N (7.34 ml, 52.70 mmol), and isobutyryl chloride (2.01 ml, 19.40 mmol); reaction time: 7 h at 40°. Evaporation yielded 3.72 g (98%) of **18c**. Colorless oil. B.p. 80°/0.15 mbar. IR (neat): 3980*s*, 1740*s*, 1640*s*, 1470*s*, 1400*s*, 1370*m*, 1270*s*, 1200*s*, 1170*m*, 1130*m*, 1080*s*, 1010*m*, 930*w*, 750*w*. ^{1}H-NMR: 5.13 (*d*, J = 10.5, CH(α)(Val)); 3.88 (*s*, MeO); 3.21 (*s*, MeN); 3.11-3.01 (*m*, Me_2CH); 2.44–2.37 (*m*, CH(β)(Val)); 1.32 (*d*, J = 6.6, Me_2CH); 1.19, 1.04 (2*d*, J = 6.6, 2 Me(Val)). ^{13}C-NMR (conformers): 177.6, 171.8 (2*s*, 2 CO); 61.1 (*d*, CH(α)(Val)); 51.5 (*q*, MeO); 31.1 (*q*, MeN); 30.5 (*d*, Me_2CH); 27.3 (*d*, CH(β)(Val)); 19.7, 19.6, 19.5, 19.2, 18.9, 18.6 (6*q*, Me_2CH, 2 Me(Val)). GC-MS: 215 ($M^{+\cdot}$), 200, 184, 172, 168, 156, 144, 130, 115, 112, 102, 86, 71, 55. Anal. calc. for $C_{11}H_{21}N_3O_3 \cdot 0.2\ H_2O$ (215.29): C 60.36, H 9.85, N 6.40; found: C 60.29, H 9.63, N 6.31.

9.2. *Methyl (*S*)-*N*-Methyl*-N-*(2-methylpropanethioyl)valinate* (**19c**). According to the *GP C*, with **18c** (1531 mg, 7.12 mmol) in abs. THF (40 ml) and *Lawesson* reagent (1582 mg, 3.91 mmol); reaction time: 23 h, temp. 60°. Drying ($MgSO_4$), evaporation, and two consecutive CC (CH_2Cl_2/hexane 1:2, AcOEt/hexane 1:4)

yielded 304 mg (18%) of **19c** and 474 mg (31%) of **18c**. Yield calc. with respect to consumed material: 27%. Yellow oil. IR (neat): 3462*w*, 2968*s*, 2923*s*, 2876*s*, 1739*s*, 1648*w*, 1596*w*, 1472*s*, 1407*s*, 1359*s*, 1263*s*, 1207*s*, 1133*s*, 1075*m*, 1015*s*, 919*m*, 870*m*, 795*w*. ^{1}H-NMR (conformers): 6.47 (*d*, *J* = 10.2, CH(*α*)(Val)); 3.76, 3.73 (2*s*, MeO); 3.35, 3.26 (2*s*, MeN); 3.32–3.15 (*m*, Me_2CH); 2.39–2.31 (*m*, CH(*β*)(Val)); 1.29–1.23 (*m*, Me_2CH); 1.10, 1.05 (2*d*, *J* = 6.8 Me(Val)); 0.91, 0.88 (2*d*, *J* = 6.8, Me(Val)). ^{13}C-NMR (conformers): 214.6, 213.6 (2*s*, CS); 170.7, 169.1 (2*s*, CO); 68.3, 67.9 (2*d*, CH(*α*)(Val)); 52.4, 51.9 (2*q*, MeO); 37.1, 36.6 (2*d*, Me_2CH); 34.7 (*q*, MeN); 28.7, 28.5 (2*d*, CH(*β*)(Val)); 23.5, 23.0 (2*q*, Me_2CH); 19.6, 18.7 (2*q*, 2 Me(Val)). CI-MS: 232 ($[M+H]^+$).

9.3. *Methyl (*S*)-*N*-(2,2-Dimethyl-2*H*-azirin-3-yl)-*N*-methylvalinate* (**20b**). According to the *GP D*, with **19c** (428 mg, 1.85 mmol) in abs. CH_2Cl_2 (10 ml), 3 drops of DMF, 2N $COCl_2$ soln. (1.40 ml, 2.78 mmol), abs. THF (20 ml), and DABCO (207 mg, 1.85 mmol). The crude methyl (*S*)-*N*-(1-chloro-2-methylprop-1-enyl)-*N*-methylvalinate was treated with NaN_3 (361 mg, 5.55 mmol) according to the *GP E*; reaction time: 18 h. Evaporation and CC (AcOEt/hexane 1:1) yielded 179 mg (46%) of **20c**. Pale yellow oil. IR (neat): 3465*w*, 2969*s*, 2877*s*, 1761*s*, 1742*s*, 1653*m*, 1468*s*, 1437*m*, 1391*m*, 1370*s*, 1294*s*, 1262*s*, 1199*s*, 1129*s*, 1088*s*, 1012*s*, 927*m*, 835*w*, 733*m*. ^{1}H-NMR: 3.72 (*s*, MeO); 3.34 (br. *s*, CH(*α*)(Val)); 3.00 (*s*, MeN); 2.29 (br. *s*, CH(*β*)(Val)); 1.355, 1.350 (2*s*, Me_2C); 0.97, 0.94 (2*d*, *J* = 6.7, 2 Me(Val)). ^{13}C-NMR: 170.6 (*s*, CO); 168.8 (*s*, C(3′)); 70.5 (*d*, CH(*α*)(Val)); 51.7 (*q*, MeO); 40.8 (*s*, C(2′)); 31.7 (*q*, MeN); 27.2 (*d*, CH(*β*)(Val)); 24.9 (*q*, Me_2C); 19.2, 18.9 (2*q*, 2 Me(Val)). CI-MS: 214 (15), 213 (100, $[M+H]^+$). Anal. calc. for $C_{11}H_{20}N_2O_2 \cdot 0.33\ H_2O$ (218.30): C 60.52, H 9.54, N 12.83; found: C 60.68, H 9.25, N 12.70.

10. *Reactions of* **20b** *with Amino Acids and Syntheses of Model Peptides.* 10.1. *Methyl* N-*[(Benzyloxy)carbonyl]-(*S*)-phenylalanyl-dimethylglycyl-(*S*)-*N*-methylvalinate* (Z-Phe-Aib-(Me)Val-OMe; **22a**). According to the *GP F*, with Z-Phe-OH (49 mg, 0.165 mmol) in MeCN (5 ml), **20b** (35 mg, 0.165 mmol); reaction time: 19 h. CC (hexane/AcOEt 2:3) gave 70 mg (83%) of **22a**. Colorless foam. IR (KBr): 3307*s*, 3063*m*, 3032*m*, 2964*s*, 2876*m*, 1736*s*, 1670*s*, 1623*s*, 1539*s*, 1498*s*, 1455*s*, 1395*s*, 1365*m*, 1290*s*, 1238*s*, 1211*s*, 1132*m*, 1084*s*, 1017*s*, 912*w*, 847*w*, 776*w*, 744*m*, 699*s*. ^{1}H-NMR: 7.36–7.16 (*m*, 10 arom. H); 6.75 (br. *s*, NH); 5.42 (*d*, *J* = 8.1, NH); 5.06 (br. *s*, PhCH_2(Z)); 4.70 (*d*, *J* = 9.9, CH(*α*)((Me)Val)); 4.48–4.33 (*m*, CH(*α*)(Phe)); 3.67 (*s*, MeO); 3.05–2.99 (*m*, CH_2(Phe)); 2.93 (*s*, MeN); 2.19–2.11 (*m*, CH(*β*)((Me)Val)); 1.49, 1.43 (2*s*, 2 Me(Aib)); 0.99, 0.82 (2*d*, *J* = 6.7, 2 Me((Me)Val)). ^{13}C-NMR: 173.2, 171.5, 168.9 (3*s*, 3 CO); 155.8 (*s*, CO(carbamate)); 136.3, 136.1 (2*s*, 2 arom. C); 129.3, 128.6, 128.4, 128.1, 127.9, 126.9 (6*d*, 10 arom. C); 66.9 (*t*, PhCH_2(Z)); 63.8 (*d*, CH(*α*)((Me)Val)); 57.2 (*s*, C(*α*)(Aib)); 56.3 (*d*, CH(*α*)(Phe)); 51.6 (*q*, MeO); 38.4 (*t*, CH_2(Phe)); 32.4 (*q*, MeN); 27.1 (*d*, CH(*β*)((Me)Val)); 24.8, 24.3 (2*q*, 2 Me(Aib)); 19.9, 18.8 (2*q*, 2 Me((Me)Val)). ESI-MS: 534 ($[M+Na]^+$). Anal. calc. for $C_{28}H_{36}N_3O_6$ (511.62): C 65.73, H 7.29, N 8.21; found: C 65.91, H 7.44, N 8.26.

