112. Novel Heterospirocyclic 3-Amino-2*H*-azirines as Synthons for Heterocyclic α-Amino Acids[1])

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Dedicated to Professor *Dieter Seebach* on the occasion of his 60th birthday

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The heterospirocyclic *N*-methyl-*N*-phenyl-2*H*-azirin-3-amines (3-(*N*-methyl-*N*-phenylamino)-2*H*-azirines) **1a–d** with a tetrahydro-2*H*-pyran, tetrahydro-2*H*-thiopyran, and a *N*-protected piperidine ring, respectively, were synthesized from the corresponding heterocyclic 4-carboxamides **2** by consecutive treatment with lithium diisopropylamide (LDA), diphenyl phosphorochloridate (DPPCl), and sodium azide (*Scheme 4*). The reaction of these aminoazirines with thiobenzoic acid in CH_2Cl_2 at room temperature gave the thiocarbamoyl-substituted benzamides **13a–d** in high yield. The azirines **1a–d** were used as synthons for heterocyclic α-amino acids in the preparation of tripeptides of the type Z-Aib-Xaa-Aib-N(Ph)Me (**18**) by following the protocol of the 'azirine/oxazolone method': treatment of Z-Aib with **1** to give the dipeptide amide **15**, followed by selective hydrolysis to the corresponding acid **16** and coupling with the 2,2-dimethyl-2*H*-azirin-3-amine **17** gave **18**, again in high yield (*Scheme 5*). With some selected examples of **18**, the selective deprotection of the amino and the carboxy group, respectively, was demonstrated (*Scheme 6*). The solid-state conformations of the protected tripeptides **18a–d**, as well as that of the corresponding carbocyclic analogue **18e**, were determined by X-ray crystallography (*Figs. 1–3* and *Tables 1–3*). All five tripeptides adopt a β-turn conformation of type III or III'. The solvent dependence of the chemical shifts of the NH resonances (*Fig. 6*) suggests that there is an intramolecular H-bond between H–N(4) and O(11) in all cases, which is an indication that a relatively rigid β-turn structure also persists in solution. Surprisingly, the tripeptide acid **20a** shows no intramolecular H-bond in the crystalline state (*Fig. 7*); O(11) is involved in an intermolecular H-bond with the OH group of the carboxy function.

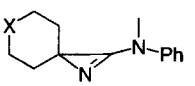
1. Introduction. – Peptides containing α,α-disubstituted α-amino acids (α,α-disubstituted glycines) are significantly restricted in their conformational freedom. As a consequence of the rigidity of the peptide backbone, secondary structures such as β-turns and α or 3_{10} helices are preferred in the solid state and in solution (see [1–6] and refs. cit. therein). Furthermore, non-protein amino acids are also of interest because of their biological activity [7–10]. A useful method for the introduction of α,α-disubstituted α-amino acids into peptides is the so-called 'azirine/oxazolone method' in which 2*H*-azirin-3-amines (3-amino-2*H*-azirines) are used as amino-acid synthons (*cf.* [6]). This strategy has been widely employed in the synthesis of linear oligopeptides [4] [5] [11–15], cyclic peptides [16], and depsipeptides [17–19] containing α,α-disubstituted amino acids.

Peptides with acyclic or carbocyclic α,α-disubstituted α-amino acids have been thoroughly investigated [4] [20–24], and the corresponding 2*H*-azirin-3-amines have been

[1]) Presented by *C. S.* at the 'Autumn Meeting of the New Swiss Chemical Society', 21.11.1996, in Basel.
[2]) Part of the Ph. D. thesis of *C. S.*, Universität Zürich, 1997.

synthesized in our laboratory [25] (*cf.* also [6]). Peptides containing heterocyclic α,α-disubstituted α-amino acids have been less extensively examined so far. Because of the heteroatom in the cyclic residue of these amino acids, not only is an influence on the peptide backbone to be expected, but an additional interaction with the environment is also possible. For example, 4-aminotetrahydro-2*H*-thiopyran-4-carboxylic acid (Tht) has been investigated as a methionine analogue [26–30].

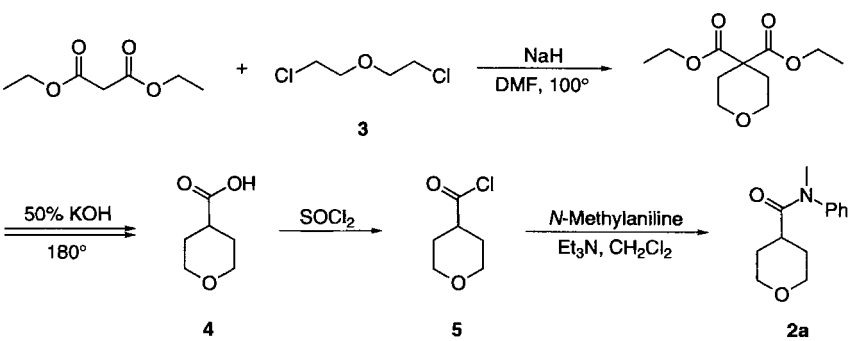
In the present paper, we describe the synthesis of four new heterospirocyclic 2*H*-azirin-3-amines of type **1** and their use as amino-acid synthons in the preparation of some model tripeptides.



1a X = O
b X = S
c X = N(Boc)
d X = NCH_2Ph

2. Results. – 2.1. *Synthesis of Heterospirocyclic 2*H*-Azirin-3-amines.* The starting materials for the synthesis of the heterospirocyclic 2*H*-azirin-3-amines **1** are the corresponding *N*-methylanilides **2** which had to be prepared first. The amide **2a** was synthesized *via* a malonic-ester synthesis according to [25]. The heterocyclic acid **4** was formed by alkylation of diethyl malonate using 2,2′-dichlorodiethyl ether (**3**) as the electrophile, followed by saponification and decarboxylation. After conversion of **4** to the acyl chloride **5** with $SOCl_2$, the reaction with *N*-methylaniline yielded the amide **2a** (*Scheme 1*).

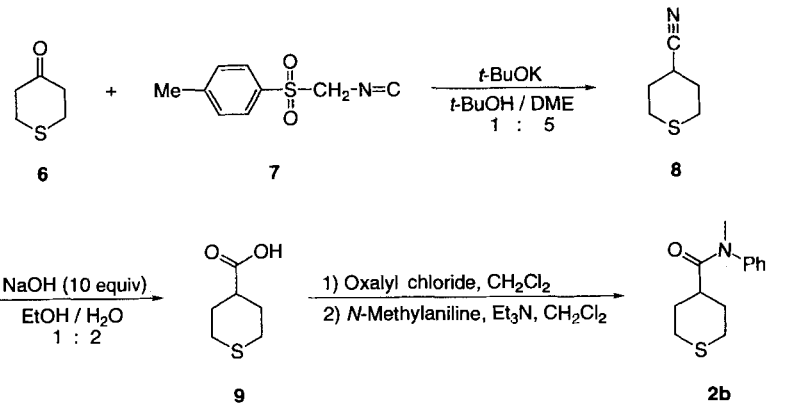
Scheme 1



For the preparation of amide **2b**, tetrahydro-2*H*-thiopyran-4-one **6** was reacted with tosylmethyl isocyanide (**7**) to give the cyanide **8** [31] which, after hydrolysis, led to the carboxylic acid **9**. Subsequent treatment of **9** with oxalyl chloride and *N*-methylaniline gave the amide **2b** (*Scheme 2*).

Protection of ethyl piperidine-4-carboxylate (**10**) with the (*tert*-butoxy)carbonyl group (Boc), followed by saponification and careful acidification, led to the carboxylic acid **11** (*Scheme 3*). Because of the acid lability of the Boc group, **11** could not be converted to the corresponding acyl chloride without extensive deprotection. Therefore, the amide **2c** was prepared by the use of dicyclohexylcarbodiimide (DCC) as the coupling reagent. The main product (60% yield) of this reaction was not the amide **2c** but the addition product **12** of DCC and the acid **11** (*cf.* [32]). Using a mixture of DCC and

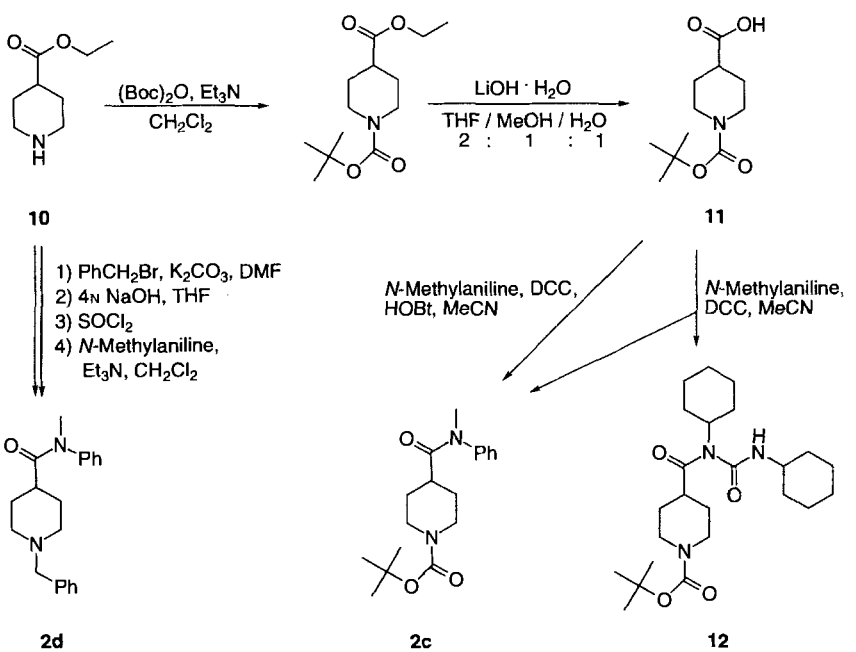
Scheme 2



6 **7** **8** **9** **2b**

1-hydroxy-1*H*-benzotriazol (HOBt) in the coupling reaction, the formation of **12** was avoided and the yield of amide **2c** increased from 33 to 70%. The *N*-benzyl derivative **2d** was prepared *via* benzylation of **10**, saponification, and successive treatment with $SOCl_2$ and *N*-methylaniline.

Scheme 3

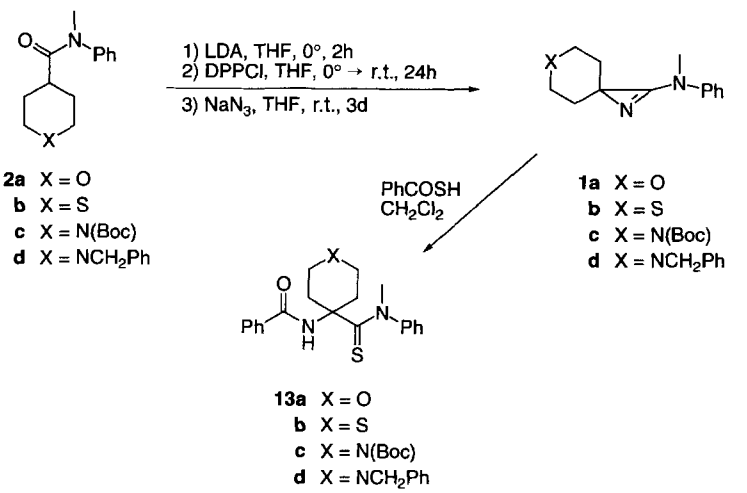


10 **11** **2d** **2c** **12**

The 2*H*-azirin-3-amines **1a–d** were prepared from the amides **2a–d**, according to the method of *Villalgordo* [33a] (*cf.* [12]) in fair-to-good yields (46–70%; *Scheme 4*). In contrast to the classical method described by *Rens* and *Ghosez* [33b], and the modification with thioamides as starting materials (*cf.* [15]), the *Villalgordo* method avoids the use

of phosgene and the isolation of the reactive α-chloroenamine intermediate. The reaction of the azirines **1** with thiobenzoic acid in CH_2Cl_2 at room temperature gave the thioamides **13** in good yields (79–97%; *Scheme 4*). This reaction shows that the reactivity of these azirines is comparable with that of other 2,2-disubstituted 2*H*-azirin-3-amines (*cf.* [4][12][14][33a]). Therefore, **1a–d** can be envisaged as synthons for 4-aminotetrahydro-2*H*-pyran-4-carboxylic acid (Thp), 4-aminotetrahydro-2*H*-thiopyran-4-carboxylic acid (Tht), and Boc- or Z-protected 4-aminopiperidine-4-carboxylic acid (Pip(Boc) and Pip(Z), resp.).

Scheme 4

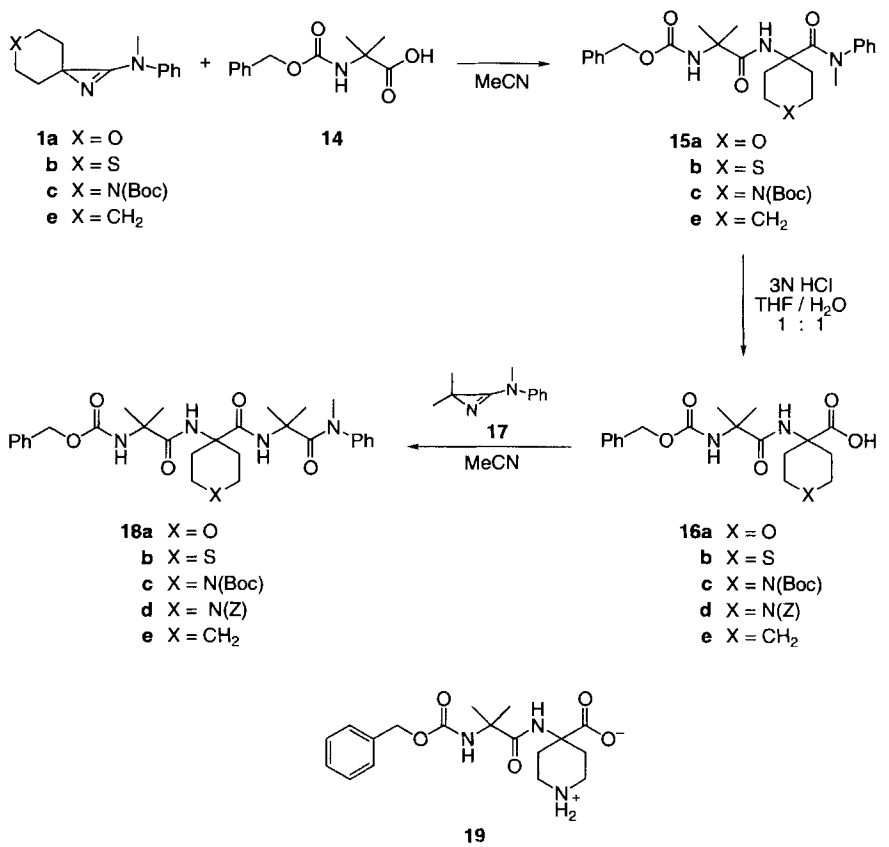


2.2. *Synthesis of Aib-Xaa-Aib Tripeptides.* Tripeptides of the type Z-Aib-Xaa-Aib-N(Ph)Me were chosen as model target molecules in preparations using the synthons **1**. These tripeptides were synthesized *via* the 'azirine/oxazolone method' mentioned above. For comparison, the corresponding tripeptide containing 1-aminocyclohexane-1-carboxylic acid (Ach) instead of the heterocyclic amino acid was also synthesized. The azirinamines **1a–c** and *N*-methyl-*N*-phenyl-1-azaspiro[2.5]oct-1-en-2-amine (**1e**) [25][34] were reacted with Z-protected aminoisobutanoic acid **14** in MeCN at room temperature to give the dipeptides **15** as white precipitates in high yields. After selective hydrolysis under standard conditions (3N HCl, THF/H_2O 1:1, room temperature), the *N*-protected dipeptide acids of type **16** were obtained (*Scheme 5*). Reaction of the latter with *N*,2,2-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**17**), a convenient Aib synthon, gave the protected triamides **18** as colorless solids.

It should be mentioned that the hydrolysis of **15c** caused some difficulties, due to the acid lability of the Boc protective group: the yield of the dipeptide acid **16c** was only 34%, compared with 70–90% in the cases of **16a**, **b**, **e**. The main product (60% yield) in this reaction was the amphoteric ion **19**, which, after protection with di(*tert*-butyl) dicarbonate ($(Boc)_2O$) or (benzyloxy)carbonyl chloride (Z–Cl), led to the protected dipeptide acids **16c** and **16d**, respectively.

To use tripeptides of the type Aib-Xaa-Aib as peptide segments in condensation reactions, the selective deprotection of the N- as well as of the C-terminus is an essential

Scheme 5

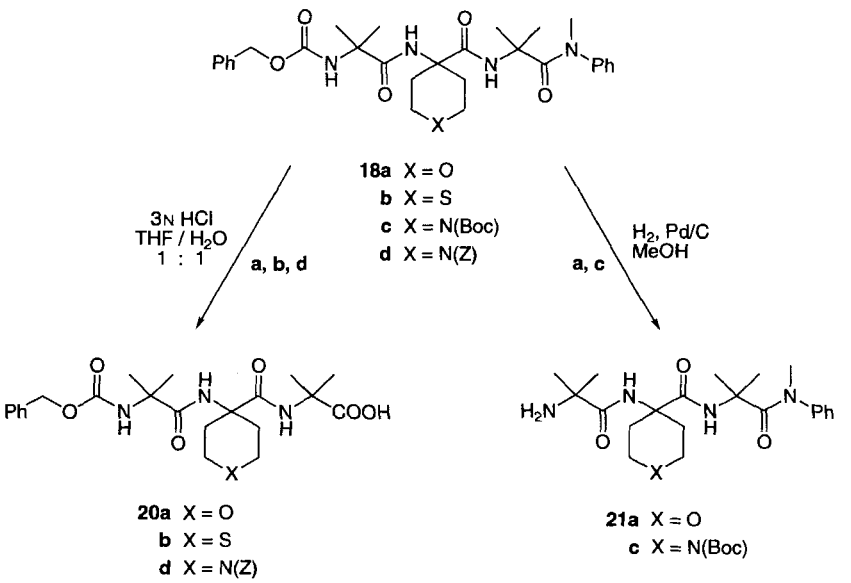


step. Therefore, **18a**, **b**, **d** were hydrolyzed with 3N HCl in THF/H_2O 1:1 at room temperature (*Scheme 6*). The Z-protected tripeptide acids **20a**, **b**, **d** were isolated in 99, 87, and 87% yield, respectively. On the other hand, hydrogenolysis of **18a**, **c** in MeOH (Pd/C) gave the tripeptides **21a**, **c** with a deprotected amino group in 98 and 97% yield, respectively. Only in the case of the S-containing **18b** was the cleavage of the Z-group with H_2 in the presence of Pd/C unsuccessful. For that reason, another N-protecting group (*e.g.*, Fmoc) must be used in the synthesis of tripeptide **21** (X = S).

2.3. *Conformational Studies of Z-Aib-Xaa-Aib-N(Ph)Me Tripeptides.* The tripeptides **18a–e** were crystallized from MeCN or $CHCl_3$/hexane, and their structures were established by X-ray crystallography (*Figs. 1–3*). As expected, all of these tripeptides adopt type-III′ or type-III β-turn conformations, similar to Aib polypeptides [36–40] and peptides with a Z-Aib terminus [41] [42]. The heteroatom seems to have relatively little influence on the folding of the peptide backbone.

The similarity of the conformations is clearly shown by the torsion angles of the tripeptide backbone (*Fig. 4*, *Table 1*). All amide bonds have the *trans*-configuration ($\omega = \pm 160–179°$), and the φ/ψ-combinations for amino acids $i-1$ and i are very close to the ideal values for β-turn conformations of type III/III′ ($\pm 60°/\pm 30°$, $\pm 60°/\pm 30°$

Scheme 6



[43])[3]: in **18b, e**, all deviations from these values are smaller than $\pm$ 3.2°. In the cases of **18a, c, d** with the more polar heterocyclic amino acids Xaa, the torsion angles ϕ_{i-1} and ψ_i for **18a**, ϕ_{i-1}, ψ_{i-1}, and ψ_i for **18c**, and ψ_{i-1} for **18d** show larger deviations from the ideal values.

In each example, there is an intramolecular H-bond between H–N(4) and O(11) which forms the molecule into a loop having the graph set [44] of S(10). This formal ten-membered ring is typical for a β-turn conformation. The average length of these H-bonds, N(4)···O(11), is 3.00 $\pm$ 0.05 Å, and the mean N(4)–H···O(11) angle is 161 $\pm$ 7° (*Table 2*). Additionally, in each structure, H–N(4) and H–N(7) have weak side-ways interactions with N(7) and N(10), respectively, although this might be mainly due to the conformation of the peptide chain.

In **18a–c, e**, the molecules are linked end-to-end by an N(10)–H···O(2′) intermolecular H-bond thus forming infinite one-dimensional chains having a graph set [44] of C(11). These chains run parallel to the [101], [$\bar{1}$01], [101] and [$\bar{1}$01] directions, respectively. This H-bond is absent in **18d**, being replaced instead by an N(10)–H···O(5′) interaction which links the molecules into infinite one-dimensional chains which run parallel to the [001] direction with a graph set of C(8) (*Fig. 5*, *Table 3*).

The presence of a H_2O molecule in the asymmetric unit of **18c** provides the opportunity for the formation of additional H-bonds. H–N(7) donates a H-bond to the H_2O molecule, which in turn acts as a donor for two H-bonds; one being to O(2) (which is, therefore, accepting two H-bonds) and the other to the carbonyl O-atom of the side chain, O(34). Thus, the H_2O molecule is H-bonded to three different peptide molecules.

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[3]) The combination of four negative angles (type III) corresponds to a right handed helical structure (part of a right-handed 3_{10} helix); four positive angles (type III′) indicate a left-handed helical structure.

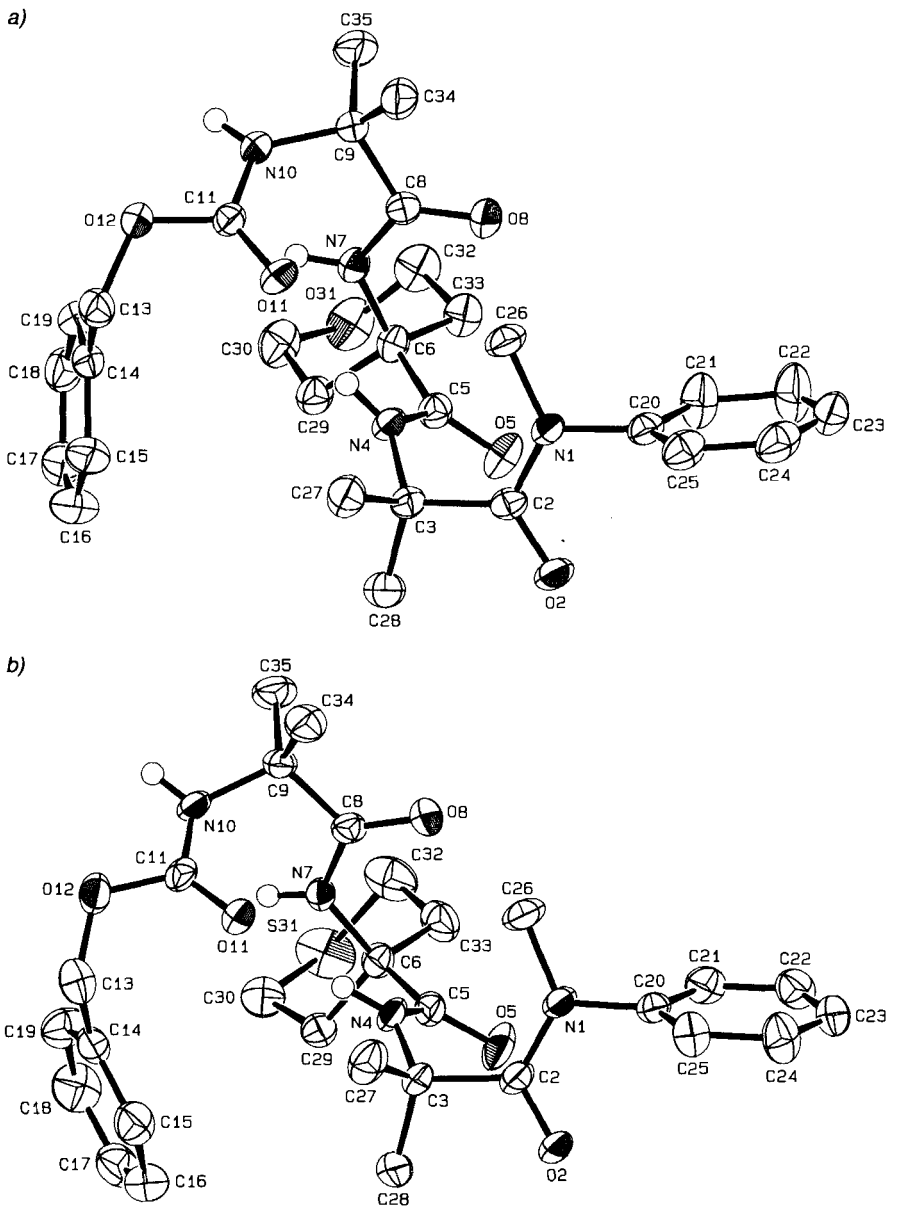

Fig. 1. *ORTEP Plots* [35] *of the molecular structures of* a) **18a** *and* b) **18b** (with 50% probability ellipsoids)

This leads to three types of binary graph sets: $C_2^2(14)$, $R_4^4(20)$, and $C_2^2(10)$ for the O(2)···H–O(1)–H···O(34), N(7)–H···O(1)–H···O(34), and N(7)–H···O(1)–H···O(2) systems, respectively (*i.e.*, infinite chains running in the [010] direction, loops involving two H_2O and two peptide molecules, and infinite chains running parallel to the

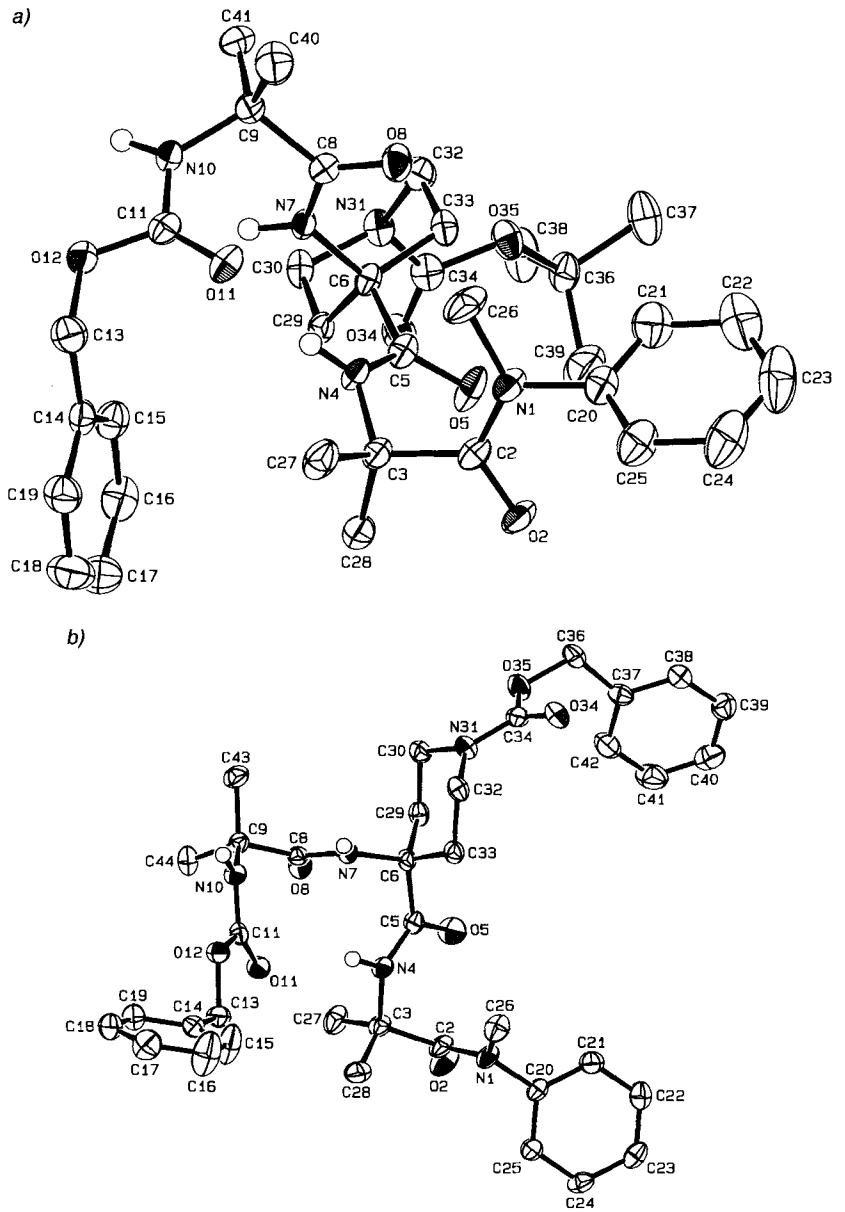

Fig. 2. *ORTEP Plots* [35] *of the molecular structures of* a) **18c** *and* b) **18d** (with 50% probability ellipsoids)

[101] direction). The combination of all intermolecular interactions in **18c** links the molecules into infinite 2-dimensional sheets which lie perpendicular to the [$\bar{1}$01] direction.