10.2. *Methyl* N-*[(Benzyloxy)carbonyl]-(*S*)-phenylalanyl-dimethylglycyl-(*S*)-*N*-methylvalyl-alaninate* (Z-Phe-Aib-(Me)Val-Ala-OMe; **24**). According to the *GP G*, with **22a** (59 mg, 0.115 mmol) in THF/MeOH/H_2O (3:1:1, 5 ml), $LiOH \cdot H_2O$ (15 mg, 0.347 mmol); reaction time: 3 h. Evaporation led to 58 mg (quant.) crude Z-Phe-Aib-(Me)Val-OH. According to the *GP H*, with crude Z-Phe-Aib-(Me)Val-OH (58 mg, 0.115 mmol), $EtN(i\text{-}Pr)_2$ (0.06 ml, 0.348 mmol), TBTU (39 mg, 0.122 mmol), HOBt (20 mg, 0.116 mmol), and H-Ala-OMe (18 mg, 0.128 mmol) in MeCN (5 ml); reaction time: 42 h. CC (AcOEt/hexane 1:1) gave 48 mg (72%) of **24**. Highly viscous oil. IR (neat): 3308*s*, 3064*s*, 2966*s*, 2611*m*, 1733*s*, 1660*s*, 1543*s*, 1455*s*, 1399*s*, 1298*s*, 1235*s*, 1084*s*, 1049*m*, 1028*s*, 984*m*, 917*m*, 848*w*, 824*w*, 775*m*, 770*s*, 700*s*. ^{1}H-NMR: 7.44–7.15 (*m*, 10 arom. H); 7.03 (br. *s*, NH); 6.77 (br. *s*, NH); 5.52 (*d*, *J* = 8.2, NH); 5.20–4.97 (*m*, PhCH_2(Z)); 4.70 (*d*, *J* = 10.2, CH(*α*)((Me)Val)); 4.49–4.35 (*m*, CH(*α*)(Phe), CH(*α*)(Ala)); 3.67 (*s*, MeO); 3.08–2.96 (*m*, CH_2(Phe)); 2.92 (*s*, MeN); 2.19–2.13 (*m*, CH(*β*)((Me)Val)); 1.70 (*d*, *J* = 5.8, Me(Ala)); 1.49, 1.44 (2*s*, 2 Me(Aib)); 0.98, 0.82 (2*d*, *J* = 6.8, 2 Me-((Me)Val)). ^{13}C-NMR: 173.1, 171.5, 169.1, 168.5 (4*s*, 4 CO); 156.3 (*s*, CO(carbamate)); 136.2, 136.1 (2*s*, 2 arom. C); 129.3, 128.7, 128.6, 128.1, 126.9, 126.4 (6*d*, 10 arom. C); 71.3 (*d*, CH(*α*)((Me)Val)); 66.9 (*t*, PhCH_2(Z)); 63.9 (*d*, CH(*α*)(Ala)); 57.3 (*s*, C(*α*)(Aib)); 56.4 (*d*, CH(*α*)(Phe)); 51.6 (*q*, MeO); 38.4 (*t*, CH_2(Phe)); 32.4 (*q*, MeN); 32.4 (*d*, CH(*β*)((Me)Val)); 27.2, 27.1 (2*q*, 2 Me(Aib)); 19.9, 18.8 (2*q*, 2 Me((Me)Val)), 17.5 (*q*, Me(Ala)). ESI-MS: 605 ($[M+Na]^+$), 534.

10.3. *Methyl* N-*[[(9*H*-Fluoren-9-yl)methoxy]carbonyl]-(*S*)-valyl-dimethylglycyl-(*S*)-*N*-methylvalinate* (Fmoc-Val-Aib-(Me)Val-OMe; **22b**). According to the *GP F*, with Fmoc-Val-OH (61 mg, 0.179 mmol) in MeCN (5 ml), **20b** (38 mg, 0.179 mmol); reaction time: 22 h. CC (hexane/AcOEt 1:1) gave 80 mg (83%) of **22b**. Colorless foam. IR (KBr): 3349*s*, 3321*s*, 3066*w*, 2967*m*, 2875*w*, 1734*s*, 1719*s*, 1686*s*, 1616*s*, 1539*s*, 1490*m*, 1470*m*, 1450*m*, 1395*m*, 1336*m*, 1316*m*, 1275*m*, 1236*s*, 1218*s*, 1183*m*, 1100*m*, 1023*m*, 960*w*, 901*w*, 778*w*, 775*m*, 735*m*. ^{1}H-NMR: 7.75–7.25 (*m*, 8 arom. H); 7.14 (br. *s*, NH); 5.46 (*d*, *J* = 9.3, NH); 4.75 (*d*, *J* = 9.2, CH(*α*)((Me)Val)); 4.39–4.35 (*m*, CH_2(Fmoc)); 4.19 (*t*, *J* = 6.9, CH(Fmoc)); 3.94 (br. *s*, CH(*α*)(Val)); 3.67 (*s*, MeO); 3.01 (*s*, MeN); 2.22–2.08 (*m*, CH(*β*)(Val), CH(*β*)((Me)Val)); 1.65, 1.59 (2*s*, 2 Me(Aib)); 0.94–0.75 (*m*, 2 Me(Val), 2 Me((Me)Val)). ^{13}C-NMR: 172.6, 170.6, 168.5 (3*s*, 3 CO); 155.4 (*s*, CO(carbamate)); 142.8, 140.3

(2*s*, 4 arom. C); 126.7, 126.0, 124.0, 119.0 (4*d*, 8 arom. C); 66.0 (*t*, CH_2(Fmoc)); 63.0, 59.4 (2*d*, CH(α)(Val), CH(α)((Me)Val)); 56.5 (*s*, C(α)(Aib)); 50.8 (*q*, MeO); 46.2 (*d*, CH(Fmoc)); 31.6 (*q*, MeN); 30.2, 26.2 (2*d*, CH(β)(Val), CH(β)((Me)Val)); 23.9, 23.4 (2*q*, 2 Me(Aib)); 19.0, 18.2, 17.9, 16.8 (4*q*, 2 Me(Val), 2 Me((Me)-Val)). ESI-MS: 574 ($[M+Na]^+$). Anal. calc. for $C_{30}H_{39}N_3O_6 \cdot 0.33\ H_2O$ (557.70): C 66.76, H 7.53, N 7.54; found: C 66.65, H 7.63, N 7.61.

10.4. *Methyl* N-*[(*tert-*Butoxy)carbonyl]-(*S*)-alanyl-(*S*)-valyl-dimethylglycyl-(*S*)*-N-*methylvalinate* (Boc-Ala-Val-Aib-(Me)Val-OMe; **25**). A soln. of **22b** (71 mg, 0.129 mmol) in Et_2NH/CH_2Cl_2 1:1 (2 ml) was stirred for 5 h at r.t. Evaporation led to crude H-Val-Aib-(Me)Val-OMe which was treated according to the *GP H*, with $EtN(i\text{-}Pr)_2$ (0.07 ml, 0.387 mmol), TBTU (43 mg, 0.135 mmol), Boc-Ala-OH (27 mg, 0.142 mmol), and MeCN (5 ml); reaction time: 21 h. CC (AcOEt/hexane 1:1) gave 47 mg (73%) of **25**. Colorless foam. IR (KBr): 3320*s*, 2974*s*, 2936*s*, 2877*m*, 1740*s*, 1656*s*, 1517*s*, 1470*s*, 1391*s*, 1366*s*, 1317*m*, 1292*m*, 1247*s*, 1210*m*, 1170*s*, 1134*m*, 1083*s*, 1017*m*, 935*w*, 863*w*, 782*w*, 758*w*. ^{1}H-NMR: 7.28 (br. *s*, NH); 6.74 (*d*, *J* = 7.8, NH); 5.17 (*d*, *J* = 8.2, NH); 4.74 (*d*, *J* = 9.6, CH(α)((Me)Val)); 4.25–4.07 (*m*, CH(α)(Val), CH(α)(Ala)); 3.69 (*s*, MeO); 3.04 (*s*, MeN); 2.23–2.09 (*m*, CH(β)(Val), CH(β)((Me)Val)); 1.61, 1.58 (2*s*, 2 Me(Aib)); 1.45 (*s*, *t*-Bu); 1.36 (*d*, *J* = 7.0, Me(Ala)); 1.00, 0.94, 0.90, 0.87 (4*d*, *J* = 6.5, 2 Me(Val), 2 Me((Me)Val)). ^{13}C-NMR: 173.2, 172.6, 171.4, 169.1 (4*s*, 4 CO); 156.3 (*s*, CO(carbamate)); 80.3 (*s*, Me_3C); 63.0, 58.2 (2*d*, CH(α)(Val), CH(α)((Me)Val)); 57.2 (*s*, C(α)(Aib)); 51.6 (*q*, MeO); 50.6 (*d*, CH(α)(Ala)); 32.6 (*q*, MeN); 30.1, 27.0 (2*d*, CH(β)(Val), CH(β)((Me)Val)); 28.2 (*q*, Me_3C); 24.9, 24.8 (2*q*, 2 Me(Aib)); 19.9, 19.2, 18.7, 17.8, 17.3 (5*q*, 2 Me(Val), 2 Me((Me)Val), Me(Ala)). ESI-MS: 523 ($[M+Na]^+$).

10.5. *Methyl* N-*{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}-(*S*)-phenylalanyl-glycyl-dimethylglycyl-(*S*)*-N-*methylvalinate* (Fmoc-Phe-Gly-Aib-(Me)Val-OMe; **23**). According to the *GP F*, with Fmoc-Phe-Gly-OH (53 mg, 0.188 mmol) in MeCN/DMF 50:1 (5 ml), **20b** (40 mg, 0.188 mmol); reaction time: 18 h. CC (AcOEt) gave 72 mg (67%) of **23**. Colorless foam. IR (KBr): 3313*s*, 3330*m*, 3064*m*, 2963*m*, 1735*s*, 1655*s*, 1526*s*, 1451*s*, 1395*m*, 1365*m*, 1331*m*, 1252*s*, 1211*m*, 1133*m*, 1083*m*, 1032*m*, 939*w*, 858*w*, 779*m*, 741*s*, 701*m*. ^{1}H-NMR: 7.75–7.18 (*m*, 13 arom. H, NH); 7.00 (br. *s*, NH); 5.58 (*d*, *J* = 8.7, NH); 4.72 (*d*, *J* = 10.0, CH(α)((Me)Val)); 4.42–4.36 (*m*, CH_2(Fmoc)); 4.23 (*t*, *J* = 9.8, CH(α)(Phe)); 4.16–4.10 (*m*, CH(Fmoc)); 3.99–3.73 (*m*, CH_2(Gly)); 3.63 (*s*, MeO); 3.19–2.96 (*m*, CH_2(Phe)); 3.01 (*s*, MeN); 2.23–2.15 (*m*, CH(β)(Val)); 1.55, 1.53 (2*s*, 2 Me(Aib)); 0.96, 0.84 (2*d*, *J* = 6.4, 2 Me(Val)). ^{13}C-NMR: 173.4, 171.6, 171.5, 167.1 (4*s*, 4 CO); 156.2 (*s*, CO(carbamate)); 143.5, 141.2, 136.2 (3*s*, 5 arom. C); 129.0, 128.6, 127.7, 126.9, 124.8, 119.9 (6*d*, 13 arom. C); 67.0 (*t*, CH_2(Fmoc)); 64.0 (*d*, CH(α)(Val)); 57.1 (*s*, C(α)(Aib)); 56.6 (*d*, CH(α)(Phe)); 51.6 (*q*, MeO); 47.0 (*d*, CH(Fmoc)); 43.2 (*t*, CH_2(Gly)); 37.7 (*t*, CH_2(Phe)); 32.5 (*q*, MeN); 27.1 (*d*, CH(β)(Val)); 25.4, 25.0 (2*q*, 2 Me(Aib)); 19.9, 19.0 (2*q*, 2 Me(Val)). ESI-MS: 679 ($[M+Na]^+$), 625, 512, 307.