Information about the three-dimensional structure of oligopeptides in solution is, *e.g.*, available from NMR measurements. A simple indication is the dependence of the

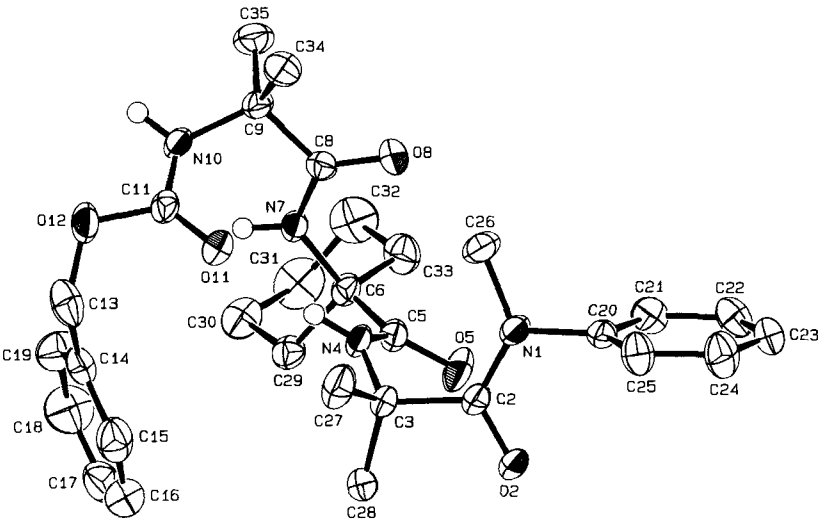

Fig. 3. *ORTEP Plot* [35] *of the molecular structures of* **18e** (with 50% probability ellipsoids)

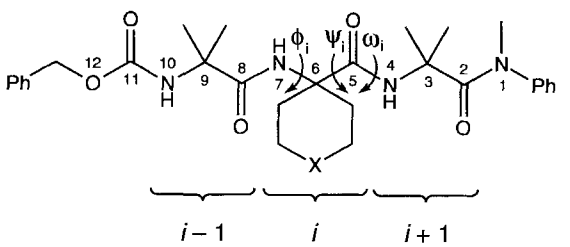

Fig. 4. *Numbering (arbitrary) and torsion angles of the peptide backbone*

Table 1. *Torsion Angles* [°] *within the Backbone of Tripeptides* **18** *and of* **22**

18	ω_{i-2}	ϕ_{i-1}	ψ_{i-1}	ω_{i-1}	ϕ_i	ψ_i	ω_i	ϕ_{i+1}	ψ_{i+1}	ω_{i+1}
a	177.7(2)	54.3(3)	29.6(3)	178.2(2)	60.1(2)	39.9(2)	163.9(2)	56.0(2)	52.9(2)	−170.9(2)
b	169.9(2)	58.7(3)	28.0(3)	177.9(2)	57.8(3)	28.2(3)	160.7(2)	53.6(3)	48.9(4)	−174.3(2)
c	176.1(2)	51.2(3)	44.9(3)	173.1(2)	68.9(3)	21.9(3)	167.7(2)	50.7(3)	54.0(3)	−175.4(2)
d	−162.7(2)	−59.4(2)	−45.6(2)	−175.8(2)	−63.2(2)	−27.6(2)	169.0(2)	41.8(2)	62.1(2)	164.2(2)
e	169.2(2)	59.5(2)	27.4(2)	178.5(2)	56.8(2)	29.9(2)	161.0(2)	53.1(2)	49.2(3)	−174.8(2)
22[a])	−178.2(2)	52.5(2)	37.4(2)	174.3(2)	61.9(2)	29.5(2)	164.7(2)	58.2(2)	58.3(2)	161.7(2)
	179.0(2)	−51.9(2)	−37.4(2)	−173.0(2)	−60.3(2)	−31.0(2)	−164.0(2)	−59.0(2)	−56.7(2)	−165.8(2)

[a]) For Z-Aib-Aib-Aib-N(Ph)Me (**22**) [36], there are two independent molecules with very similar conformations in the asymmetric unit.

NH shift on the temperature or on the polarity of the solvent: NH groups involved in intramolecular H-bonds show a very small dependence, whereas the chemical shifts of solvent-exposed NH groups are influenced more significantly (*cf.*, *e.g.*, [4a] [45] [46]). For the tripeptides **18a–c**, **e**, the involvement of the NH groups in intramolecular H-bonds

Table 2. *Intramolecular Hydrogen Bonds in Tripeptides* **18** *and* **22**

18	Type	H ··· X [Å]	N ··· X [Å]	N–H ··· X [°]
a	N(4)–H ··· O(11)	2.19(2)	3.028(2)	159(2)
	N(4)–H ··· N(7)	2.45(2)	2.824(2)	106(2)
	N(7)–H ··· N(10)	2.40(2)	2.769(3)	107(2)
b	N(4)–H ··· O(11)	2.09(3)	2.952(3)	168(2)
	N(4)–H ··· N(7)	2.40(2)	2.764(3)	105(2)
	N(7)–H ··· N(10)	2.31(2)	2.725(3)	112(2)
c	N(4)–H ··· O(11)	2.23(2)	3.041(3)	157(2)
	N(4)–H ··· N(7)	2.43(2)	2.801(3)	107(2)
	N(7)–H ··· N(10)	2.50(2)	2.829(3)	102(2)
d	N(4)–H ··· O(11)	2.23(2)	3.018(2)	154(2)
	N(4)–H ··· N(7)	2.41(2)	2.788(2)	108(2)
	N(7)–H ··· N(10)	2.57(2)	2.853(2)	101(2)
e	N(4)–H ··· O(11)	2.11(2)	2.955(2)	167(2)
	N(4)–H ··· N(7)	2.39(2)	2.769(2)	107(2)
	N(7)–H ··· N(10)	2.31(2)	2.721(2)	110(2)
22[a])	N(4)–H ··· O(11)	2.25(2)	3.026(2)	161(2)
		2.30(2)	3.071(2)	162(2)

[a]) For Z-Aib-Aib-Aib-N(Ph)Me (**22**) [36], there are two independent molecules with very similar conformations in the asymmetric unit.

was evaluated on the basis of the solvent dependence of δ(NH) in $CDCl_3/(D_6)DMSO$ (solvent-titration experiment [46]). For the assignment of the NH resonances (all three appear as *s*), 2D NMR experiments and the chemical shifts relative to those of the corresponding Z-Phe-Xaa-Val-N(Ph)Me tripeptides [47] were used. As shown in *Fig. 6*, one NH group is nearly unaffected by an increase of the proportion of $(D_6)DMSO$ over the range from 0 to 12% ($\Delta\delta < 0.05$ ppm). We presume that this signal emanates from H–N(4), which is involved in an intramolecular H-bond with O(11), forming a β-turn as in the crystalline state. In contrast, $\Delta\delta$ of H–N(10) is *ca.* 1.8 ppm which is typical for a solvent-exposed NH group. The solvent dependence of H–N(7) ($\Delta\delta = 0.2 - 0.3$ ppm) is relatively small; it can be explained by the fact that the position of this NH within the β-turn is partially shielded from the solvent by the ring atoms of Xaa.

The tripeptide Z-Aib-Xaa-Aib (**20a**), deprotected at the C-terminus, was crystallized from $CHCl_3$/hexane, and its structure was established by X-ray crystallography (*Fig. 7*). Surprisingly, the conformation of the molecule is completely different compared with the conformations of the peptide amides **18**. There is no intramolecular H-bond characteristic for a β-turn, and the torsion angles of the backbone deviate markedly from those of **18**: the values for ϕ_{i-1}/ψ_{i-1} are $58.5(7)/-135.7(6)°$, and ϕ_i/ψ_i are $-52.0(7)/-46.8(7)°$. In **20a**, the atom O(11), which in **18** is the acceptor for H–N(4), forms a very strong intermolecular H-bond with the OH of the carboxylic group of a second molecule.

The O(1)–H ··· O(11′) H-bond in **20a** forms infinite one-dimensional chains, which have a graph set [44] of C(13) and run in the [001] direction (*Fig. 8*, *Table 3*). H–N(7) and H–N(4) form intermolecular H-bonds with the carbonyl O-atoms of an amide (O(5))

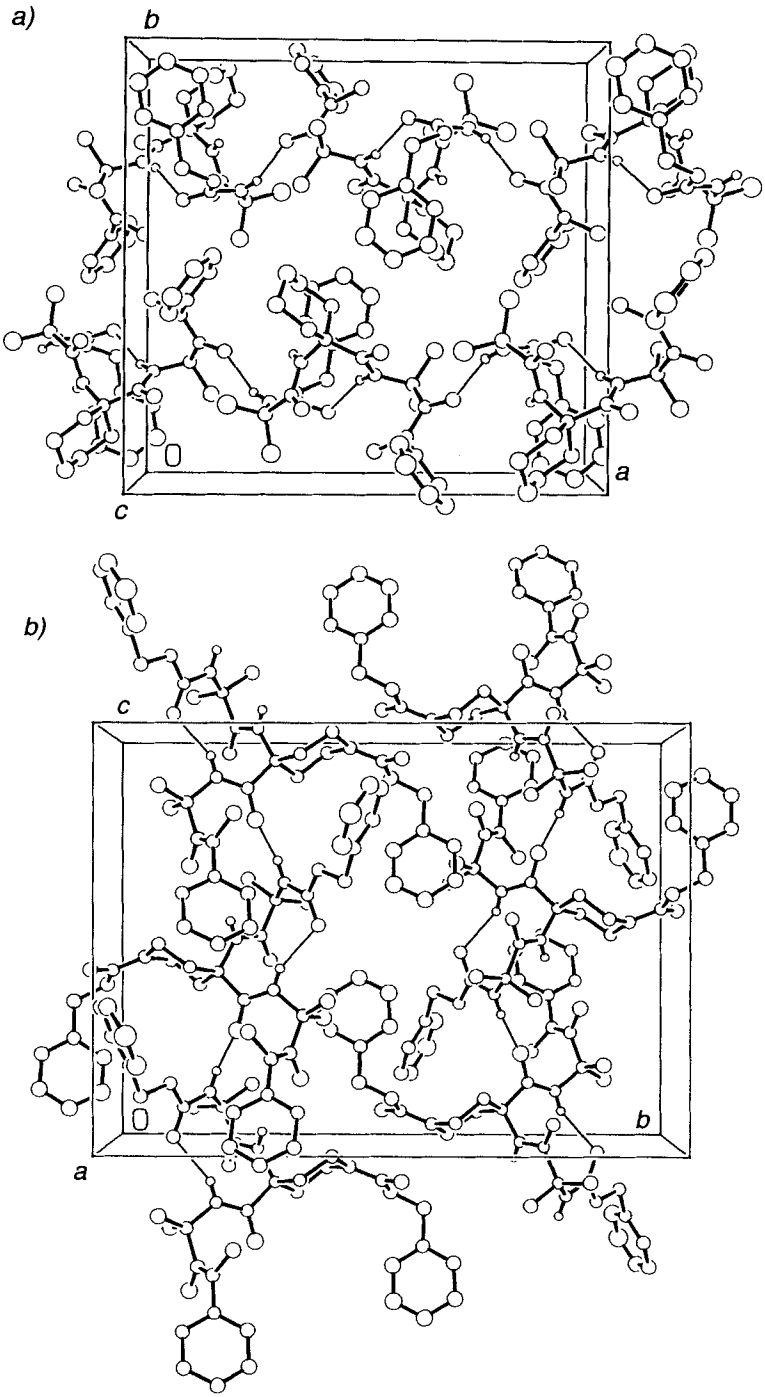

Fig. 5. *Packing diagrams of* a) **18a** *and* b) **18d**

Table 3. *Intermolecular Hydrogen Bonds in* **18** *and* **20a**

Compound	D–H···A[a])	D–H [Å]	H···A [Å]	D···A [Å]	D–H···A [°]
18a	N(10)–H(10)···O(2^{i})	0.84(2)	2.05(2)	2.841(2)	158(2)
18b	N(10)–H(10)···O(2^{ii})	0.81(3)	2.02(3)	2.774(3)	154(3)
18c	O(1)–H(11)···O(34^{iii})	0.96(3)	1.79(3)	2.750(3)	176(3)
	O(1)–H(12)···O(2^{iv})	0.72(3)	2.09(3)	2.759(3)	155(3)
	N(7)–H(7)···O(1^{v})	0.89(2)	2.12(2)	2.988(3)	165(2)
	N(10)–H(10)···O(2^{vi})	0.86(2)	2.17(2)	3.009(3)	163(2)
18d	N(10)–H(10)···O(5^{vii})	0.89(2)	1.83(2)	2.706(2)	169(2)
18e	N(10)–H(10)···O(2^{viii})	0.85(2)	2.03(2)	2.786(2)	149(2)
20a	O(1)–H(1)···O(11^{ix})	0.98	1.72	2.693(6)	173
	N(10)–H(10)···O(8^{v})	0.87	2.10	2.944(7)	163
	N(7)–H(7)···O(5^{x})	0.95	2.04	2.937(6)	158
	N(4)–H(4)···O(2^{x})	0.95	2.03	2.939(6)	160

[a]) Superscripted atoms refer to molecules in the following symmetry-related positions: *i*: $-\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$; *ii*: $-\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; *iii*: $1+x, -1+y, 1+z$; *iv*: $\frac{1}{2}-x, -\frac{1}{2}+y, \frac{1}{2}-z$; *v*: $1-x, 1-y, 1-z$; *vi*: $\frac{1}{2}+x, 1\frac{1}{2}-y, \frac{1}{2}+z$; *vii*: $x, -\frac{1}{2}-y, -\frac{1}{2}+z$; *viii*: $\frac{1}{2}+x, \frac{1}{2}-y, -\frac{1}{2}+z$; *ix*: $x, \frac{1}{2}-y, \frac{1}{2}+z$; *x*: $x, \frac{1}{2}-y, -\frac{1}{2}+z$.

and the carboxylate moieties, respectively, and link the molecules into infinite one-dimensional chains which run parallel to the [001] direction; graph set: C(5) for each H-bond motif. H–N(10) forms an intermolecular H-bond with the amide O-atom, O(8), of a molecule related by a center of inversion, thus forming a dimer; graph set: $R_2^2(10)$. The combination of all the intermolecular interactions links the molecules of **20a** into infinite two-dimensional networks which lie perpendicular to the [100] direction.

3. Conclusions – The present studies have shown that *N*-methyl-*N*-phenyl-substituted-6-oxa-1-aza-, 6-thia-1-aza-, and 1,6-diazaspiro[2.5]oct-1-en-2-amines **1a–d** are easily accessible and useful synthons of cyclic, six-membered 4-amino-4-carboxylic acids (Xaa) with the heteroatom in position 1. These 2*H*-azirin-3-amine derivatives were shown to react with thiobenzoic acid in a similar manner to other 2*H*-azirin-3-amines and were successfully applied in the preparation of tripeptides of the type Z-Aib-Xaa-Aib-N(Ph)Me according to the 'azirine/oxazolone method'. They proved to have a similar reactivity to previously studied 2*H*-azirin-3-amines [6].