11. *Attempted Synthesis of Methyl* N-*(2,2-Dimethyl-2*H*-azirin-3-yl)-2,2,*N*-trimethylglycinate.* 11.1. *Z-(Me)Aib-OMe.* To a soln. of Z-Aib-OH (4.98 g, 21.0 mmol) in THF/DMF 10:1 (150 ml) was added first MeI (10.5 ml, 168 mmol), then NaH (1500 mg, 63 mmol, washed with hexane). After stirring for 26 h at 70°, the solvent was evaporated, the residue was dissolved in Et_2O, and the org. phase was washed with H_2O. Drying ($MgSO_4$) and CC (AcOEt/hexane, 1:1) gave 5.49 g (96%) of Z-(Me)Aib-OMe. Colorless oil. IR (neat): 3610*w*, 3065*w*, 3033*m*, 2989*s*, 2952*s*, 1960*w*, 1745*s*, 1699*s*, 1587*w*, 1470*s*, 1393*s*, 1350*s*, 1285*s*, 1213*s*, 1162*s*, 1129*s*, 1028*s*, 995*m*, 906*w*, 885*w*, 861*w*, 827*w*, 772*s*, 753*s*, 700*s*. ^{1}H-NMR: 7.36–7.29 (*m*, 5 arom. H); 5.11 (*s*, PhCH_2); 3.61 (br. *s*, MeO); 2.97 (*s*, MeN); 1.45 (*s*, 2 Me(Aib)). ^{13}C-NMR: 175.0 (*s*, CO); 155.8 (*s*, CO(carbamate)); 136.4, 128.3, 127.9 (6 arom. C); 67.2 (PhCH_2); 60.7 (*s*, C(α)(Aib)); 52.0 (*q*, MeO); 29.6 (*q*, MeN); 23.8 (*q*, 2 Me(Aib)). EI-MS: 265 (2, ($M^{+\cdot}$), 206 (35, $[M-COOMe]^+$), 162 (16), 92 (7), 91 (100). Anal. calc. for $C_{14}H_{19}NO_3$ (265.31): C 63.38, H 7.22, N 5.28; found: C 63.32, H 7.15, N 5.35.

11.2. *H-(Me)Aib-OMe · HBr.* Z-(Me)Aib-OMe (4.83 g, 18.2 mmol) was dissolved at 0° in AcOH saturated with HBr (11 ml) and stirred for 2 h. Then, the solvent was evaporated, the residue was dissolved in H_2O (25 ml), washed twice with Et_2O (15 ml), and evaporated to dryness, to give 3.85 g (quant.) of H-(Me)Aib-OMe · HBr. Colorless hygroscopic solid. IR (KBr): 3450*s*, 2962*s*, 2776*s*, 2431*m*, 2081*w*, 1745*s*, 1615*m*, 1578*m*, 1487*m*, 1430*m*, 1396*m*, 1377*m*, 1298*s*, 1219*s*, 1182*s*, 1112*s*, 1038*w*, 1012*w*, 973*m*, 880*w*, 860*w*, 788*w*, 767*w*. ^{1}H-NMR ((D_6)DMSO): 9.20 (br. *s*, NH_2); 3.78 (*s*, MeO); 2.53 (*s*, MeN); 1.50 (*s*, 2 Me(Aib)). ^{13}C-NMR ((D_6)DMSO): 171.0 (*s*, CO); 60.8 (*s*, C(α)(Aib)); 53.3 (*q*, MeO); 27.5 (*q*, MeN); 21.1 (*q*, 2 Me(Aib)). ESI-MS: 343 ($[(2M+H)+Br]^+$).

11.3. *Methyl* N-*(2-Methylpropanoyl)-2,2,*N*-trimethylglycinate* (**18d**). According to the *GP B*, with H-(Me)Aib-OMe · HBr (3.31 g, 15.6 mmol) in abs. CH_2Cl_2 (100 ml), Et_3N (6.52 ml, 46.8 mmol), and isobutyryl chloride (1.82 ml, 17.2 mmol); reaction time: 5 h, temp. r.t. → 35°. Evaporation yielded 2.61 g (83%) of **18d**. Colorless oil. IR (KBr): 3455*w*, 2983*s*, 2876*m*, 1742*s*, 1641*s*, 1476*s*, 1410*s*, 1382*s*, 1363*s*, 1325*s*, 1275*s*, 1240*s*, 1198*s*, 1158*s*, 1086*s*, 1024*m*, 1001*m*, 954*w*, 934*w*, 901*w*, 860*m*, 805*w*, 750*m*, 733*m*. ^{1}H-NMR: 3.67 (*s*, MeO); 3.1 (*s*, MeN);

2.79 (*sept.*, $J = 6.7$, Me_2CH); 1.41 (*s*, 2 Me(Aib)); 1.06 (*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 176.5, 174.6 (2*s*, 2 CO); 60.2 (*s*, C(α)(Aib)); 51.8 (*q*, MeO); 31.0 (Me_2CH); 30.0 (*q*, MeN); 23.1 (*q*, 2 Me(Aib)); 18.7 (*q*, Me_2CH). EI-MS: 201 (3, ($M^{+\cdot}$)), 170 (5, [M – COOMe]$^+$), 142 (41), 143 (3), 130 (6, [M – Me_2CHCO]$^+$), 72 (100). Anal. calc. for $C_{10}H_{19}NO_3 \cdot 0.33\ H_2O$ (207.28): C 57.95, H 9.56, N 6.76; found: C 57.96, H 9.54, N 6.63.

11.4. *Attempted Thionation of* **18d**. According to the *GP C*, with **18d** (699 mg, 3.73 mmol) in abs. toluene (30 ml), and *Davy* reagent [41] (815 mg, 1.87 mmol); reaction time: 20 h, temp. 100°. The residue was dissolved in Et_2O and washed twice with 1N aq. HCl soln., H_2O, sat. aq. $NaHCO_3$ soln., and once with brine. After drying ($MgSO_4$) and evaporation, only decomposed material was obtained.

12. *Attempted Synthesis of Methyl (*S*)-*N*-(2,2-Dimethyl-2*H*-azirin-3-yl)-*N*-(methyl)phenylalaninate.* 12.1. *Methyl (*S*)-*N*-Methyl-*N*-(2-methylpropanoyl)phenylalaninate* (**18e**). According to the *GP B*, with H-(Me)Phe-OMe (83 mg, 0.43 mmol) in abs. CH_2Cl_2 (15 ml), Et_3N (0.17 ml, 1.29 mmol), and isobutyryl chloride (0.05 ml, 0.47 mmol); reaction time: 20 h at r.t. → 35°. Evaporation yielded 97 mg (86%) of **18e**. Colorless oil. ^{1}H-NMR (conformers): 7.22 – 7.06 (*m*, 5 arom. H); 5.24, 4.59 (2*dd*, $J = 11.1$, 5.4, CH(α)(Phe)); 3.68, 3.65 (2*s*, MeO); 3.30 (*dd*-like, H_a of CH_2(Phe)); 3.02 – 2.93 (*m*, H_b of CH_2(Phe)); 2.82, 2.76 (2*s*, MeN); 2.59, 2.28 (2 *sept.*, $J = 6.7$, Me_2CH); 0.99, 0.75 (2*d*, $J = 6.7$, Me_2CH). ^{13}C-NMR: 177.4, 171.5, 170.0 (3*s*, 2 CO); 137.0 (*s*, 1 arom. C); 128.8, 128.3, 126.3 (3*d*, 5 arom. C); 61.4, 58.0 (2*d*, CH(α)(Phe)); 52.5, 52.1 (2*q*, MeO); 35.3, 34.7 (2*t*, CH_2(Phe)); 32.8 (*q*, MeN); 30.2 (*d*, Me_2CH); 18.7 (*q*, Me_2CH).

12.2. *Attempted Thionation of* **18e**. According to the *GP C*, with **18e** (114 mg, 0.43 mmol) in abs. toluene (15 ml), and *Davy* reagent [41][20]) (96 mg, 0.22 mmol); reaction time: 1 h, temp. 100°. The residue was dissolved in Et_2O and washed twice with 1N aq. HCl soln., 1N aq. NaOH soln., and 1N aq. HCl soln. Drying ($MgSO_4$), evaporation, and CC (AcOEt/hexane 1:3) yielded 28 mg (25%) of **18e**. Otherwise, only decomposition could be detected.