By X-ray crystallography it was shown that the protected tripeptides **18a–e** all adopt very similar conformations, namely β-turns of type III or III′, analogous to Z-$(Aib)_3$-N(Ph)Me (**22**) [36] (*cf. Tables 1* and *2*), Z-$(Aib)_3$-O*t*Bu [38], Bzl-$(Aib)_3$-OMe [39], and other Z-Aib oligopeptides. Again, the same conformations have been described for peptides containing 1-aminocyclohexane-1-carboxylic acid (Ach) [23] [48] (*cf.* [1]). Thus, the exchange of the carbocyclic Ach for a heterocyclic six-membered α,α-disubstituted α-amino acid does not affect the conformational properties of the tripeptide.

It is especially worth mentioning that Z-Aib-Tht-Aib-N(Ph)Me (**18b**, Tht = 4-amino-tetrahydro-2*H*-thiopyran-4-carboxylic acid) forms a β-turn conformation in the crystal and, most likely, also in solution. It was previously reported [30] that the conformational energy map computed for Ac-Tht-NHMe shows the γ-turn as the lowest minimum, and

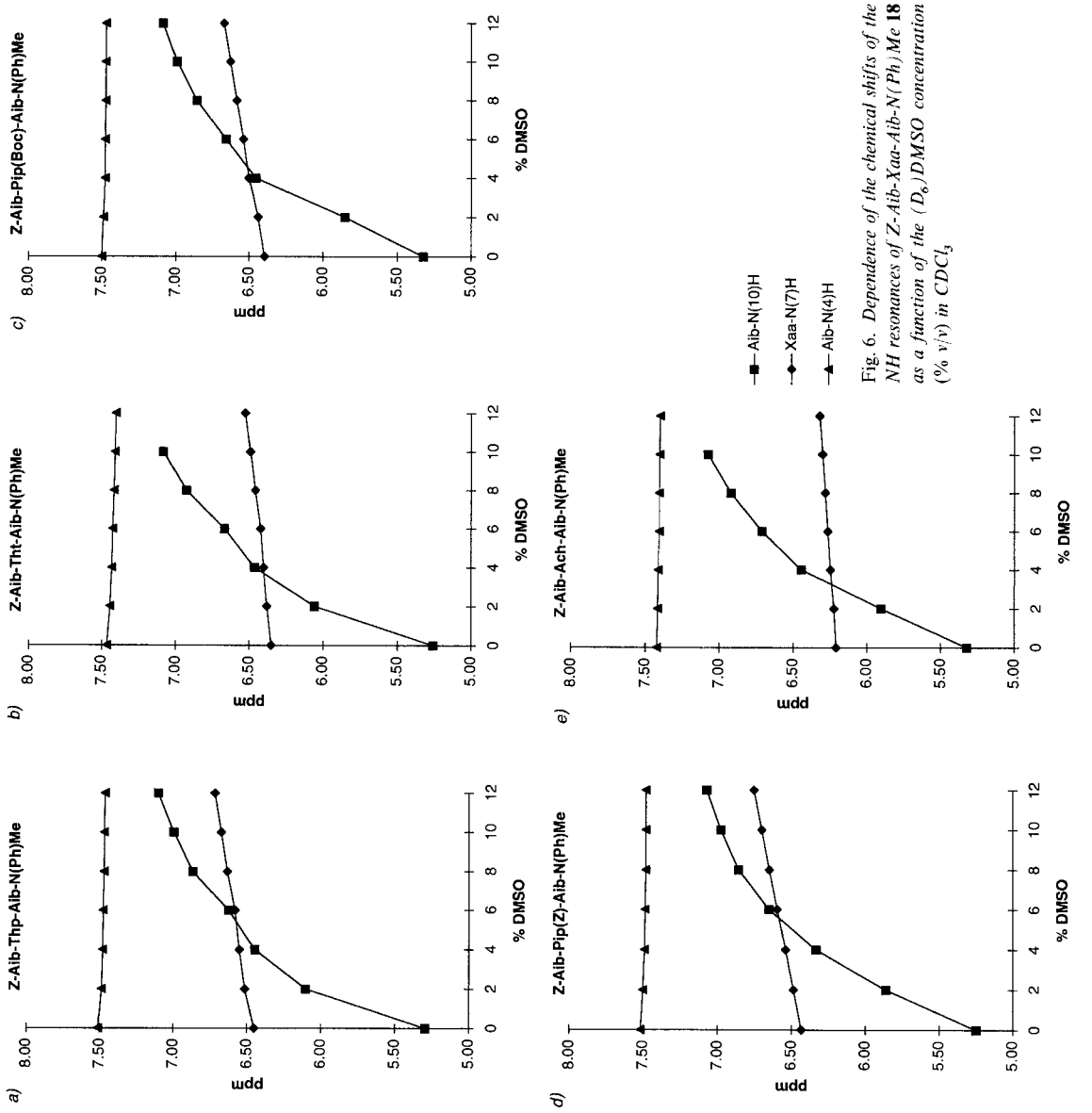

Fig. 6. *Dependence of the chemical shifts of the NH resonances of Z-Aib-Xaa-Aib-N(Ph)Me* **18** *as a function of the (D_6)DMSO concentration (% v/v) in $CDCl_3$*

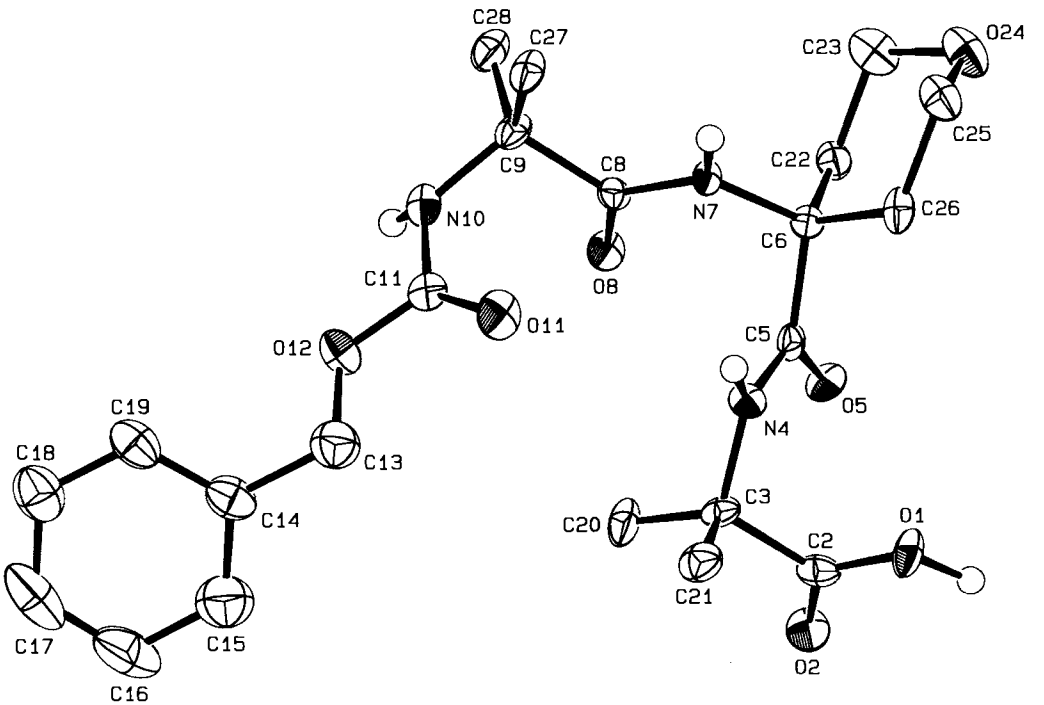

Fig. 7. *ORTEP Plot* [35] *of the molecular structure of* **20a** (with 50% probability ellipsoids)

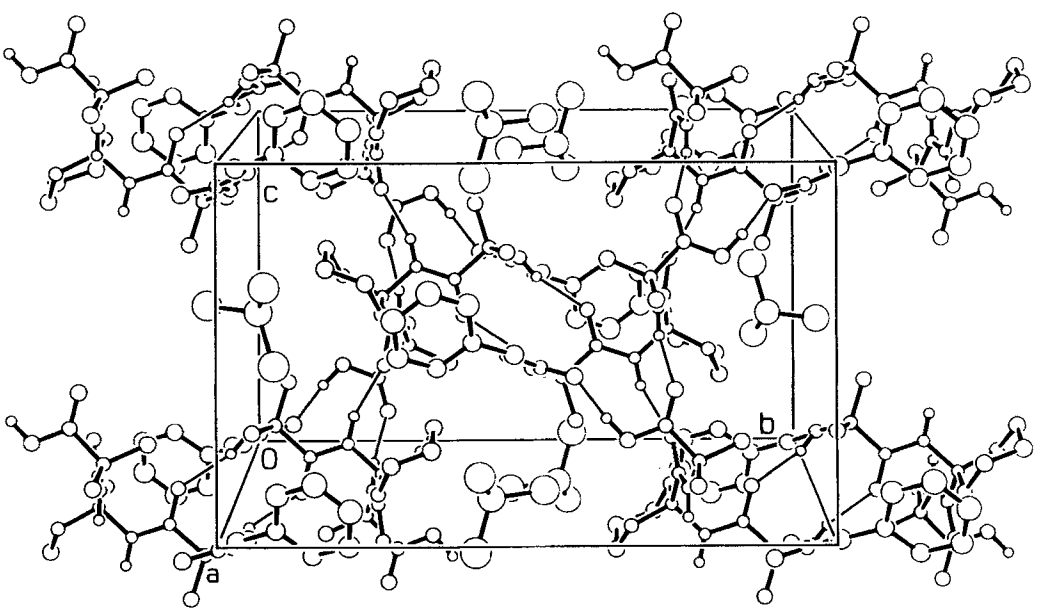

Fig. 8. *Packing diagram of compound* **20a**

^{1}H-NMR and IR studies performed on the *N*-formyl dipeptide For-Tht-Leu-OMe indicated that the γ-turn is adopted in $CDCl_3$ solution. The analogous conformation in solution has been observed for the related For-Ach-Leu-OMe with the carbocyclic six-membered analogue of Tht. From our results it appears that the β-turn is preferred over the γ-turn also for Tht, if the formation of the 4 → 1 H-bond in the peptide is possible. Further studies aimed at proving this hypothesis are in progress.

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

Experimental Part

General. See [11] [15]. Unless otherwise stated, IR spectra in KBr and ^{1}H- (300 MHz) and ^{13}C-NMR spectra (75.6 MHz) in $CDCl_3$. CI-MS: with NH_3 as carrier gas.

1. N-*Methyl*-N-*phenylcarboxamides* **2a–d**. – 1.1. *Tetrahydro*-N-*methyl*-N-*phenyl*-2H-*pyran-4-carboxamide* (**2a**). *Diethyl Tetrahydro*-2H-*pyran-4,4-dicarboxylate*. A suspension of NaH (80%, stabilized with white oil; 12.5 g, 416 mmol) in DMF (400 ml) was cooled to 0°. Then, diethyl malonate (22.22 g, 138 mmol) was dropped slowly into this suspension (evolution of H_2). After stirring for an additional 2 h, 2,2'-dichlorodiethyl ether (**3**; 25.67 g, 179.5 mmol) was added and the mixture heated to 100° and stirred for 3 days. Then, DMF was evaporated and the residue suspended in H_2O and extracted with Et_2O. The org. layer was dried ($MgSO_4$) and the solvent evaporated. Distillation ($77°/7 \cdot 10^{-2}$ mbar) yielded 16.51 g (52%) of diethyl tetrahydro-2*H*-pyran-4,4-dicarboxylate. Colorless oil. IR (film): 2980*m*, 2940*m*, 2870*w*, 1730*s*, 1470*w*, 1445*m*, 1430*w*, 1390*w*, 1370*m*, 1350*w*, 1300*m*, 1250*s*, 1240*s*, 1190*s*, 1160*m*, 1130*s*, 1105*m*, 1070*m*, 1035*m*, 1020*m*, 920*w*, 860*w*. ^{1}H-NMR: 4.10 (*q*, J = 7.1, 2 MeCH_2O); 3.62 (*t*, J = 5.4, CH_2(2), CH_2(6)); 2.04 (*t*, J = 5.4, CH_2(3), CH_2(5)); 1.19 (*t*, J = 7.1, 2 *Me*CH_2O). ^{13}C-NMR: 170.7 (*s*, 2 C=O); 64.5 (*t*, C(2), C(6)); 61.3 (*t*, 2 MeCH_2O); 52.2 (*s*, C(4)); 30.8 (*t*, C(3), C(5)); 13.8 (*q*, 2 *Me*CH_2O). CI-MS: 248 (58, $[M + 1 + NH_3]^+$), 231 (12, $[M + 1]^+$), 187 (43), 160 (100). Anal. calc. for $C_{11}H_{18}O_5$ (230.26): C 57.38, H 7.88; found: C 57.44, H 8.08.

Tetrahydro-2H-*pyran-4,4-dicarboxylic Acid.* Diethyl tetrahydro-2*H*-pyran-4,4-dicarboxylate (10.04 g, 43.59 mmol) was added to a 30% aq. NaOH soln. (25 ml) at 0° and stirred for 3 days at r.t. After acidification with 6N HCl, extraction with AcOEt, drying ($MgSO_4$), and evaporation, recrystallization from AcOEt yielded 5.43 g (72%) of tetrahydro-2*H*-pyran-4,4-dicarboxylic acid. White crystals. M.p. 181–182° (decarboxylation). IR: 3400*m* (br.), 2980*m*, 2940*m*, 2850*m*, 1720*s*, 1445*m*, 1420*m*, 1400*m*, 1385*m*, 1350*w*, 1330*m*, 1315*m*, 1280*s*, 1250*s*, 1240*s*, 1205*s*, 1170*m*, 1140*m*, 1110*m*, 1075*m*, 1035*m*, 1020*w*, 930*s*, 895*m*, 800*m*, 760*m*, 740*m*. ^{1}H-NMR ((D$_6$)DMSO): 12.79 (br. *s*, 2 COOH); 3.43 (*t*, J = 5.1, CH_2(2), CH_2(6)); 1.78 (*t*, J = 5.1, CH_2(3), CH_2(5)). ^{13}C-NMR ((D$_6$)DMSO): 172.3 (*s*, 2 C=O); 64.0 (*t*, C(2), C(6)); 51.4 (*s*, C(4)); 30.8 (*t*, C(3), C(5)). CI-MS: 209 (22.5, $[M + 1 + 2\ NH_3]^+$), 192 (100, $[M + 1 + NH_3]^+$). Anal. calc. for $C_7H_{10}O_5$ (174.15): C 48.28, H 5.79; found: C 48.08, H 6.00.