13. *Synthesis of Methyl (*S*)-*N*-(2,2-Dimethyl-2*H*-azirin-3-yl)homoprolinate* (**28**). 13.1. *Methyl (*S*)-*N*-(2-Methylpropanoyl)homoprolinate* (**26**). According to the *GP A*, with $SOCl_2$ (0.28 ml, 3.91 mmol), MeOH (5 ml), and (*S*)-picoleinic acid (499 mg, 3.86 mmol). The crude methyl (*S*)-picoleinate in abs. CH_2Cl_2 (25 ml) was treated with Et_3N (1.62 ml, 11.6 mmol) and isobutyryl chloride (0.40 ml, 3.9 mmol) according to the *GP B*; reaction time: 3 h at r.t. Evaporation yielded 790 mg (96%) of **26**. Colorless oil. IR (neat): 3569*w*, 2910*m*, 2865*m*, 1742*s*, 1647*s*, 1471*m*, 1424*m*, 1383*w*, 1364*w*, 1314*m*, 1244*s*, 1206*s*, 1172*m*, 1155*m*, 1106*w*, 1089*w*, 1076*w*, 1020*m*, 994*w*, 920*w*, 868*w*, 821*w*, 780*w*, 750*w*. ^{1}H-NMR: 5.35 (*d*, $J = 5.5$, CH(α)(homoproline)); 3.85 (*d*, $J = 14.7$, 1 H); 3.75, 3.72 (2*s*, MeO); 3.23 – 3.13 (*m*, 1 H); 2.79 (*sept.*, $J = 6.8$, Me_2CH); 2.22 – 2.17 (*m*, 1 H); 1.67 – 1.02 (*m*, 5 H); 1.16 – 1.09 (*m*, Me_2CH). ^{13}C-NMR: 176.8, 171.9 (2*s*, 2 CO); 52.3 (*q*, MeO); 51.7 (*d*, CH(α)(homoproline)); 43.1 (*t*, CH_2(ε)(homoproline)); 30.0 (*d*, Me_2CH); 26.5, 25.4, 20.9 (3*t*, CH_2(β)-, CH_2(γ)-, CH_2(δ)(homoproline)); 18.7, 18.1 (2*q*, Me_2CH). EI-MS: 214 (0.8, [M + H]$^+$), 213 (3, $M^{+\cdot}$), 154 (19, [M – COOMe]$^+$), 142 (6, [M – Me_2CHCO]$^+$), 85 (6), 84 (100, [M – Me_2CHCO – (COOMe + H)]$^+$). Anal. calc. for $C_{11}H_{19}NO_3$ (213.28): C 61.95, H 8.98, N 6.57; found: C 61.71, H 9.13, N 6.53.

13.2. *Methyl (*S*)-*N*-(2-Methylpropanethioyl)homoprolinate* (**27**). According to the *GP C*, with **26** (790 mg, 3.70 mmol) in abs. toluene (20 ml) and *Lawesson* reagent (822 mg, 2.04 mmol); reaction time: 0.5 h, temp. 90°. CC (Et_2O/hexane 1:2) and (CH_2Cl_2/hexane, 2:1) gave 184 mg (22%) of **27**. Colorless oil. IR ($CHCl_3$): 3852*w*, 3750*w*, 3675*w*, 3648*w*, 3566*w*, 2955*s*, 2360*w*, 1735*s*, 1646*w*, 1596*w*, 1558*w*, 1540*w*, 1436*s*, 1362*m*, 1336*m*, 1278*s*, 1167*s*, 1122*m*, 1074*m*, 1009*s*, 918*w*, 868*w*, 821*w*. ^{1}H-NMR: 6.72 (*d*, $J = 5.7$, CH(α)(homoproline)); 4.31 (*d*, $J = 14.0$, 1 H); 3.71, 3.68 (2*s*, MeO); 3.34 – 3.24 (*m*, 1 H); 3.14 (*sept.*, $J = 6.6$, Me_2CH); 2.33 – 2.24 (*m*, 1 H); 1.76 – 1.41 (*m*, 5 H); 1.22 – 1.07 (*m*, Me_2CH). ^{13}C-NMR: 212.7 (*s*, CS); 170.6 (*s*, CO); 59.6 (*d*, CH(α)(homoproline)); 52.2 (*q*, MeO); 46.2 (*t*, CH_2(ε)(homoproline)); 36.5 (*d*, Me_2CH); 26.6, 25.7, 20.8 (3*t*, CH_2(β)-, CH_2(γ)-, CH_2(δ)(homoproline)); 23.3, 23.1 (*q*, Me_2CH). CI-MS: 232 (6), 231 (13), 230 (100, [M + H]$^+$). Anal. calc. for $C_{11}H_{19}NO_2S$ (229.34): C 57.61, H 8.35, N 6.11, S 13.98; found: C 57.36, H 8.37, N 5.95, S 14.12.

13.3. *Methyl (*S*)-*N*-(2,2-Dimethyl-2*H*-azirin-3-yl)homoprolinate* (**28**). According to the *GP D*, with **27** (163 mg, 0.71 mmol) in abs. CH_2Cl_2 (10 ml), 2 drops of DMF, 2N $COCl_2$ soln. (1.82 ml, 3.64 mmol), abs. THF (10 ml), and DABCO (138 mg, 0.71 mmol). The crude methyl (*S*)-*N*-(1-chloro-2-methylprop-1-enyl)homoprolinate was treated with NaN_3 (82 mg, 2.13 mmol) according to the *GP E*; reaction time: 26 h. CC (AcOEt) yielded 105 mg (71%) of **28**[21]). Pale yellow solid. M.p. 47 – 50°. IR ($CHCl_3$): 3854*w*, 3752*w*, 3676*w*, 3650*w*, 3630*w*, 3568*w*, 2945*s*, 2862*m*, 1770*s*, 1735*s*, 1638*m*, 1458*m*, 1368*m*, 1356*m*, 1310*m*, 1255*m*, 1218*s*, 1155*s*, 1100*w*, 1036*m*, 991*m*, 968*w*, 920*m*, 859*w*, 820*w*, 787*w*. ^{1}H-NMR: 4.35 (br. *s*, CH(α)(homoproline)); 3.75 (*s*, MeO); 3.60, 3.41

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[20]) When the same reaction was carried out with *Lawesson* reagent, similar results were obtained.

[21]) Analogously, *rac*-**28** was synthesized (yield: 47%).

(2br. *s*, 2 H); 2.27–2.22 (*m*, 1 H); 1.85–1.32 (*m*, 5 H); 1.35 (*s*, Me_2C). ^{13}C-NMR: 171.4 (*s*, CO); 168.1 (*s*, C(3′)); 58.6, 55.1 (2*d*, CH(α)(homoproline)); 52.1 (*q*, MeO); 45.9 (*t*, CH_2(ε)(homoproline)); 39.6 (*s*, C(2′)); 26.8, 24.4, 20.8 (3*t*, CH_2(β)-, CH_2(γ)-, CH_2(δ)(homoproline)); 24.7, 24.6 (2*q*, *Me*$_2$C). CI-MS: 212 (11), 211 (100, $[M+H]^+$). Anal. calc. for $C_{11}H_{18}N_2O_2 \cdot 0.1\ H_2O$ (212.08): C 62.30, H 8.65, N 13.20; found: C 62.15, H 8.46, N 12.93.

14. *Reactions of* **28** *with Amino Acids.* 14.1. *Methyl* N-*[(*tert-*Butoxy)carbonyl]-(*S*)-alanyl-dimethylglycyl-(*S*)-homoprolinate* (Boc-Ala-Aib-Homoproline-OMe; **29c**). According to the *GP F*, with Boc-Ala-OH (**13f**, 57 mg, 0.30 mmol) in CH_2Cl_2 (10 ml), **28** (63 mg, 0.30 mmol); reaction time: 16 h. CC (hexane/AcOEt 1:4) gave 100 mg (83%) of **29c**. Colorless, viscous oil which solidified. IR ($CHCl_3$): 3334*s*, 2979*m*, 2940*m*, 2866*w*, 1746*s*, 1708*s*, 1666*s*, 1624*s*, 1532*s*, 1514*s*, 1447*m*, 1420*s*, 1388*m*, 1377*m*, 1344*m*, 1332*m*, 1296*s*, 1250*s*, 1204*s*, 1154*s*, 1070*m*, 1034*m*, 1024*m*, 874*w*. ^{1}H-NMR: 5.39 (br. *s*, NH); 4.98 (br. *s*, NH); 4.23–4.08 (*m*, CH(α)(Ala), CH(α)(homoproline)); 3.73 (*s*, MeO); 3.18, (br. *s*, H_a of CH_2(ε)(homoproline)); 2.27–2.19 (*m*, H_b of CH_2(ε)(homoproline)); 1.69–1.33 (*m*, CH_2(β)-, CH_2(γ)-, CH_2(δ)(homoproline)); 1.63 (*s*, 2 Me(Aib)); 1.45 (*s*, *t*-Bu); 1.34 (*d*, *J* = 5.3, Me(Ala)). ^{13}C-NMR: 172.5, 171.6, 170.9 (3*s*, 3 CO); 155.4 (*s*, CO(carbamate)); 79.9 (*s*, Me_3C); 56.7 (*s*, C(α)(Aib)); 53.2, 50.1 (2*d*, CH(α)(Ala), CH(α)(homoproline)); 52.0 (*q*, MeO); 44.3 (*t*, CH_2(ε)(homoproline)); 28.1 (*q*, *Me*$_3$C); 26.5, 25.0, 20.9 (3*t*, CH_2(β)-, CH_2(γ)-, CH_2(δ)(homoproline)); 25.2 (*q*, 2 Me(Aib)); 18.1 (*q*, Me(Ala)). ESI-MS: 423, 422 ($[M+Na]^+$). Anal. calc. for $C_{19}H_{33}N_3O_6$ (399.23): C 57.13, H 8.33, N 10.52; found: C 56.99, H 8.44, N 10.43.

Crystal-Structure Determination of **29c**[22]). All measurements were made on a *Rigaku AFC5R* diffractometer with graphite-monochromated MoK_α radiation ($\lambda = 0.71069$ Å) and a 12-kW rotating-anode generator. The $\omega/2\Theta$ scan mode was employed for data collection. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are given in *Table 6*. A view of the molecule is shown in *Fig. 1*.

The structure was solved by direct methods using *SIR92* [41], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. All of the H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å) and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent atom. Refinement of the structure was carried out on *F* using full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_o| - |F_c|)^2$. A correction for secondary extinction was not applied. Neutral atom scattering factors for non-H-atoms were taken from [42a], and the scattering factors for H-atoms were taken from [43]. Anomalous dispersion effects were included in F_c [44]; the values for f' and f'' were those of [42b]. The values of the mass attenuation coefficients are those of [42c]. All calculations were performed using the *teXsan* crystallographic software package [45].

Each N–H group forms an intermolecular H-bond with an amide O-atom of the same neighboring molecule. These interactions link the molecules into infinite one-dimensional chains which run parallel to the *x*-axis, and both H-bond interactions have a graph set motif of C(5) [46]. There are no intramolecular H-bonds (*Fig. 2*).

14.2. *Methyl* N-*{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}-(*S*)-valyl-dimethylglycyl-(*S*)-homoprolinate* (Fmoc-Val-Aib-Homoproline-OMe; **29b**). According to the *GP F*, with Fmoc-Val-OH (**13d**, 68 mg, 0.20 mmol) in CH_2Cl_2 (10 ml), **28** (68 mg, 0.20 mmol); reaction time: 15 h. CC (AcOEt/hexane, 4:1) gave 100 mg (91%) of **29b**. Colorless, viscous oil which solidified. IR (KBr): 3303*m*, 3365*w*, 2950*m*, 2873*m*, 1736*s*, 1667*s*, 1625*s*, 1531*s*, 1467*m*, 1449*s*, 1389*m*, 1362*m*, 1339*m*, 1322*m*, 1218*s*, 1154*s*, 1140*m*, 1108*m*, 1028*m*, 928*w*, 869*w*, 822*w*, 760*m*, 741*m*. ^{1}H-NMR: 7.67–7.17 (*m*, 8 arom. H); 5.55 (br. *d*, *J* = 8.3, NH); 5.29 (br. *s*, NH); 4.35–4.05 (*m*, CH_2(Fmoc), CH(α)(homoproline)); 4.11 (*t*, *J* = 7.0, CH(Fmoc)); 3.93–3.88 (*m*, CH(α)(Val)); 3.62 (*s*, MeO); 3.03 (br. *s*, H_a of CH_2(ε)(homoproline)); 2.15–1.98 (*m*, H_b of CH_2(ε)(homoproline), CH(β)(Val)); 1.57, 1.53 (2*s*, 2 Me(Aib)); 1.59–1.09 (*m*, CH_2(β)-, CH_2(γ)-, CH_2(δ)(homoproline)); 0.94–0.75 (*m*, 2 Me(Val)). ^{13}C-NMR: 172.6, 171.6, 169.6 (3*s*, 3 CO); 156.0 (*s*, CO(carbamate)); 143.7, 141.2 (2*s*, 2 arom. C); 127.6, 126.9, 124.9, 119.9 (4*d*, 8 arom. C); 66.9 (*t*, CH_2(Fmoc)); 60.3 (*d*, CH(α)(Val)); 57.0 (*s*, C(α)(Aib)); 53.4 (*d*, CH(α)(homoproline)); 52.0 (*q*, MeO); 47.0 (*d*, CH(Fmoc)); 44.4 (CH_2(ε)(homoproline)); 31.2 (*d*, CH(β)(Val)); 26.5, 24.8, 20.9 (3*t*, CH_2(β)-, CH_2(γ)-, CH_2(δ)(homoproline)); 24.9, 24.2 (2*q*, 2 Me(Aib)); 18.9, 17.8 (2*q*, 2 Me(Val)). ESI-MS: 573, 572 ($[M+Na]^+$). Anal. calc. for $C_{31}H_{39}N_3O_6 \cdot 0.6\ H_2O$ (560.48): C 66.43, H 7.23, N 7.50; found: C 66.25, H 7.48, N 7.20.

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[22]) Crystallographic data (excluding structure factors) for structure **29c** have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC-167150. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table 6. *Crystallographic Data of* **29c**

Crystallized from	CH_2Cl_2/Et_2O/MeOH/hexane
Empirical formula	$C_{19}H_{33}N_3O_6$
Formula weight [g mol^{-1}]	399.48
Crystal color, habit	colorless, plate
Crystal dimensions [mm]	$0.10 \times 0.43 \times 0.43$
Temp. [K]	173(1)
Crystal system	monoclinic
Space group	$P2_1$
Z	2
Reflections for cell determination	25
2Θ Range for cell determination [°]	26 – 37
Unit-cell parameters a [Å]	6.175(6)
b [Å]	20.413(5)
c [Å]	8.872(5)
β [°]	105.52(5)
V [Å^3]	1078(1)
D_x [g cm^{-3}]	1.231
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	0.0913
Scan type	$\omega/2\Theta$
$2\Theta_{(\max)}$ [°]	55
Total reflections measured	2770
Symmetry-independent reflections	2535
Reflections used [$I > 2\sigma(I)$]	1863
Parameters refined	252
Final R	0.0497
wR ($w = [\sigma^2(F_o) + (0.005F_o)^2]^{-1}$)	0.0436
Goodness-of-fit	1.860
Final $\Delta_{\max}/\sigma$	0.0001
$\Delta\varrho$ (max; min) [e Å^{-3}]	0.23; −0.22

14.3. *Methyl* N-*[(Benzyloxy)carbonyl]-(*S*)-phenylalanyl-dimethylglycyl-(*R/S*)-homoprolinate* (Z-Phe-Aib-Homoproline-OMe; **29a**). According to the *GP F*, with Z-Phe-OH (**13a**, 55.7 mg, 0.186 mmol) in Et_2O (5 ml), *rac*-**28** (39.1 mg, 0.186 mmol); reaction time: 24 h. CC (AcOEt/hexane, 2:1) gave 95 mg (87%) of **29a** (mixture of diastereoisomers). Colorless, viscous oil which solidified. IR (KBr): 3296*m*, 3062*w*, 3032*w*, 2946*m*, 2860*w*, 1736*s*, 1670*s*, 1622*s*, 1535*s*, 1498*m*, 1455*m*, 1444*m*, 1364*m*, 1338*m*, 1252*s*, 1211*s*, 1154*m*, 1141*m*, 1108*w*, 1083*w*, 1027*m*, 922*w*, 871*w*, 821*w*, 778*w*, 744*m*, 699*m*. ^{1}H-NMR: 7.37-7.18 (*m*, 10 arom. H); 7.05, 6.88 (2br. *s*, NH); 5.41 – 5.25 (*m*, NH); 5.08 (*s*, PhCH_2(Z)); 4.38 – 4.34 (*m*, CH(α)(Phe)); 4.10 – 3.93 (*m*, CH(α)(homoproline)); 3.72, 3.70 (2*s*, MeO); 3.14 – 2.99 (*m*, H_a of CH_2(ε)(homoproline), CH_2(Phe)); 2.22 (br. *d*, $J = 12.4$, H_b of CH_2(ε)(homoproline)); 1.67 – 1.35 (*m*, CH_2(β)-, CH_2(γ)(homoproline)); 1.55, 1.51, 1.50, 1.47 (4*s*, 2 Me(Aib)); 1.38 – 1.21 (*m*, CH_2(δ)(homoproline)). ^{13}C-NMR: 171.6, 168.9 (2*s*, 3 CO); 156.1 (*s*, CO(carbamate)); 136.2, 136.1 (2*s*, 2 arom. C); 129.4, 128.6, 128.4, 128.1, 127.9, 126.9 (6*d*, 10 arom. C); 67.0 (*t*, PhCH_2(Z)); 57.0 (*s*, C(α)(Aib)); 56.3, 56.1 (2*d*, CH(α)(homoproline), CH(α)(Phe)); 52.1 (*q*, MeO); 44.2 (*t*, CH_2(ε)(homoproline)); 38.1 (*t*, CH_2(Phe)); 26.5, 24.8, 20.9 (3*t*, CH_2(β)-, CH_2(γ)-, CH_2(δ)(homoproline)); 24.4, 24.3 (2*q*, 2 Me(Aib)). ESI-MS: 549, 548 ([M+K]$^+$), 532 ([M+Na]$^+$), 537, 510 ([M+H]$^+$), 478, 367. Anal. calc. for $C_{31}H_{39}N_3O_6 \cdot 0.5\ H_2O$ (518.62): C 64.85, H 7.00, N 8.10; found: C 64.77, H 7.22, N 7.96.

15. *Attempted Synthesis of Methyl (*S*)-*N*-(2,2-Dimethyl-2*H*-azirin-3-yl)norprolinate.* 15.1. *Methyl (*S*)-*N*-(2-Methylpropanoyl)norprolinate.* According to the *GP A*, with $SOCl_2$ (0.125 ml, 1.71 mmol), MeOH (2 ml), and (*S*)-azetidine-2-carboxylic acid (170 mg, 1.68 mmol). The crude methyl (*S*)-azetidine-2-carboxylate in abs. CH_2Cl_2 (20 ml) was treated with Et_3N (0.70 ml, 5.04 mmol) and isobutyryl chloride (0.18 ml, 1.68 mmol) according to the *GP B*; reaction time: 4 h at r.t. Evaporation yielded 288 mg (quant.) of methyl (*S*)-*N*-(2-methylpropanoyl)norprolinate. Colorless oil. IR (neat): 3468*w*, 2971*m*, 2890*w*, 1747*s*, 1652*s*, 1474*m*, 1433*s*, 1361*m*, 1318*m*, 1284*m*, 1244*m*, 1208*s*, 1171*m*, 1133*w*, 1090*m*, 1066*m*, 989*w*, 928*w*, 902*w*, 863*w*, 825*w*, 790*w*, 751*w*. ^{1}H-NMR (conformers): 4.88 – 4.84, 4.71 – 4.67 (2*m*, CH(α)(norproline)); 4.31 – 3.94 (*m*, CH_2(γ)(norproline));

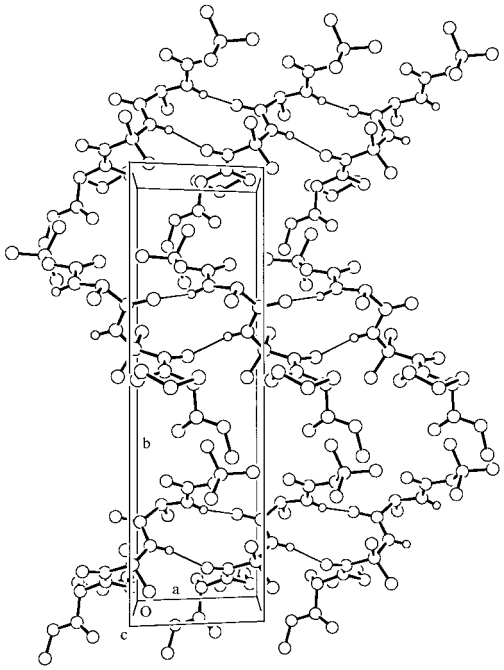

Fig. 2. *Molecular packing projected down the* c-*axis showing the H-bonding scheme* (equivalent isotropic spheres for atoms; uninvolved H-atoms omitted for clarity)

3.81, 3.76 (2*s*, MeO); 2.69–2.18 (*m*, $CH_2(\alpha)$(norproline), Me_2CH); 1.12, 1.09 (2*d*, $J=6.9$, Me_2CH). ^{13}C-NMR (conformers): 177.7, 176.8, 171.5 (3*s*, 2 CO); 61.2, 58.9 (2*d*, CH(α)(norproline)); 52.5, 52.2 (2*q*, MeO); 48.7, 46.2 (2*t*, $CH_2(\gamma)$(norproline)); 29.6 (*d*, Me_2CH); 20.3, 19.7 (2*t*, $CH_2(\beta)$(norproline)); 18.4, 18.2 (2*q*, Me_2CH). CI-MS: 389 (11), 388 (49, $[2M+NH_4]^+$), 372 (20), 371 (100, $[2M+H]^+$), 186 (6, $[M+H]^+$). Anal. calc. for $C_9H_{15}NO_3\cdot 0.5\ H_2O$ (188.82): C 57.25, H 8.22, N 7.42; found: C 57.46, H 8.21, N 7.79.