Tetrahydro-2H-*pyran-4-carboxylic Acid* (**4**). Tetrahydro-2*H*-pyran-4,4-dicarboxylic acid (8.693 g, 49.92 mmol) was heated to 180° until the CO_2 evolution ceased (2 h). Recrystallization of the residue from toluene gave 5.533 g (85%) of **4**. Colorless crystals. M.p. 82–84°. IR ($CHCl_3$): 3000*m*, 2960*s*, 2930*m*, 2860*s*, 1710*s*, 1470*w*, 1450*m*, 1420*m*, 1390*m*, 1350*w*, 1335*w*, 1320*m*, 1295*s*, 1280*s*, 1240*s*, 1190*m*, 1170*m*, 1130*s*, 1115*m*, 1090*s*, 1065*m*, 1040*m*, 1015*m*, 980*m*, 935*m*, 910*m*, 860*m*, 820*m*. ^{1}H-NMR: 9.35 (br. *s*, COOH); 3.99 (*dt*, J = 11.6, 3.6, 2 H_{eq} of CH_2(2) and CH_2(6)); 3.46 (*td*, J = 11.5, 3.0, 2 H_{ax} of CH_2(2) and CH_2(6)); 2.65–2.55 (*m*, CH(4)); 1.9–1.75 (*m*, CH_2(3), CH_2(5)). ^{13}C-NMR: 180.2 (*s*, C=O); 67.0 (*t*, C(2), C(6)); 39.8 (*d*, C(4)); 28.4 (*t*, C(3), C(5)). CI-MS: 148 (100, $[M + 1 + NH_3]^+$). Anal. calc. for $C_6H_{10}O_3$ (130.14): C 55.37, H 7.74; found: C 55.56, H 7.69.

Tetrahydro-2H-*pyran-4-carbonyl Chloride* (**5**). At r.t., $SOCl_2$ (4.5 ml, 62 mmol) was added to **4** (5.419 g, 41.64 mmol), and the mixture was heated under reflux until the evolution of SO_2 ceased (45 min). Distillation at 80°/20 mbar yielded 5.617 g (91%) of **5**. IR (film): 2960*m*, 2930*m*, 2850*m*, 2760*w*, 2700*w*, 1795*s*, 1730*w*, 1470*w*, 1450*m*, 1390*m*, 1330*w*, 1270*m*, 1260*m*, 1240*m*, 1140*m*, 1115*m*, 1090*m*, 1070*m*, 1050*m*, 1010*m*, 985*m*, 965*s*, 940*m*, 870*w*, 820*m*, 760*s*. ^{1}H-NMR: 3.99 (*dt*, J = 11.8, 3.6, 2 H_{eq} of CH_2(2) and CH_2(6); 3.44 (*td*, J = 11.4, 2.4, 2 H_{ax} of CH_2(2) and CH_2(6)); 3.0–2.9 (*m*, CH(4)); 2.03 ('*dd*', 2 H_{eq} of CH_2(3) and CH_2(5)); 1.95–1.8 (*m*, 2 H_{ax} of CH_2(3) and CH_2(5)). ^{13}C-NMR: 175.8 (*s*, C=O); 66.6 (*t*, C(2), C(6)); 51.8 (*d*, C(4)); 28.9 (*t*, C(3), C(5)).

Amid **2a**. *N*-Methylaniline (4.6 ml, 42 mmol) and Et_3N (5.8 ml, 42 mmol) were added at 0° to a soln. of **5** (5.617 g, 37.80 mmol) in CH_2Cl_2. After stirring for 2 h, the solvent was evaporated and the residue dissolved in

AcOEt. After filtration and evaporation, purification by FC (SiO_2, hexane/AcOEt 1:2) yielded 8.157 g (98%) of **2a**. Colorless solid. M.p. 84–85°. IR ($CHCl_3$): 3060*w*, 3000*s*, 2960*m*, 2920*m*, 2850*m*, 2760*w*, 2700*w*, 1640*s*, 1595*s*, 1500*s*, 1470*m*, 1445*s*, 1430*s*, 1395*s*, 1385*s*, 1350*s*, 1315*m*, 1300*s*, 1265*m*, 1240*s*, 1170*w*, 1120*s*, 1085*s*, 1050*w*, 1025*m*, 1010*w*, 1000*w*, 980*m*, 940*w*, 915*w*, 870*m*, 820*m*, 700*s*. ^{1}H-NMR: 7.45–7.35, 7.2–7.15 (2*m*, 5 arom. H); 3.89 (*dd*, $J \approx 11.3$, 3.2, 2 H_{eq} of CH_2(2) and CH_2(6)); 3.26 (*s*, MeN); 3.13 (*t*, $J \approx 11.7$, 2 H_{ax} of CH_2(2) and CH_2(6)); 2.45–2.35 (*m*, CH(4)); 1.91 (*qd*, $J \approx 12.4$, 4.3, 2 H_{ax} of CH_2(3) and CH_2(5)); 1.48 (*d*, $J \approx 12.9$, 2 H_{eq} of CH_2(3) and CH_2(5)). ^{13}C-NMR: 174.6 (*s*, C=O); 143.9 (*s*, 1 arom. C); 129.9, 128.0, 127.2 (3*d*, 5 arom. CH); 67.0 (*t*, C(2), C(6)); 38.5 (*d*, C(4)); 37.6 (*q*, MeN); 29.1 (*t*, C(3), C(5)). CI-MS: 220 (100, $[M + 1]^+$). Anal. calc. for $C_{13}H_{17}NO_2$ (219.28): C 71.21, H 7.81, N 6.39; found: C 71.06, H 8.01, N 6.61.

1.2. N-*Methyl*-N-*phenyltetrahydro-2*H-*thiopyran-4-carboxamide* (**2b**). *Tetrahydro-2*H-*thiopyran-4-carbonitrile* (**8**). A soln. of *t*-BuOK (13.87 g, 123.6 mmol) in *t*-BuOH/1,2-dimethoxyethan 1:1 (200 ml) was added at 0° to a soln. of tetrahydro-2*H*-thiopyran-4-one (**6**; 7.143 g, 61.48 mmol) and tosylmethyl isocyanide (**7**; 13.21 g, 67.63 mmol) in 1,2-dimethoxyethane (250 ml). The soln. was stirred for 3 h at r.t. After addition of Et_2O, the mixture was washed with 5% $NaHCO_3$ soln., dried ($MgSO_4$), and evaporated. Distillation at 80°/0.8 mbar gave 6.663 g (85%) of **8**. Colorless oil. IR (film): 2940*m*, 2920*s*, 2850*w*, 2240*m*, 1445*m*, 1430*s*, 1360*w*, 1290*m*, 1270*m*, 1245*w*, 1190*w*, 1180*w*, 1160*w*, 1030*w*, 1000*w*, 985*w*, 960*m*, 940*w*, 910*m*. ^{1}H-NMR: 2.9–2.8 (*m*, 3H); 2.6–2.55 (*m*, 2H); 2.2–2.05 (*m*, 4H). ^{13}C-NMR: 121.1 (*s*, CN); 30.1 (*t*, C(3), C(5)); 27.9 (*d*, C(4)); 25.9 (*t*, C(2), C(6)). EI-MS: 128 (38), 127 (100, $M^{+\cdot}$), 126 (23), 99 (35), 86 (21), 81 (20), 80 (32), 74 (23), 68 (39), 67 (35), 61 (39), 60 (23), 59 (28), 54 (31), 53 (21). Anal. calc. for C_6H_9NS (127.21): C 56.65, H 7.13, N 11.01, S 25.21; found: C 56.95, H 7.23, N 10.70, S 25.47.

*Tetrahydro-2*H-*thiopyran-4-carboxylic Acid* (**9**). Nitrile **8** (6.663 g, 52.38 mmol) was dissolved in a small amount of EtOH and added to a soln. of NaOH (21.04 g, 526 mmol) in H_2O (90 ml) and EtOH (45 ml). The mixture was heated under reflux and stirred for 5 h. After cooling to 0°, conc. HCl soln. (60 ml) was added, EtOH was evaporated, and the residue was extracted 3× with CH_2Cl_2. After drying of the org. layers ($MgSO_4$) and evaporation of the solvent, recrystallization of the crude product from Et_2O gave 7.414 g (97%) of **9**. White crystals. M.p. 109–110°. IR: 3500*w*, 3000*m*, 2950*s*, 2920*s*, 2860*m*, 1710*s*, 1450*m*, 1430*s*, 1310*m*, 1275*m*, 1230*s*, 1180*m*, 1120*w*, 1040*w*, 990*m*, 960*m*, 940*m*, 910*m*, 895*m*. ^{1}H-NMR: 9.1 (br. *s*, COOH); 2.75–2.65 (*m*, 4H); 2.43 (*tt*, $J = 10.8$, 3.4, 1H); 2.3–2.2 (*m*, 2H); 1.95–1.8 (*m*, 2H). ^{13}C-NMR: 181.0 (*s*, C=O); 42.2 (*d*, C(4)); 29.5, 27.5 (2*t*, 4CH_2). EI-MS: 146 (100, $M^{+\cdot}$), 128 (20), 100 (71), 99 (21), 87 (28), 86 (33), 85 (28), 74 (25), 73 (31), 67 (23), 61 (34), 55 (30). Anal. calc. for $C_6H_{10}O_2S$ (146.21): C 49.29, H 6.87, S 21.93; found: C 49.06, H 6.56, S 21.94.

Amide **2b**. To an ice-cooled soln. of **9** (8.477 g, 57.98 mmol) in CH_2Cl_2 (350 ml), oxalyl chloride (6.5 ml, 76 mmol) was added. The mixture was stirred at 0° (4 h) and for an additional hour at r.t., again cooled to 0°, and Et_3N (21.5 ml, 154 mmol) and *N*-methylaniline (8.3 ml, 76 mmol) were added. After stirring at r.t. (16 h), the mixture was cooled to 0° and acidified with 6N HCl to pH *ca.* 1. Washing with 1N HCl and 5% Na_2CO_3 soln., extraction of the aq. layers with CH_2Cl_2, drying ($MgSO_4$), and evaporation yielded a crude product, which was purified by FC (SiO_2, hexane/AcOEt 3:1) and recrystallization from toluene: 12.24 g (90%) of **2b**. Colorless crystals. M.p. 102–103°. IR ($CHCl_3$): 3000*s*, 2960*m*, 2920*m*, 2850*w*, 1720*m*, 1650*s*, 1600*s*, 1500*s*, 1450*m*, 1430*s*, 1395*s*, 1355*m*, 1310*w*, 1270*m*, 1260*m*, 1240*m*, 1190*w*, 1180*w*, 1120*m*, 1075*w*, 1030*w*, 980*m*, 910*m*, 700*s*. ^{1}H-NMR: 7.45–7.35, 7.2–7.15 (2*m*, 5 arom. H); 3.24 (*s*, MeN); 2.55–2.5, 2.45–2.35, 2.3–2.25 (3*m*, 5H); 2.05–1.9 (*m*, CH_2(3), CH_2(5)). ^{13}C-NMR: 174.9 (*s*, C=O); 143.9 (*s*, 1 arom. C); 129.9, 128.0, 127.2 (3*d*, 5 arom. CH); 40.8 (*d*, C(4)); 37.5 (*q*, MeN); 30.1, 27.6 (2*t*, 4 CH_2). EI-MS: 236 (64), 235 (100, $M^{+\cdot}$), 162 (28), 129 (33), 107 (33), 101 (22). Anal. calc. for $C_{13}H_{17}NOS$ (235.35): C 66.34, H 7.28, N 5.95, S 13.62; found: C 66.06, H 7.13, N 5.99, S 13.64.

1.3. tert-*Butyl 4-[Methyl(phenyl)carbamoyl]piperidine-1-carboxylate* (**2c**). *1-(*tert-*Butyl) 4-Ethyl Piperidine-1,4-dicarboxylate*. Ethyl piperidine-4-carboxylate (**10**; 14.09 g, 89.62 mmol) and Et_3N (10.05 g, 108 mmol) were dissolved in CH_2Cl_2 (250 ml) and cooled to 0°. A soln. of di(*tert*-butyl) dicarbonate (19.96 g, 89.62 mmol) in CH_2Cl_2 (50 ml) was added, and the mixture was stirred for 16 h at r.t. After evaporation, distillation of the residue at 125°/7 · 10^{-2} mbar gave 22.90 g (99%) of 1-(*tert*-butyl) 4-ethyl piperidine-1,4-dicarboxylate. Colorless oil. IR (film): 2965*m*, 2920*m*, 2855*w*, 1725*s*, 1690*s*, 1475*m*, 1460*m*, 1450*m*, 1420*s*, 1390*m*, 1360*m*, 1310*m*, 1270*m*, 1245*m*, 1160*s*, 1040*m*, 940*w*, 865*w*, 810*w*, 765*w*. ^{1}H-NMR: 4.11 (*q*, $J = 7.1$, MeCH_2O); 3.99 (*d*, $J = 11.5$, 2H_{eq} of CH_2(2) and CH_2(6)); 2.80 (*t*, $J = 11.5$, 2H_{ax} of CH_2(2) and CH_2(6)); 2.45–2.35 (*m*, CH(4)); 1.9–1.8, 1.65–1.55 (2*m*, CH_2(3), CH_2(5)); 1.42 (*s*, Me_3C); 1.22 (*t*, $J = 7.1$, *Me*CH_2O). ^{13}C-NMR: 174.5 (*s*, C=O); 154.6 (*s*, OCONH); 79.4 (*s*, Me_3C); 60.4 (*t*, MeCH_2O); 43.0 (*d*, C(4)); 41.1 (*t*, C(2), C(6)); 28.4 (*t*, C(3), C(5)); 27.9 (*q*, Me_3C); 14.1 (*q*, *Me*CH_2O). CI-MS: 258 (10, $[M + 1]^+$), 219 (40), 202 (13), 158 (100). Anal. calc. for $C_{13}H_{23}NO_4$ (257.33): C 60.68, H 9.01, N 5.44; found: C 60.50, H 9.09, N 5.24.