15.2. *Methyl (*S*)-*N*-(2-Methylpropanethioyl)norprolinate* (**30**). According to the *GP C*, with methyl (*S*)-*N*-(2-methylpropanoyl)norprolinate (489 mg, 2.68 mmol) in abs. toluene (30 ml) and *Lawesson* reagent (563 mg, 1.39 mmol); reaction time: 1 h, temp. 100°. CC (CH_2Cl_2/hexane, 2:1) gave 500 mg (93%) of **30**. Colorless oil. IR (neat): 3626*w*, 2971*m*, 2871*w*, 1745*s*, 1488*s*, 1464*s*, 1439*s*, 1381*w*, 1335*m*, 1255*s*, 1204*s*, 1176*m*, 1117*m*, 1063*m*, 1033*w*, 1008*m*, 973*w*, 921*w*, 896*w*, 857*w*, 841*w*, 814*w*, 784*w*, 732*w*. ^{1}H-NMR (conformers): 5.00–4.91 (*m*, CH(α)(norproline); 4.46–4.19 (*m*, $CH_2(\gamma)$(norproline)); 3.82, 3.78 (2*s*, MeO); 2.83 (*sept.*, $J=6.6$, Me_2CH); 2.69–2.56, 2.34–2.23 (2*m*, $CH_2(\beta)$(norproline); 1.21, 1.20 (2*d*, $J=6.6$, Me_2CH). ^{13}C-NMR (conformers): 210.3, 209.3 (2*s*, CS); 169.6 (*s*, CO); 63.3, 63.2 (2*d*, CH(α)(norproline)); 52.9, 52.4 (2*q*, MeO); 51.7, 51.4 (2*t*, $CH_2(\gamma)$(norproline)); 35.7, 35.4 (2*d*, Me_2CH); 22.7, 22.3, 22.2, 21.8 (4*q*, Me_2CH); 19.9, 19.0 (2*t*, $CH_2(\beta)$(norproline)). CI-MS: 204 (5), 203 (9), 202 (100, $[M+H]^+$). Anal. calc. for $C_9H_{15}NO_2S$ (201.29): C 53.70, H 7.51, N 6.90, S 15.93; found: C 53.55, H 7.58, N 6.90, S 15.77.

15.3. *Attempted Synthesis of Methyl (*S*)-*N*-(2,2-Dimethyl-2*H*-azirin-3-yl)norprolinate*. According to the *GP D*, with **30** (500 mg, 2.48 mmol) in abs. CH_2Cl_2 (10 ml), 3 drops of DMF, 2N $COCl_2$ soln. (2.5 ml, 5.0 mmol), abs. THF (15 ml), and DABCO (279 mg, 2.48 mmol). The crude intermediate was treated with NaN_3 (485 mg, 7.45 mmol) according to the *GP E*; reaction time: 48 h. CC (AcOEt/hexane, 1:2) gave 303 mg (67%) of **31**. IR (neat): 3650*w*, 3339*w*, 2977*m*, 2937*w*, 2876*w*, 2500*w*, 2113*s*, 1745*s*, 1670*w*, 1509*m*, 1459*m*, 1438*m*, 1388*w*, 1368*m*, 1323*m*, 1261*s*, 1212*s*, 1100*m*, 1070*w*, 1047*w*, 996*m*, 915*w*, 755*w*. ^{1}H-NMR: 4.47–4.39 (*m*, $CH_2(\gamma)$(norproline)); 4.19–4.15 (*m*, CH(α)(norproline)); 3.80 (*s*, MeO); 3.20 (*sept.*, $J=6.9$, Me_2CH); 2.55–2.45, 2.38–2.28 (2*m*, $CH_2(\beta)$(norproline)); 1.42 (*d*, $J=6.9$, Me_2CH). ^{13}C-NMR: 169.5 (*s*, CO); 159.4 (*s*); 58.7 (*d*, CH(α)(norproline)); 52.9, (*q*, MeO); 42.6 (*t*, $CH_2(\gamma)$(norproline)); 30.7 (*t*, $CH_2(\beta)$(norproline)); 23.8 (*d*, Me_2CH); 21.0 (*q*, Me_2CH). CI-MS: 254 (5, $[M+H]^+$), 226 (5, $[M-N_2]^+$), 212 (11), 211 (100, $[M-C_3H_7]^+$), 114 (10). Anal. calc. for $C_9H_{15}N_7O_2$ (253.27): C 42.68, H 5.97, N 38.71; found: C 43.33, H 6.21, N 37.28.

16. *Synthesis of Methyl (*S*)-*N*-(2-Ethyl-2-methyl-2*H*-azirin-3-yl)prolinate* (**33**). 16.1. *Methyl (*S*)-*N*-[(*R*/*S*)-2-Methylbutanoyl]prolinate*. According to the *GP A*, with $SOCl_2$ (2.0 ml, 27.5 mmol), MeOH (10 ml), and H-

Pro-OH (2330 mg, 20 mmol). The crude methyl (*S*)-prolinate in abs. CH_2Cl_2 (50 ml) was treated with Et_3N (8.35 ml, 60 mmol) and (*R/S*)-2-methylbutyryl chloride (2.48 ml, 20 mmol) according to the *GP B*; reaction time: 15 h at r.t. Evaporation and distillation (85°, $2 \cdot 10^{-2}$ mbar) gave 4012 mg (94%) of methyl (*S*)-*N*-[(*R/S*)-2-methylbutanoyl)]prolinate. Colorless oil. IR (neat): 3479*w*, 2965*m*, 2876*m*, 1747*s*, 1646*s*, 1464*m*, 1426*s*, 1367*m*, 1342*m*, 1322*m*, 1280*m*, 1197*s*, 1174*s*, 1095*w*, 1048*w*, 1014*w*, 943*w*, 876*w*, 796*w*, 750*w*. ^{1}H-NMR (diastereoisomers): 4.49 (*dd*, $J = 8.3$, 2.7, CH(α)(Pro)); 3.75–3.61 (*m*, CH_2(δ)(Pro)); 3.71, 3.70 (2*s*, MeO); 2.55–2.45 (*m*, MeC*H*); 2.23–1.90 (*m*, CH_2(β)-, CH_2(γ)(Pro)); 1.78–1.66, 1.48–1.36 (2*m*, MeCH_2); 1.10, 1.09 (2*d*, $J = 6.7$, *Me*CH); 0.97–0.80 (*m*, *Me*CH_2). ^{13}C-NMR (diastereoisomers): 175.4, 175.3, 172.8 (3*s*, 2 CO); 58.6, 58.4 (2*d*, CH(α)(Pro)); 51.8 (*q*, MeO); 46.7 (*t*, CH_2(δ)(Pro)); 39.3, 39.1 (2*d*, Me*C*H); 31.9, 28.9, 27.0, 26.4, 24.7, 22.3 (6*t*, CH_2(β)-, CH_2(γ)(Pro), MeCH_2); 16.6 (*q*, *Me*CH); 11.8, 11.5 (2*q*, *Me*CH_2). ESI-MS: 236 ([M + Na]$^+$), 214 ([M + H]$^+$). Anal. calc. for $C_{11}H_{19}NO_3 \cdot 0.1\ H_2O$ (215.08): C 61.43, H 9.00, N 6.51; found: C 61.57, H 9.03, N 6.73.

16.2. *Methyl (*S*)-*N*-[(*R/S*)-2-Methylbutanethioyl]prolinate* (**32**). According to the *GP C*, with methyl (*S*)-*N*-[(*R/S*)-2-methylbutanoyl]prolinate (3362 mg, 15.76 mmol) in abs. toluene (80 ml) and *Lawesson* reagent (3315 mg, 8.19 mmol); reaction time: 1.25 h, reflux. CC (CH_2Cl_2/hexane, 2:1) and distillation (130°, $3 \cdot 10^{-2}$ mbar) gave 2530 mg (70%) of **32**. Pale yellow oil. IR (KBr): 3461*w*, 2984*m*, 2959*m*, 2875*m*, 1740*s*, 1470*s*, 1445*s*, 1381*w*, 1357*m*, 1341*m*, 1303*w*, 1269*m*, 1245*w*, 1202*s*, 1164*s*, 1130*m*, 1092*w*, 1040*m*, 1016*w*, 997*m*, 972*w*, 953*m*, 928*w*, 905*w*, 859*w*, 844*w*, 801*w*, 778*w*. ^{1}H-NMR (diastereoisomers): 5.08 (*dd*, $J = 8.6$, 8.3, CH(α)(Pro)); 3.96–3.74 (*m*, CH_2(δ)(Pro)); 3.72 (*s*, MeO); 2.91–2.79 (*m*, MeC*H*); 2.33–2.04 (*m*, CH_2(β)-, CH_2(γ)(Pro)); 1.91–1.80, 1.61–1.51 (2*m*, MeCH_2); 1.22, 1.21 (2*d*, $J = 6.5$, *Me*CH); 0.95–0.77 (*m*, *Me*CH_2). ^{13}C-NMR (diastereoisomers): 209.1, 208.9 (2*s*, CS); 170.9 (*s*, CO); 65.1, 64.9 (2*d*, CH(α)(Pro)); 52.0 (*q*, MeO); 50.5, 50.3 (*t*, CH_2(δ)(Pro)); 46.7, 45.8 (2*d*, Me*C*H); 31.3, 31.1, 30.4, 29.8, 28.7, 24.5 (6*t*, CH_2(β)-, CH_2(γ)(Pro), MeCH_2); 20.7 (*q*, *Me*CH); 11.9, 11.7 (2*q*, *Me*CH_2). ESI-MS: 481 ([$2M$ + Na]$^+$), 284 ([M + Na + MeOH]$^+$), 252 ([M + Na]$^+$), 231 ([M + 1]$^+$). Anal. calc. for $C_{11}H_{19}NO_2S$ (229.34): C 57.61, H 8.35, N 6.11, S 13.98; found: C 57.58, H 8.44, N 6.14, S 13.95.