*1-(*tert*-Butyl) 4-Hydrogen Piperidine-1,4-dicarboxylate* (**11**). A soln. of (1-(*tert*-butyl) 4-ethyl piperidine-1,4-dicarboxylate (14.79 g, 57.5 mmol) in THF/MeOH/H_2O 2:1:1 (300 ml) was cooled to 0°. After addition of LiOH · H_2O (6.04 g, 144 mmol), the soln. was stirred for 2 h at r.t., cooled again to 0°, and acidified with 6N HCl to pH *ca.* 1. Then, the solvents were evaporated, and the aq. residue was extracted with CH_2Cl_2. The org. layer was dried ($MgSO_4$), the solvent evaporated, and the residue recrystallized from toluene: 12.52 g (95%) of **11**. Colorless crystals. M.p. 147–148°. IR ($CHCl_3$): 2990*m*, 2970*m*, 2920*m*, 2850*m*, 1705*s*, 1670*s*, 1475*m*, 1465*m*, 1450*m*, 1420*m*, 1390*m*, 1365*m*, 1270*m*, 1240*m*, 1160*s*, 1120*m*, 1080*w*, 940sh, 925*w*, 860*w*, 810*w*. ^{1}H-NMR: 3.95 (*d*, $J \approx 11.9$, 2 H_{eq} of CH_2(2) and CH_2(6)); 2.79 (*t*, $J \approx 11.4$, 2 H_{ax} of CH_2(2) and CH_2(6)); 2.5–2.35 (*m*, CH(4)); 1.85–1.8, 1.65–1.5 (2*m*, CH_2(3), CH_2(5)); 1.39 (*s*, Me_3C). ^{13}C-NMR: 180.0 (*s*, C=O); 154.8 (*s*, OCONH); 79.8 (*s*, Me_3C); 43.0 (*d*, C(4)); 40.8 (*t*, C(2), C(6)); 28.4 (*t*, C(3), C(5)); 27.7 (*q*, Me_3C). CI-MS: 247 (46, $[M + 1 + NH_3]^+$), 230 (39, $[M + 1]^+$), 191 (100), 130 (42). Anal. calc. for $C_{11}H_{19}NO_4$ (229.28): C 57.62, H 8.35, N 6.11; found: C 57.38, H 8.61, N 6.32.

Amide **2c**. a) *Reaction without 1-Hydroxy-1*H*-benzotriazol* (HOBt). *N*-Methylaniline (68 mg, 0.64 mmol) and DCC (96 mg, 0.46 mmol) were added to a soln. of **11** (105 mg, 0.46 mmol) in MeCN (3 ml). After stirring for 16 h at 50°, the solvent was evaporated and the residue dissolved in AcOEt and washed with 5% citric acid, brine, and 10% $NaHCO_3$ soln. The aq. layers were extracted with AcOEt, and the combined org. layers were dried ($MgSO_4$). Evaporation and purification by FC (SiO_2, hexane/AcOEt 4:1) yielded 120 mg (60%) of tert-*butyl 4-[cyclohexyl(cyclohexylcarbamoyl)carbamoyl]piperidine-1-carboxylate* (**12**) and 48 mg (33%) of **2c**. **12**: Colorless solid. M.p. 175°. IR ($CHCl_3$): 3420*w*, 2980sh, 2920*s*, 2850*m*, 1680*m* (br.), 1490*m*, 1445*m*, 1420*m*, 1390*m*, 1360*m*, 1340*m*, 1270*m*, 1160*s*, 1120*m*, 1075*m*, 1035*m*, 965*w*, 890*w*. ^{1}H-NMR: 6.13 (br. *s*, NH); 4.1–3.95 (*m*, 3H); 3.65–3.6 (*m*, 1H); 2.65–2.5 (*m*, 3H); 1.95–1.85 (*m*, 1H); 1.7–1.5 (*m*, 15H); 1.4–1.05 (*m*, 17H). ^{13}C-NMR: 174.2 (*s*, C=O); 154.7, 154.1 (2*s*, OCONH, NCONH); 79.6 (*s*, Me_3C); 54.6, 50.1 (2*d*, 2CH–N); 43.1 (*t*, C(2), C(6)); 42.0 (*d*, C(4)); 32.7, 31.1, 28.9, 26.1, 25.4, 25.3, 24.7 (7*t*, 12CH_2); 28.4 (*q*, Me_3C). CI-MS: 436 (29, $[M + 1]^+$), 131 (100). Anal. calc. for $C_{24}H_{41}N_3O_4$ (435.61): C 66.18, H 9.49, N 9.65; found: C 65.99, H 9.45, N 9.48.

b) *Reaction with HOBt*. Reaction of **11** (5.49 g, 23.9 mmol), *N*-methylaniline (3.15 ml, 28.9 mmol), DCC (4.95 g, 24.0 mmol), and HOBt (3.56 g, 26.4 mmol) in MeCN (300 ml) as described above: 5.87 g (70%) of **2c**. Colorless crystals. M.p. 119–120°. IR ($CHCl_3$): 3680*w*, 3620*w*, 3440*w* (br.), 3000*s*, 2970*m*, 2850*w*, 1670*s*, 1640*s*, 1595*m*, 1495*m*, 1465*m*, 1450*m*, 1420*s*, 1390*m*, 1365*m*, 1350*m*, 1310*m*, 1280*m*, 1165*s*, 1130*m*, 1025*w*, 1115*w*, 1000*w*, 990*w*, 935*w*, 865*w*, 700*w*. ^{1}H-NMR: 7.4–7.3, 7.15–7.1 (2*m*, 5 arom. H); 3.98 (br. *s*, 2 H_{eq} of CH_2(2) and CH_2(6)); 3.18 (*s*, MeN); 2.35–2.25 (*m*, 2 H_{ax} of CH_2(2) and CH_2(6), CH(4)); 1.7–1.45 (*m*, CH_2(3), CH_2(5)); 1.36 (*s*, Me_3C). ^{13}C-NMR: 174.6 (*s*, C=O); 154.5 (*s*, OCONH); 143.7 (*s*, 1 arom. C); 129.8, 127.9, 127.1 (3*d*, 5 arom. CH); 79.3 (*s*, Me_3C); 42.8 (*t*, C(2), C(6)); 39.2 (*d*, C(4)); 37.5 (*q*, MeN); 28.4 (*t*, C(3), C(5)); 28.3 (*q*, Me_3C). CI-MS: 320 (20), 319 (100, $[M + 1]^+$). Anal. calc. for $C_{18}H_{26}N_2O_3$ (318.42): C 67.90, H 8.23, N 8.80; found: C 68.08, H 8.35, N 8.60.

1.4. *1-Benzyl-*N*-methyl-*N*-phenylpiperidine-4-carboxamide* (**2d**). *Ethyl 1-Benzylpiperidine-4-carboxylate*. To a soln. of ethyl piperidine-4-carboxylate (**10**; 10.74 g, 68.3 mmol) in DMF (50 ml), benzyl chloride (9.8 ml, 82.7 mmol) and K_2CO_3 (14.15 g, 102 mmol) were added. The mixture was warmed to 120° and stirred for 3 h. Then, the solvent was evaporated, the residue dissolved in AcOEt, and the soln. washed twice with 5% $NaHCO_3$ soln. The aq. layer was extracted with AcOEt and the combined org. phase dried ($MgSO_4$), and evaporated. Distillation at 100°/8 · 10^{-2} mbar ('Kugelrohr') yielded 11.82 g (70%) of ethyl 1-benzylpiperidine-4-carboxylate. Colorless oil. IR (film): 3060*w*, 3020*w*, 2940*m*, 2800*m*, 2760*m*, 1730*s*, 1600*w*, 1495*m*, 1470*w*, 1450*m*, 1390*w*, 1370*m*, 1340*w*, 1320*m*, 1285*m*, 1270*m*, 1180*s*, 1165*s*, 1145*w*, 1050*s*, 1030*m*, 995*m*, 740*m*, 700*m*. ^{1}H-NMR: 7.35–7.2 (*m*, 5 arom. H); 4.12 (*q*, $J = 7.1$, MeCH_2O); 3.49 (*s*, PhCH_2); 2.85 (*dt*, $J \approx 11.6$, 6.6, 2 H_{eq} of CH_2(2) and CH_2(6)); 2.27 (*tt*, $J = 10.9$, 4.2, CH(4)); 2.02 (*td*, $J \approx 11.3$, 2.5, 2 H_{ax} of CH_2(2) and CH_2(6)); 1.9–1.75 (*m*, CH_2(3), CH_2(5)); 1.24 (*t*, $J = 7.1$, *Me*CH_2O). ^{13}C-NMR: 175.3 (*s*, C=O); 138.3 (*s*, 1 arom. C); 129.1, 128.2, 127.0 (3*d*, 5 arom. CH); 63.2, 60.3 (2*t*, PhCH_2, MeCH_2O); 52.9 (*t*, C(2), C(6)); 41.2 (*d*, C(4)); 28.3 (*t*, C(3), C(5)); 14.2 (*q*, *Me*CH_2O). CI-MS: 249 (20), 248 (100, $[M + 1]^+$). Anal. calc. for $C_{15}H_{21}NO_2$ (247.34): C 72.84, H 8.56, N 5.66; found: C 72.60, H 8.40, N 5.50.

Amide **2d**. To a soln. of ethyl 1-benzylpiperidine-4-carboxylate (11.61 g, 46.95 mmol) in THF (30 ml), 4N NaOH (25 ml) was added and the soln. stirred at r.t. for 3 days. After cooling to 0°, 1N HCl was added until pH 7 was reached. The solvent was evaporated and the residue dried *i.v.* Then, $SOCl_2$ (25 ml) was added and the stirred mixture was heated to reflux for 2 h. Excess $SOCl_2$ was evaporated, the residue suspended in CH_2Cl_2 (50 ml), and the mixture cooled to 0°. After the addition of *N*-methylaniline (10 ml, 92 mmol) and Et_3N (12 ml, 86 mmol), the mixture was stirred at r.t. for 48 h. The soln. was washed with 5% $NaHCO_3$ soln., the aq. layer extracted with CH_2Cl_2, the org. phase dried ($MgSO_4$), and the solvent evaporated. FC (twice, SiO_2, AcOEt/Et_2O 3:1) and distillation ('Kugelrohr', 150°/4 · 10^{-5} mbar) yielded 9.03 g (62%) of **2d**. Pale yellow viscous oil.

IR (film): 3060*m*, 3020*m*, 2940*m*, 2800*m*, 2760*m*, 1640*s*, 1600*s*, 1500*s*, 1450*m*, 1430*m*, 1390*m*, 1365*m*, 1355*m*, 1340*m*, 1315*w*, 1300*m*, 1270*m*, 1240*m*, 1125*m*, 1110*m*, 1070*w*, 1030*m*, 990*m*. ^{1}H-NMR: 7.45–7.15 (*m*, 10 arom. H); 3.40 (*s*, PhCH_2); 3.24 (*s*, MeN); 2.82 (*d*, J = 11.3, 2 H_{eq} of CH_2(2) and CH_2(6)); 2.25–2.15 (*m*, CH(4)); 1.95–1.8 (*m*, 2 H_{ax} of CH_2(2) and CH_2(6)); 1.70 (*t*, J = 11.5, 2 H_{ax} of CH_2(3) and CH_2(5)); 1.56 (*d*, J = 12.5, 2 H_{eq} of CH_2(3) and CH_2(5)). ^{13}C-NMR: 175.3 (*s*, C=O); 144.0, 138.3 (2*s*, 2 arom. C); 129.7, 129.0, 128.0, 127.7, 127.1, 126.8 (6*d*, 10 arom. CH); 63.0 (*t*, PhCH_2); 52.7 (*t*, C(2), C(6)); 39.3 (*d*, C(4)); 37.4 (*q*, MeN); 28.6 (*t*, C(3), C(5)). CI-MS: 310 (21), 309 (100, $[M + 1]^+$). Anal. calc. for $C_{20}H_{24}N_2O$ (308.42): C 77.89, H 7.84, N 9.08; found: C 78.10, H 7.94, N 8.99.

2. *Heterospirocyclic* N-*Methyl*-N-*phenyl*-2H-*azirin-3-amines* (**1a–d**). 2.1. *General Procedure A*. To a soln. of *N*-methylanilide **2** in dry THF at 0° under Ar, 1.2 equiv. of LDA (2M in THF/heptane/ethylbenzene) were added, and the mixture was stirred for 90 min at 0°. Then, diphenyl phosphorochloridate (DPPCl, 1.1 equiv.) was added *via* a syringe at 0°. This soln. was stirred for 30 min at 0°, warmed to r.t., and stirred for an additional 24 h. The solid that precipitated was removed by filtration under Ar and the THF soln. poured into a flask containing 3 equiv. of NaN_3. This mixture was stirred for 3 days at r.t., then Et_2O was added, the mixture filtered through a *Celite* pad, and the solvent evaporated. The residue was dissolved in CH_2Cl_2, the soln. washed with 5% $NaHCO_3$ soln. (3×), and the aq. layer was washed twice with CH_2Cl_2. The combined org. layer was dried ($MgSO_4$) and evaporated. Purification by FC (SiO_2, AcOEt/Et_2O 3:1) yielded the azirines **1**.

2.2. N-*Methyl*-N-*phenyl*-6-*oxa*-1-*azaspiro*[2.5]*oct*-1-*en*-2-*amine* (**1a**). According to *Procedure A*, **2a** (10.035 g, 45.76 mmol) in THF (40 ml) was treated with LDA (37 ml, 55 mmol), DPPCl (10.5 ml, 50.8 mmol), and NaN_3 (8.964 g, 137.9 mmol): 5.745 g (58%) of **1a**. Colorless solid. M.p. 87–89°. IR ($CHCl_3$): 3040*w*, 2970*s*, 2910*m*, 2860*m*, 1755*s*, 1600*s*, 1500*s*, 1470*m*, 1460*w*, 1420*m*, 1190*m*, 1165*m*, 1100*s*, 1035*m*, 1025*m*, 1010*m*, 960*w*, 840*w*, 820*w*. ^{1}H-NMR: 7.45–7.35, 7.15–7.1 (2*m*, 5 arom. H); 4.0–3.9 (*m*, CH_2(5), CH_2(7)); 3.47 (*s*, MeN); 2.16, 1.36 (2 br. *s*, CH_2(4), CH_2(8)). ^{13}C-NMR: 142.2 (*s*, 1 arom. C); 129.3, 123.4, 116.6 (3*d*, 5 arom. CH); 66.6 (*t*, C(5), C(7)); 36.1 (*t*, C(4), C(8)); C(2), C(3), and MeN could not be detected. CI-MS: 217 (100, $[M + 1]^+$), 216 (59). Anal. calc. for $C_{13}H_{16}N_2O$ (216.28): C 72.19, H 7.46, N 12.95; found: C 72.02, H 7.24, N 12.72.

2.3. N-*Methyl*-N-*phenyl*-6-*thia*-1-*azaspiro*[2.5]*oct*-1-*en*-2-*amine* (**1b**). According to *Procedure A*, **2b** (5.378 g, 22.85 mmol) in THF (50 ml) was treated with LDA (18.5 ml, 27.7 mmol), DPPCl (5.2 ml, 25 mmol), and NaN_3 (4.463 g, 68.65 mmol): 3.735 g (70%) of **1b**. Colorless solid. M.p. 73–75°. IR ($CHCl_3$): 2980*m*, 2930*m*, 2820*w*, 1755*s*, 1600*s*, 1500*s*, 1455*w*, 1425*m*, 1350*m*, 1315*m*, 1270*m*, 1240*m*, 1190*m*, 1140*w*, 1100*m*, 1035*m*, 1010*m*, 970*m*, 920*w*, 690*m*. ^{1}H-NMR ((D_6)DMSO, 353 K): 7.45–7.35, 7.15–7.1 (2*m*, 5 arom. H); 3.42 (*s*, MeN); 2.94 (*ddd*, J = 13.3, 10.1, 3.2, 2 H_{ax} of CH_2(5) and CH_2(7)); 2.65–2.55 (*m*, 2 H_{eq} of CH_2(5) and CH_2(7)); 2.11 (*ddd*, J = 13.6, 10.1, 3.5, 2 H_{ax} of CH_2(4) and Cl_2(8)); 1.60 (*ddd*, J = 13.6, 6.1, 3.2, 2 H_{eq} of CH_2(4) and CH_2(8)). ^{13}C-NMR ((D_6)DMSO, 353 K): 166.5 (*s*, C(2)); 142.0 (*s*, 1 arom. C); 128.7, 122.7, 116.7 (3*d*, 5 arom. CH); 41.8 (*s*, C(3)); 36.5 (*t*, C(4), C(8)); 35.2 (*q*, MeN); 26.2 (*t*, C(5), C(7)). CI-MS: 233 (100, $[M + 1]^+$). Anal. calc. for $C_{13}H_{16}N_2S$ (232.35): C 67.20, H 6.94, N 12.06, S 13.80; found: C 67.13, H 6.92, N 11.79, S 13.91.

2.4. tert-*Butyl* 2-[*Methyl*(*phenyl*)*amino*]-1,6-*diazaspiro*[2.5]*oct*-1-*ene*-6-*carboxylate* (**1c**). According to *Procedure A*, **2c** (1.845 g, 5.794 mmol) in THF (40 ml) was treated with LDA (4.8 ml, 7.2 mmol), DPPCl (1.4 ml, 6.8 mmol), and NaN_3 (1.14 g, 17.5 mmol): 1.265 g (69%) of **1c**. Colorless solid. M.p. 82–83°. IR ($CHCl_3$): 3000*m*, 2980*m*, 2910*m*, 2860*w*, 1750*s*, 1680*s*, 1600*m*, 1500*m*, 1480*m*, 1450*m*, 1425*s*, 1390*m*, 1370*m*, 1350*m*, 1320*m*, 1275*m*, 1240*s*, 1170*s*, 1120*m*, 1100*m*, 1030*m*, 1020*m*, 1010*m*, 995*w*, 950*w*, 860*w*, 815*w*. ^{1}H-NMR: 7.45–7.1 (*m*, 5 arom. H); 4.00 (br. *s*, 2H of CH_2(5), CH_2(7)); 3.47 (*s*, MeN); 3.38 (br. *s*, 2H of CH_2(5), CH_2(7)); 2.05 (br. *s*, 2H of CH_2(4), CH_2(8)); 1.49 (*s*, Me_3C); 1.32 (br. *s*, 2H of CH_2(4), CH_2(8)). ^{13}C-NMR: 154.8 (*s*, OCONH); 142.3 (*s*, 1 arom. C); 129.5, 123.6, 116.7 (3*d*, 5 arom. CH); 79.6 (*s*, Me_3C); 42.3 (*t*, C(5), C(7)); 35.2 (*t*, C(4), C(8)); 28.5 (*q*, Me_3C); C(2), C(3), and MeN could not be detected. CI-MS: 317 (17), 316 (100, $[M + 1]^+$). Anal. calc. for $C_{18}H_{25}N_3O_2$ (315.42): C 68.54, H 7.99, N 13.32; found: C 68.40, H 8.13, N 13.08.

2.5. 6-*Benzyl*-N-*methyl*-N-*phenyl*-1,6-*diazaspiro*[2.5]*oct*-1-*en*-2-*amine* (**1d**). According to *Procedure A*, **2d** (1.134 g, 3.677 mmol) in THF (25 ml) was treated with LDA (3 ml, 4.5 mmol), DPPCl (840 µl, 4.06 mmol), and NaN_3 (730 mg, 11.2 mmol): 516 mg (46%) of **1d**. Colorless oil. IR ($CHCl_3$): 2950*m*, 2910*w*, 2800*m*, 2760*w*, 1750*s*, 1600*s*, 1505*s*, 1470*w*, 1455*w*, 1420*w*, 1365*w*, 1350*w*, 1340*w*, 1320*m*, 1300*m*, 1270*w*, 1250*m*, 1190*w*, 1100*m*, 1070*w*, 1035*m*, 990*w*, 700*m*. ^{1}H-NMR ($CDCl_3$, 318 K): 7.4–7.05 (*m*, 10 arom. H); 3.61 (*s*, PhCH_2); 3.44 (*s*, MeN); 2.85–2.75 (*m*, 2 H_{eq} of CH_2(5) and CH_2(7)); 2.7–2.6 (*m*, 2 H_{ax} of CH_2(5) and CH_2(7)); 2.25–2.1 (*m*, 2 H_{ax} of CH_2(4) and CH_2(8)); 1.45–1.35 (*m*, 2 H_{eq} of CH_2(4) and CH_2(8)). ^{13}C-NMR ($CDCl_3$, 318 K): 167.7 (*s*, C=N); 142.6, 138.7 (2*s*, 2 arom. C); 129.4, 129.2, 128.2, 127.0, 123.4, 116.8 (6*d*, 10 arom. CH); 63.4 (*t*, PhCH_2); 52.2 (*t*, C(5), C(7)); 35.5 (*t*, C(4), C(8)); C(2), C(3), and MeN could not be detected. EI-MS: 305 (11, $M^{+\cdot}$), 304 (41), 199 (29), 185 (37), 91 (100). Anal. calc. for $C_{20}H_{23}N_3$ (305.42): C 78.65, H 7.59, N 13.76; found: C 78.87, H 7.84, N 13.55.

3. *Reaction of Azirines* **1a–d** *with Thiobenzoic Acid.* 3.1. *General Procedure B.* To a soln. of **1** in CH_2Cl_2 at 0°, a soln. of thiobenzoic acid in CH_2Cl_2 was added, and the mixture was stirred at r.t. for 14 h. After evaporation, FC (SiO_2, AcOEt/hexane 2:1 (**13a**), 1:3 (**13b**), and 1:1 (**13c**)) of the residue yielded the benzamides **13**.

3.2. N-{*4-[Methyl(phenyl)thiocarbamoyl]tetrahydro-2H-pyran-4-yl*}*benzamide* (**13a**). According to *Procedure B*, **1a** (110 mg, 0.508 mmol) in CH_2Cl_2 (4 ml) was treated with thiobenzoic acid (77 mg, 0.557 mmol): 175 mg (97%) of **13a**. Yellowish crystals. M.p. 172–173°. IR ($CHCl_3$): 3440*m*, 3060*m*, 3000*m*, 2970*m*, 2930*m*, 2860*m*, 1670*s*, 1595*m*, 1580*m*, 1510*s*, 1480*s*, 1460*s*, 1440*m*, 1430*m*, 1390*m*, 1370*s*, 1315*m*, 1300*m*, 1280*s*, 1240*m*, 1185*w*, 1170*w*, 1160*w*, 1140*m*, 1100*s*, 1070*m*, 1065*m*, 1030*m*, 1015*m*, 1005*m*, 935*w*, 860*w*, 840*m*, 700*s*. ^{1}H-NMR: 7.55–7.45, 7.4–7.35, 7.15–7.1 (3*m*, 10 arom. H); 5.58 (*s*, NH); 3.81 (*dd*, J = 11.8, 4.2, 2 H_{eq} of CH_2(2′) and CH_2(6′)); 3.71 (*s*, MeN); 3.49 (‘t’, 2 H_{ax} of CH_2(2′) and CH_2(6′)); 2.77 (*td*, J = 13.3, 4.8, 2 H_{ax} of CH_2(3′) and CH_2(5′)); 2.33 (*d*, J = 13.7, 2 H_{eq} of CH_2(3′) and CH_2(5′)). ^{13}C-NMR: 207.4 (*s*, C=S); 165.7 (*s*, C=O); 147.2, 134.0 (2*s*, 2 arom. C); 131.8, 129.5, 128.4, 127.9, 126.7, 125.5 (6*d*, 10 arom. CH); 63.4 (*s*, C(4′)); 63.2 (*t*, C(2′), C(6′)); 51.2 (*q*, MeN); 37.1 (*t*, C(3′), C(5′)). CI-MS: 356 (23), 355 (100, $[M + 1]^+$). Anal. calc. for $C_{20}H_{22}N_2O_2S$ (354.47): C 67.77, H 6.26, N 7.90, S 9.05; found: C 67.87, H 6.12, N 7.73, S 9.25.

3.3. N-{*4-[Methyl(phenyl)thiocarbamoyl]tetrahydro-2H-thiopyran-4-yl*}*benzamide* (**13b**). According to *Procedure B*, **1b** (162 mg, 0.697 mmol) in CH_2Cl_2 (4 ml) was treated with thiobenzoic acid (135 mg, 0.977 mmol): 245 mg (95%) of **13b**. Yellowish crystals. M.p. 127–129°. IR ($CHCl_3$): 3450*w*, 3060*w*, 3000*m*, 2960*m*, 2920*m*, 2830*w*, 1670*s*, 1595*w*, 1580*w*, 1510*m*, 1490*s*, 1485*s*, 1460*m*, 1430*m*, 1365*s*, 1315*w*, 1285*m*, 1240*m*, 1170*w*, 1150w, 1120*m*, 1100*w*, 1070*w*, 1065*w*, 1045*w*, 1020*w*, 1000*w*, 985*w*, 940*w*, 700*s*. ^{1}H-NMR (400 MHz): 7.5–7.45, 7.35–7.3, 7.1–7.05 (3*m*, 10 arom. H); 5.38 (*s*, NH); 3.68 (*s*, MeN); 2.85–2.65 (*m*, CH_2(2′), CH_2(6′), 2H of CH_2(3′), CH_2(5′)); 2.45–2.4 (*m*, 2H of CH_2(3′), CH_2(5′)). ^{13}C-NMR (100.8 MHz): 207.8 (*s*, C=S); 165.5 (*s*, C=O); 147.5, 134.0 (2*s*, 2 arom. C); 131.8, 129.6, 128.4, 127.8, 126.7, 125.2 (6*d*, 10 arom. CH); 65.0 (*s*, C(4′)); 51.4 (*q*, MeN); 37.6 (*t*, C(3′), C(5′)); 23.7 (*t*, C(2′), C(6′)). CI-MS: 372 (20), 371 (100, $[M + 1]^+$). Anal. calc. for $C_{20}H_{22}N_2OS_2$ (370.54): C 64.83, H 5.98, N 7.56, S 17.31; found: C 64.87, H 5.95, N 7.63, S 17.38.

3.4. tert-*Butyl-4-[Methyl(phenyl)thiocarbamoyl]-4-[(phenylcarbonyl)amino]piperidine-1-carboxylate* (**13c**). According to *Procedure B*, **1c** (148 mg, 0.469 mmol) in CH_2Cl_2 (4 ml) was treated with thiobenzoic acid (65 mg, 0.470 mmol): 186 mg (87%) of **13c**. Yellowish crystals. M.p. 85–86°. IR ($CHCl_3$): 3450*w*, 2980*m*, 2930*w*, 2860*w*, 1730*w*, 1670*s*, 1595*w*, 1580*w*, 1505*m*, 1480*s*, 1455*m*, 1420*s*, 1365*s*, 1280*m*, 1245*s*, 1160*s*, 1120*m*, 1110*m*, 1090*m*, 1070*m*, 1000*w*, 920*w*, 970*w*, 860*w*, 700*w*. ^{1}H-NMR: 7.5–7.4, 7.35–7.3, 7.1–7.05 (3*m*, 10 arom. H); 5.39 (*s*, NH); 4.0–3.9 (*m*, 2H of CH_2(2), CH_2(6)); 3.70 (*s*, MeN); 2.8–2.35 (*m*, 2H of CH_2(2) and CH_2(6), CH_2(3), CH_2(5)); 1.42 (*s*, Me_3C). ^{13}C-NMR: 208.5 (*s*, C=S); 166.8 (*s*, C=O); 155.7 (*s*, OCONH); 148.5, 135.1 (2*s*, 2 arom. C); 133.0, 130.7, 129.5, 129.0, 127.8, 126.5 (6*d*, 10 arom. CH); 80.9 (*s*, Me_3C); 65.2 (*s*, C(4)); 52.3 (*q*, MeN); 40.1 (*t*, C(2), C(6)); 37.5 (*t*, (C(3), C(5)); 29.5 (*q*, Me_3C). CI-MS: 455 (29), 454 (100, $[M + 1]^+$), 398 (11). Anal. calc. for $C_{25}H_{31}N_3O_3S$ (453.61): C 66.20, H 6.89, N 9.26, S 7.07; found: C 66.46, H 6.89, N 8.97, S 7.34.

3.5. N-{*1-Benzyl-4-[methyl(phenyl)thiocarbamoyl]piperidin-4-yl*}*benzamide* (**13d**). According to *Procedure B*, **1d** (211 mg, 0.69 mmol) in THF (3 ml) was treated with thiobenzoic acid (121 mg, 0.875 mmol): 242 mg (79%) of **13d**. Yellowish crystals. M.p. 123–124°. IR ($CHCl_3$): 3440*m*, 3060*w*, 3020*m*, 2970*w*, 2940*w*, 2800*m*, 2760*m*, 1725*w*, 1670*s*, 1595*m*, 1580*m*, 1510*s*, 1485*s*, 1460*m*, 1430*m*, 1395*w*, 1365*s*, 1280*m*, 1240*m*, 1180*w*, 1160*w*, 1120*w*, 1100*s*, 1070*m*, 1020*w*, 1000*w*, 980*w*, 910*m*, 700*m*. ^{1}H-NMR: 7.5–7.45, 7.35–7.2, 7.1–7.05 (3*m*, 10 arom. H); 5.40 (*s*, NH); 3.70 (*s*, MeN); 3.48 (*s*, PhCH_2); 2.85–2.75 (*m*, CH_2(2′), CH_2(6′)); 2.4–2.35, 2.1–2.0 (2*m*, CH_2(3′), CH_2(5′)). ^{13}C-NMR: 207.9 (*s*, C=S); 165.3 (*s*, C=O); 147.4, 137.4, 134.3 (3*s*, 3 arom. C); 131.6, 129.3, 129.0, 128.3, 128.1, 127.6, 127.0, 126.7, 125.4 (9*d*, 15 arom. CH); 63.9 (*s*, C(4′)); 62.6 (*t*, PhCH_2); 51.1 (*q*, MeN); 49.1 (*t*, C(2′), C(6′)); 36.6 (*t*, C(3′, C(5′)). ESI-MS: 466 (100, $[M + Na]^+$), 444 (82, $[M + 1]^+$). Anal. calc. for $C_{27}H_{29}N_3OS$ (443.61): C 73.10, H 6.59, N 9.47, S 7.23; found: C 73.37, H 6.69, N 9.68, S 7.52.