16.3. *Methyl (*S*)-*N*-[(*R/S*)-2-Ethyl-2-methyl-2*H*-azirin-3-yl]prolinate* (**33**). According to the *GP D*, with **32** (981 mg, 4.28 mmol) in abs. CH_2Cl_2 (20 ml), 3 drops of DMF, 2N $COCl_2$ soln. (3.20 ml, 6.40 mmol), abs. THF (30 ml), and DABCO (480 mg, 4.28 mmol). The crude methyl (*S*)-*N*-(1-chloro-2-methylbut-1-enyl)prolinate was treated with NaN_3 (835 mg, 12.84 mmol) according to the *GP E*; reaction time: 21 h. Evaporation and CC (AcOEt/hexane 2:1) yielded 450 mg (50%) of **33**. Pale yellow oil. IR (neat): 3461*w*, 2961*s*, 2879*s*, 1766*s*, 1745*s*, 1649*m*, 1570*w*, 1454*s*, 1417*m*, 1370*s*, 1344*s*, 1283*s*, 1209*s*, 1173*s*, 1093*m*, 1063*m*, 1043*m*, 998*m*, 969*m*, 914*w*, 876*w*, 837*w*, 808*w*, 794*w*, 747*w*. ^{1}H-NMR (diastereoisomers): 4.31 (br. *s*, CH(α)(Pro)); 3.73 (*s*, MeO); 3.71–3.51 (*m*, CH_2(δ)(Pro)); 2.34–1.98 (*m*, CH_2(β)-, CH_2(γ)(Pro)); 1.71–1.60 (*m*, MeCH_2); 1.29, 1.26 (2*s*, Me); 0.84–0.77 (*m*, *Me*CH_2). ^{13}C-NMR (diastereoisomers): 172.3 (*s*, CO); 164.7, 164.4 (2*s*, C(3′)); 60.1 (*d*, CH(α)(Pro)); 52.1 (*q*, MeO); 46.7 (*t*, CH_2(δ)(Pro)); 43.7, 43.5 (2*s*, C(2′)); 30.4, 30.1 (2*t*, CH_2(β)(Pro), MeCH_2); 23.9 (*t*, CH_2(δ)(Pro)); 23.2, 22.9 (2*q*, Me); 10.0, 9.8 (2*q*, *Me*CH_2). CI-MS: 212 (15), 211 (100, [M + H]$^+$).

17. *Reaction of* **33** *with Amino Acids and Syntheses of Model Peptides.* 17.1. *Methyl* N-*[(Benzyloxy)carbonyl]-(*S*)-phenylalanyl-(*R/S*)-methyl(ethyl)glycyl-(*S*)-prolinate* (Z-Phe-D/L-Iva-Pro-OMe, **34a**). According to the *GP F*, with Z-Phe-OH (**13a**, 81 mg, 0.271 mmol) in MeCN (5 ml), **33** (57 mg, 0.271 mmol); reaction time: 22 h. CC (hexane/AcOEt 1:4) gave 124 mg (90%) of **34a**. Colorless foam. IR (KBr): 3311*s*, 3063*m*, 3032*m*, 2952*s*, 2881*m*, 1745*s*, 1666*s*, 1535*s*, 1497*s*, 1454*s*, 1410*s*, 1370*m*, 1331*m*, 1240*s*, 1212*s*, 1174*s*, 1086*m*, 1049*m*, 1027*s*, 914*w*, 878*w*, 775*w*, 745*m*, 699*s*. ^{1}H-NMR (diastereoisomers): 7.46 (br. *s*, NH); 7.35–7.16 (*m*, 10 arom. H); 6.89 (br. *s*, NH); 5.53, 5.48 (2*d*, $J = 8.1$, NH); 5.06 (*s*, PhCH_2(Z)); 4.52–4.48, 4.43–4.39 (2*m*, CH(α)(Phe), CH(α)(Pro)); 3.69, 3.68 (2*s*, MeO); 3.64–3.44 (CH_2(δ)(Pro)); 3.12–3.03 (*m*, CH_2(Phe)); 2.55–1.81 (*m*, CH_2(β)-, CH_2(γ)(Pro), MeCH_2); 1.54, 1.50 (2*s*, Me(Iva)); 0.76–0.65 (*m*, *Me*CH_2). ^{13}C-NMR (diastereoisomers): 172.8, 172.5, 171.7, 169.1, 168.8 (5*s*, 3 CO); 155.7 (*s*, CO(carbamate)); 136.4, 136.3 (2*s*, 2 arom. C); 129.3, 129.2, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 126.8, 126.7 (10*d*, 10 arom. C); 66.7 (*t*, PhCH_2(Z)); 61.1, 60.7 (*d*, CH(α)(Pro)); 60.2 (*s*, C(α)(Iva)); 56.5 (*d*, CH(α)(Phe)); 51.9 (*q*, MeO); 47.8, 47.6 (2*t*, CH_2(δ)(Pro)); 38.4 (*t*, CH_2(Phe)); 27.6, 26.9, 25.7 (3*t*, CH_2(β)-, CH_2(γ)(Pro), MeCH_2); 21.4 (*q*, Me(Iva)); 7.8 (*q*, *Me*CH_2). ESI-MS: 548 ([M + K]$^+$), 537, 529 ([M + Na]$^+$), 510 ([M + H]$^+$), 381, 308. Anal. calc. for $C_{28}H_{35}N_3O_6 \cdot 0.5\ H_2O$ (518.62): C 64.85, H 7.00, N 8.10; found: C 65.00, H 7.04, N 8.01.

17.2. *Methyl* N-*[(Benzyloxy)carbonyl]-(*S*)-phenylalanyl-(*R/S*)-methyl(ethyl)glycyl-(*S*)-prolyl-(*S*)-alaninate* (Z-Phe-D/L-Iva-Pro-Ala-OMe, **36**). According to the *GP G*, with **34a** (91 mg, 0.179 mmol) in THF/MeOH/H_2O (3:1:1, 5 ml), LiOH · H_2O (23 mg, 0.537 mmol); reaction time: 4 h. Evaporation led to 90 mg (quant.) crude Z-Phe-D/L-Iva-Pro-OH. According to the *GP H*, with Z-Phe-D/L-Iva-Pro-OH (90 mg, 0.179 mmol), EtN(i-Pr)$_2$ (0.09 ml, 0.54 mmol), TBTU (60 mg, 0.188 mmol), H-Ala-OMe (28 mg, 0.197 mmol), and MeCN (5 ml); reaction time: 18 h. CC (AcOEt) gave 85 mg (82%) of **36**. IR (KBr): 3301*s*, 3063*m*, 3032*m*,

2948*s*, 2881*m*, 1724*s*, 1655*s*, 1542*s*, 1455*s*, 1408*s*, 1383*s*, 1334*m*, 1253*s*, 1151*s*, 1084*m*, 1058*m*, 914*w*, 881*w*, 846*w*, 778*w*, 744*m*, 699*s*. ^{1}H-NMR ((D$_6$)DMSO, diastereoisomers): 8.18 (br. *d*, *J* = 10.8, NH); 8.08–8.02 (br. *s*, NH); 7.57 (*t*-like, NH); 7.35–7.19 (*m*, 10 arom. H); 5.05–4.90 (*m*, PhC*H*$_2$(Z)); 4.36–4.32 (*m*, CH(*α*)(Phe), CH(*α*)(Pro)); 4.24–4.19 (*m*, CH(*α*)(Ala)); 3.61 (*s*, MeO); 3.56–3.32 (CH$_2$(*δ*)(Pro)); 3.01–2.73 (*m*, CH$_2$(Phe)); 1.90–1.63 (*m*, CH$_2$(*β*)-, CH$_2$(*γ*)(Pro), MeC*H*$_2$); 1.32–1.22 (*m*, Me(Iva), Me(Ala)); 0.78–0.67 (*m*, *Me*CH$_2$). ^{13}C-NMR ((D$_6$)DMSO, diastereoisomers): 172.9, 172.0, 171.8, 170.6, 170.3, 170.0 (6*s*, 4 CO); 155.7 (*s*, CO(carbamate)); 137.8, 137.0 (2*s*, 2 arom. C); 129.1, 129.0, 128.1, 127.9, 127.5, 126.1 (6*d*, 10 arom. C); 65.0 (*t*, PhCH$_2$(Z)); 60.6 (*d*, CH(*α*)(Pro)); 59.0, 58.9 (2*s*, C(*α*)(Iva)); 55.9, 55.6 (2*d*, CH(*α*)(Phe)); 51.5 (*q*, MeO); 47.4 (*d*, CH(*α*)(Ala)); 47.1 (*t*, CH$_2$(*δ*)(Pro)); 38.1 (*t*, CH$_2$(Phe)); 28.9, 27.7, 27.5, 25.0 (4*t*, CH$_2$(*β*)-, CH$_2$(*γ*)(Pro), MeCH$_2$); 21.1 (*q*, Me(Iva)); 16.6 (*q*, Me(Ala)); 7.7 (*q*, *Me*CH$_2$). ESI-MS: 603 ([*M* + Na]$^+$).

17.3. *Methyl* N-*[[(9*H*-Fluoren-9-yl)methoxy]carbonyl]-(*S*)-valyl-(*R/S*)-methyl(ethyl)glycyl-(*S*)-prolinate* (Fmoc-Val-D/L-Iva-Pro-OMe; **34b**). According to the *GP F*, with Fmoc-Val-OH (**13d**, 78 mg, 0.229 mmol) in MeCN (5 ml), **33** (48 mg, 0.229 mmol); reaction time: 17 h. CC (hexane/AcOEt 2:3) gave 114 mg (91%) of **34b**. Colorless foam. IR (KBr): 3325*s*, 3065*m*, 2966*s*, 2879*w*, 1745*s*, 1669*s*, 1623*s*, 1507*s*, 1450*s*, 1410*m*, 1370*m*, 1328*m*, 1288*s*, 1240*s*, 1175*s*, 1095*m*, 1031*m*, 948*w*, 928*w*, 842*w*, 760*s*, 741*s*. ^{1}H-NMR (diastereoisomers): 7.76–7.27 (*m*, 8 arom. H); 7.20 (br. *s*, NH); 5.51 (*d*, *J* = 7.9, NH); 4.55–4.51 (*m*, CH(*α*)(Val)); 4.42–4.36 (*m*, CH$_2$(Fmoc)); 4.24–4.18 (*m*, CH(Fmoc)); 4.05–3.99 (*m*, CH(*α*)(Pro)); 3.71 (*s*, MeO); 3.70–3.67 (*m*, CH$_2$(*δ*)(Pro)); 2.17–1.71 (*m*, CH$_2$(*β*)-, CH$_2$(*γ*)(Pro), MeC*H*$_2$); 1.68, 1.67 (2*s*, Me(Iva)); 0.98–0.82 (*m*, 2 Me(Val), *Me*CH$_2$). ^{13}C-NMR (diastereoisomers): 172.7, 172.5, 172.0, 171.2, 169.4, 169.2 (6*s*, 3 CO); 156.2 (*s*, CO(carbamate)); 143.9, 143.8, 141.2 (3*s*, 4 arom. C); 127.5, 126.9, 125.0, 119.8 (4*d*, 8 arom. C); 66.9 (*t*, CH$_2$(Fmoc)); 61.5 (*s*, C(*α*)(Iva)); 61.3, 60.9, 60.4 (3*d*, CH(*α*)(Val), CH(*α*)(Pro)); 52.0 (*q*, MeO); 47.8, 47.7 (2*t*, CH$_2$(*δ*)(Pro)); 47.1 (*d*, CH(Fmoc)); 31.5 (*d*, CH(*β*)(Val)); 27.6, 26.8, 25.8 (3*t*, CH$_2$(*β*)-, CH$_2$(*γ*)(Pro), MeCH$_2$); 21.6 (*q*, Me(Iva)); 19.0, 17.6 (2*q*, 2 Me(Val)); 8.2, 7.9 (*q*, *Me*CH$_2$). ESI-MS: 572 ([*M* + Na]$^+$). Anal. calc. for C$_{31}$H$_{39}$N$_3$O$_6$·0.5 H$_2$O (558.68): C 66.65, H 7.22, N 7.52; found: C 66.56, H 7.25, N 7.32.

17.4. *Methyl* N-*[(*tert-*Butoxy)carbonyl]-(*S*)-alanyl-(*S*)-valyl-(*R/S*)-methyl(ethyl)glycyl-(*S*)-prolinate* (Boc-Ala-Val-D/L-Iva-Pro-OMe; **37**). A soln. of **34b** (103 mg, 0.187 mmol) in Et$_2$NH/CH$_2$Cl$_2$ 1:1 (2 ml) was stirred at r.t. for 4 h. Evaporation led to crude H-Val-D/L-Iva-Pro-OMe, which was treated according to the *GP H*, with EtN(i-Pr)$_2$ (0.10 ml, 0.56 mmol), TBTU (63 mg, 0.196 mmol), Boc-Ala-OH (39 mg, 0.206 mmol), and MeCN (8 ml); reaction time: 17 h. CC (AcOEt) gave 90 mg (97%) of **37**. IR (KBr): 3303*s*, 2976*s*, 2880*m*, 1746*s*, 1655*s*, 1623*s*, 1523*s*, 1453*s*, 1409*s*, 1393*m*, 1367*m*, 1327*m*, 1248*s*, 1171*s*, 1124*m*, 1084*s*, 1052*m*, 1027*m*, 953*w*, 928*w*, 864*w*, 825*w*, 773*w*, 762*w*. ^{1}H-NMR ((D$_6$)DMSO): 8.31, 8.25 (2*s*, NH); 7.90 (*d*, *J* = 7.4, NH); 5.51 (*t*, *J* = 7.4, NH); 4.29–4.21 (*m*, CH(*α*)(Val), CH(*α*)(Ala)); 4.05–4.00 (*m*, CH(*α*)(Pro)); 3.58 (*s*, MeO); 3.31–3.25 (*m*, CH$_2$(*δ*)(Pro)); 2.00–1.71 (*m*, CH$_2$(*β*)-, CH$_2$(*γ*)(Pro), CH(*β*)(Val), MeC*H*$_2$); 1.37 (*s*, *t*-Bu); 1.29, 1.26 (2*s*, Me(Iva)); 1.16–1.13 (*m*, Me(Ala)); 0.88–0.78 (*m*, 2 Me(Val)); 0.74 (*t*, *J* = 7.4, *Me*CH$_2$)). ^{13}C-NMR ((D$_6$)DMSO): 172.6, 172.5, 172.3, 171.2, 169.9, 169,8, 169.6 (7*s*, 4 CO); 154.8 (*s*, CO(carbamate)); 77.9 (*s*, Me$_3$*C*); 59.9, 56.8 (2*d*, CH(*α*)(Val), CH(*α*)(Pro)); 59.0, 58.2 (2*s*, C(*α*)(Iva)); 51.3 (*q*, MeO); 49.6 (*d*, CH(*α*)(Ala)); 47.0 (2*t*, CH$_2$(*δ*)(Pro)); 30.9 (*d*, CH(*β*)(Val)); 29.2, 27.1, 25.3, 25.1 (4*t*, CH$_2$(*β*)-, CH$_2$(*γ*)(Pro), MeCH$_2$); 28.0 (*q*, *Me*$_3$C); 21.3 (*q*, Me(Iva)); 20.0, 19.1, 18.8, 18.2, 18.0, 17.6 (6*q*, 2 Me(Val), Me(Ala)); 7.3, 7.2 (2*q*, *Me*CH$_2$). ESI-MS: 521 ([*M* + Na]$^+$), 421.

17.5. *Methyl* N-*{[(9*H*-Fluoren-9-yl)methoxy]carbonyl}-(*S*)-phenylalanyl-glycyl-(*R/S*)-methyl(ethyl)glycyl-(*S*)prolinate* (Fmoc-Phe-Gly-D/L-Iva-Pro-OMe; **35**). According to the *GP F*, with Fmoc-Phe-Gly-OH (**13e**, 121 mg, 0.271 mmol) in CH$_2$Cl$_2$/DMF 50:1 (5 ml), **33** (57 mg, 0.271 mmol); reaction time: 20 h. CC (AcOEt) gave 177 mg (99%) of **35**. Colorless foam. IR (KBr): 3310*s*, 3063*m*, 2950*m*, 2881*m*, 1744*s*, 1664*s*, 1531*s*, 1450*s*, 1408*s*, 1332*m*, 1251*s*, 1210*m*, 1174*m*, 1094*m*, 1045*m*, 877*w*, 843*w*, 760*m*, 741*s*, 701*m*. ^{1}H-NMR (diastereoisomers): 7.75–7.20 (*m*, 13 arom. H, NH); 7.06, 6.89 (2*s*, NH); 5.68 (*dd*, *J* = 20.6, 6.8, NH); 4.53–4.50 (*m*, CH(*α*)(Phe)); 4.43–4.36 (*m*, CH$_2$(Fmoc)); 4.32–4.26 (*m*, CH(*α*)(Pro)); 4.17–4.10 (*m*, CH(Fmoc)); 3.98–3.93 (*m*, CH$_2$(Gly)); 3.81–3.54 (*m*, CH$_2$(*δ*)(Pro)); 3.66, 3.65 (*s*, MeO); 3.20–3.03 (*m*, CH$_2$(Phe)); 2.13–1.74 (*m*, CH$_2$(*β*)-, CH$_2$(*γ*)(Pro), MeC*H*$_2$); 1.60, 1.56 (2*s*, Me(Iva)); 0.85–0.78 (*m*, *Me*CH$_2$). ^{13}C-NMR (diastereoisomers): 172.9, 172.6, 171.9, 171.7, 171.4, 171.2, 167.1, 166.6 (8*s*, 4 CO); 156.0 (*s*, CO(carbamate)); 143.6, 141.2, 136.5 (3*s*, 5 arom. C); 129.1, 128.5, 127.6, 127.0, 124.9, 119.9 (6*d*, 13 arom. C); 67.0 (*t*, CH$_2$(Fmoc)); 61.0, 60.9 (2*s*, C(*α*)(Iva)); 60.8, 60.2 (2*d*, CH(*α*)(Pro)); 56.3 (*s*, CH(*α*)(Phe)); 51.9 (*q*, MeO); 47.9 (*t*, CH$_2$(*δ*)(Pro)); 46.9 (*d*, CH(Fmoc); 43.2 (*t*, CH$_2$(Gly)); 38.1 (*t*, CH$_2$(Phe)); 27.6, 27.3, 25.8 (3*t*, CH$_2$(*β*)-, CH$_2$(*γ*)(Pro), MeCH$_2$); 21.3 (*q*, Me(Iva)); 8.0, 7.0 (2*q*, *Me*CH$_2$). ESI-MS: 677 ([*M* + Na]$^+$), 526, 421, 411, 292, 233, 211.

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