4. *Tripeptides Z-Aib-Xaa-Aib-N(Ph)Me* **18**. 4.1. *General Procedure C: Coupling with Azirines.* To a soln. of the corresponding 2*H*-azirin-3-amine **1** or *N*,2,2-trimethyl-*N*-phenyl-2*H*-azirin-3-amine (**17**) in MeCN at 0°, 2-[(benzyloxycarbonyl)amino]-2-methylpropanoic acid (Z-Aib) or dipeptide acid **16** was added and the mixture stirred for 16 h at r.t. The solvent was evaporated and the residue purified by crystallization or FC.

4.2. *General Procedure D: Hydrolysis of* N-*Methylanilides.* To a suspension of the *N*-methylanilides in THF at 0°, 6N HCl was added and the mixture stirred for 4 h at r.t. The mixture was extracted with CH_2Cl_2, the org. layer dried ($MgSO_4$) and evaporated and the residue purified by crystallization or CC.

4.3. *Benzyl* {*2-*{{*4-*{{{*1,1-Dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl*}*amino*}*carbonyl*}*-tetrahydro-2H-pyran-4-yl*}*amino*}*-1,1-dimethyl-2-oxoethyl*}*carbamate* (**18a**; Z-Aib-Thp-Aib-N(Ph)Me). *Benzyl* {*1,1-Dimethyl-2-oxo-2-*{{*tetrahydro-4-*{[*methyl(phenyl)amino*]*carbonyl*}*-2H-pyran-4-yl*}*amino*}*ethyl*}*carbamate* (**15a**). Reaction of **1a** (415 mg, 1.919 mmol) with Z-Aib (500 mg, 2.107 mg) in MeCN (5 ml) according to *Procedure C*. The colorless precipitate was removed by filtration and dried *i.v.*: 728 mg (84%) of **15a**. Colorless powder. M.p. 198°.

IR ($CHCl_3$): 3430*m*, 3300*m*, 3000*m*, 2860*m*, 1700*s*, 1675*s*, 1640*s*, 1595*m*, 1510*s*, 1495*s*, 1470*m*, 1455*m*, 1370*m*, 1330*w*, 1240*s*, 1170*w*, 1150*w*, 1110*m*, 1090*m*, 1075*m*, 1030*m*, 950*w*, 915*w*, 850*w*. ^{1}H-NMR: 7.3–7.1 (*m*, 10 arom. H, 1 NH); 4.94 (*s*, PhCH_2O); 4.91 (*s*, NH); 3.65 (*dt*, $J \approx 11.9$, 3.5, 2 H_{eq} of CH_2(2′) and CH_2(6′)); 3.41 (*td*, $J \approx 11.6$, 1.6, 2 H_{ax} of CH_2(2′) and CH_2(6′)); 3.15 (*s*, MeN); 2.12 (*td*, $J \approx 12.7$, 4.5, 2 H_{ax} of CH_2(3′) and CH_2(5′)); 1.82 (*d*, $J \approx 12.8$, 2 H_{eq} of CH_2(3′) and CH_2(5′)); 1.38 (*s*, Me_2C). ^{13}C-NMR: 173.0, 165.7 (2*s*, 2 C=O); 155.7 (*s*, OCONH); 144.9, 136.0 (2*s*, 2 arom. C); 129.3, 128.6, 128.4, 128.2, 127.6, 127.5 (6*d*, 10 arom. CH); 67.0, 63.2 (2*t*, PhCH_2O, C(2′), C(6′)); 58.0, 57.4 (2*s*, C(4′), Me_2C); 41.4 (*q*, MeN); 33.7 (*t*, C(3′), C(5′)); 25.5 (*q*, Me_2C). CI-MS: 455 (24), 454 (100, $[M + 1]^+$), 347 (66, $[M - (PhNCH_3)]^+$), 346 (73, $[M - (PhCH_2O)]^+$). Anal. calc. for $C_{25}H_{31}N_3O_5$ (453.54): C 66.21, H 6.89, N 9.26; found: C 66.21, H 6.84, N 9.43.

*4-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}tetrahydro-2*H*-pyran-4-carboxylic Acid* (**16a**). According to *Procedure D*, **15a** (708 mg, 1.561 mmol) in THF (4 ml) was treated with 6N HCl (4 ml). CC (CH_2Cl_2/MeOH 4:1) and recrystallization yielded 504 mg (89%) of **16a**. Colorless crystals. M.p. 147–148°. IR ($CHCl_3$): 3420*m*, 3300*m*, 3000*m*, 2960*m*, 2860*m*, 1700*s*, 1660*s*, 1610*s*, 1510*s*, 1465*m*, 1455*m*, 1445*m*, 1410*m*, 1385*m*, 1250*m*, 1190*w*, 1170*w*, 1145*w*, 1100*m*, 1075*m*, 1030*w*, 1015*w*, 965*w*, 919*w*, 840*w*, 815*w*, 700*m*. ^{1}H-NMR (CD_3OD): 7.65–7.55 (*m*, 5 arom. H); 5.36 (*s*, PhCH_2O); 3.95–3.9 (*m*, 2 H_{eq} of CH_2(2) and CH_2(6)); 3.77 (*t*, $J = 9.6$, 2 H_{ax} of CH_2(2) and CH_2(6)); 2.25–2.2 (*m*, CH_2(3), CH_2(5)); 1.38 (*s*, Me_2C). ^{13}C-NMR (CD_3OD): 179.4, 175.5 (2*s*, 2 C=O); 155.8 (*s*, OCONH); 136.5 (*s*, 1 arom. C); 128.0, 127.6, 127.5 (3*d*, 5 arom. CH); 66.2, 63.4 (2*t*, PhCH_2O, CH_2(2), CH_2(6)); 57.3, 56.5 (2*s*, C(4), Me_2C); 32.1 (*t*, C(3), C(5)); 24.2 (*q*, Me_2C). CI-MS: 365 (22), 364 (100, $[M - OH + NH_3]^+$), 347 (84, $[M - OH]^+$).

Carbamate **18a**. According to *Procedure C*, **16a** (189 mg, 0.519 mmol) and **17** (105 mg, 0.603 mmol) in THF (2 ml) yielded 235 mg (84%) of **18a**. Colorless crystals. M.p. 178–180°. IR ($CHCl_3$): 3420*m*, 3360*m*, 3000*m*, 2850*w*, 1720*s*, 1660*s*, 1595*m*, 1495*s*, 1455*m*, 1390*m*, 1365*m*, 1240*m*, 1185*w*, 1170*w*, 1110*m*, 1090*m*, 1075*m*, 1030*w*, 1015*w*, 950*w*, 900*w*, 845*w*, 700*m*. ^{1}H-NMR: 7.50 (*s*, NH); 7.35–7.25 (*m*, 10 arom. H); 6.46, 5.63 (2*s*, 2 NH); 5.10 (*s*, PhCH_2O); 3.79 (*d*, $J \approx 11.6$, 2 H_{eq} of CH_2(2′) and CH_2(6′)); 3.44 (*td*, $J \approx 11.6$, 1.6, 2 H_{ax} of CH_2(2′) and CH_2(6′)); 3.27 (*s*, MeN); 2.19 ('*td*', 2 H_{ax} of CH_2(3′) and CH_2(5′)); 1.85 (*d*, $J \approx 13.8$, 2 H_{eq} of CH_2(3′) and CH_2(5′)); 1.48, 1.42 (2*s*, 2 Me_2C). ^{13}C-NMR: 173.6, 173.5, 171.9 (3*s*, 3 C=O); 155.8 (*s*, OCONH); 145.3, 136.1 (2*s*, 2 arom. C); 129.2, 128.7, 128.5, 128.0, 127.9, 127.3 (6*d*, 10 arom. CH); 67.1, 63.1 (2*t*, PhCH_2O, C(2′), C(6′)); 57.9, 57.6, 57.5 (3*s*, C(4′), 2 Me_2C); 40.8 (*q*, MeN); 32.1 (*t*, C(3′), C(5′)); 25.9, 25.5 (2*q*, 2 Me_2C). CI-MS: 539 (20, $[M + 1]^+$), 433 (33), 432 (100, $[M - (PhNCH_3)]^+$). Anal. calc. for $C_{29}H_{38}N_4O_6$ (538.64): C 64.67, H 7.11, N 10.40; found: C 64.53, H 6.96, N 10.60.

4.4. *Benzyl {2-{{4-{{{1,1-Dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}carbonyl}tetrahydro-2*H*-thiopyran-4-yl}amino}-1,1-dimethyl-2-oxoethyl}carbamate* (**18b**; Z-Aib-Tht-Aib-N(Ph)Me). *Benzyl {1,1-Dimethyl-2-oxo-2-{{tetrahydro-4-{[methyl(phenyl)amino]carbonyl}-2*H*-thiopyran-4-yl}amino}ethyl}carbamate* (**15b**). Reaction of **1b** (254 mg, 1.093 mmol) with Z-Aib (290 mg, 1.222 mmol) in MeCN (2 ml) according to *Procedure C*. The colorless precipitate was removed by filtration and dried *i.v.*: 409 mg (80%) of **15b**. Colorless powder. M.p. 182–184°. IR ($CHCl_3$): 3430*m*, 3300*w*, 3000*m*, 2940*w*, 1700*s*, 1675*s*, 1640*s*, 1595*m*, 1510*m*, 1495*s*, 1470*w*, 1455*m*, 1440*m*, 1430*w*, 1370*m*, 1250*m*, 1180*w*, 1130*w*, 1090*m*, 1075*m*, 1030*w*, 980*w*, 940*w*, 910*w*, 700*m*. ^{1}H-NMR (400 MHz): 7.4–7.15 (*m*, 10 arom. H); 7.06 (*s*, NH); 5.03 (*s*, PhCH_2O); 4.90 (*s*, NH); 3.20 (*s*, MeN); 2.72 (*t*, $J = 13.0$, 2 H of CH_2(2′), CH_2(6′)); 2.45–2.4, 2.35–2.3 (2*m*, 2 H of CH_2(2′) and CH_2(6′), 2 H of CH_2(3′) and CH_2(5′)); 2.10 (*t*, $J = 12.9$, 2 H of CH_2(3′) and CH_2(5′)); 1.45 (*s*, Me_2C). ^{13}C-NMR (100.8 MHz): 172.9, 172.1 (2*s*, 2 C=O); 155.7 (*s*, OCONH); 145.1, 136.0 (2*s*, 2 arom. C); 129.3, 128.6, 128.4, 128.3, 127.6, 127.5 (6*d*, 10 arom. CH); 67.0 (*t*, PhCH_2O); 59.7, 57.5 (2*s*, C(4′), Me_2C); 41.5 (*q*, MeN); 34.2 (*t*, C(3′), C(5′)); 25.5 (*q*, Me_2C); 23.3 (*t*, C(2′), C(6′)). ESI-MS: 492 (100, $[M + Na]^+$). Anal. calc. for $C_{25}H_{31}N_3O_4S$ (469.60): C 63.94, H 6.65, N 8.95, S 6.83; found: C 64.20, H 6.85, N 9.15, S 6.81.

*4-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}tetrahydro-2*H*-thiopyran-4-carboxylic Acid* (**16b**). According to *Procedure D*, **15b** (344 mg, 0.732 mmol) in THF (2 ml) was treated with 6N HCl (2 ml). Recrystallization yielded 265 mg (95%) of **16b**. Colorless powder. M.p. 166–169°. IR: 3320*s*, 3090*w*, 3040*m*, 2980*m*, 2950*m*, 2920*m*, 2580*w*, 1715*s*, 1660*s*, 1535*s*, 1500*m*, 1465*m*, 1455*m*, 1420*s*, 1370*m*, 1345*s*, 1290*m*, 1250*m*, 1240*m*, 1170*m*, 1120*w*, 1090*m*, 1070*s*, 1030*w*, 985*w*, 945*w*, 910*w*, 845*w*, 830*w*, 785*m*, 765*w*, 740*w*, 700*m*. ^{1}H-NMR (CD_3OD): 7.4–7.25 (*m*, 5 arom. H); 5.10 (*s*, PhCH_2O); 2.85–2.75, 2.45–2.35, 2.15–2.05 (3*m*, 4 CH_2); 1.44 (*s*, Me_2C). ^{13}C-NMR (CD_3OD): 175.6, 175.5 (2*s*, 2 C=O); 155.8 (*s*, OCONH); 136.6 (*s*, 1 arom. C); 128.1, 127.6 (2*d*, 5 arom. CH); 66.0 (*t*, PhCH_2O); 57.8, 56.4 (2*s*, C(4), Me_2C); 32.8 (*t*, C(3), C(5)); 24.0 (*q*, Me_2C); 22.6 (*t*, C(2), C(6)). ESI-MS: 381 (100, $[M + 1]^+$). Anal. calc. for $C_{18}H_{24}N_2O_5S$ (380.47): C 56.82, H 6.36, N 7.36, S 8.43; found: C 56.85, H 6.08, N 7.53, S 8.42.

Carbamate **18b**. According to *Procedure C*, **16b** (126 mg, 0.331 mmol) and **17** (69 mg, 0.396 mmol) in THF (2 ml) yielded 140 mg (76%) of **18b**. Colorless crystals. M.p. 200–202°. IR ($CHCl_3$): 3420*m*, 3350*m*, 3020*w*,

3000*m*, 2940*m*, 1715*s*, 1670*s*, 1640*s*, 1595*m*, 1495*s*, 1455*m*, 1430*m*, 1390*m*, 1365*m*, 1280*m*, 1255*m*, 1245*m*, 1170*m*, 1220*w*, 1090*m*, 1015*w*, 970*w*, 920*w*, 700*m*. ^{1}H-NMR: 7.46 (*s*, NH); 7.35–7.25 (*m*, 10 arom. H); 6.33, 5.52 (2*s*, 2 NH); 5.12 (*s*, PhC*H*$_2$O); 3.27 (*s*, MeN); 2.65–2.6, 2.5–2.45, 2.25–2.2 (3*m*, 4 CH$_2$); 1.48, 1.41 (2*s*, 2 Me$_2$C). ^{13}C-NMR: 173.5, 173.2, 172.2 (3*s*, 3 C=O); 155.8 (*s*, OCONH); 145.2, 136.1 (2*s*, 2 arom. C); 129.2, 128.7, 128.5, 128.0, 127.9, 127.3 (6*d*, 10 arom. CH); 67.2 (*t*, PhCH$_2$O); 58.9, 57.9, 57.7 (3*s*, C(4'), 2 Me$_2$*C*); 40.7 (*q*, MeN); 32.8 (*t*, C(3'), C(5')); 25.8, 25.5 (2*q*, 2 *Me*$_2$C); 23.2 (*t*, C(2'), C(6')). ESI-MS: 577 (100, [*M* + Na]$^+$).

4.5. tert-*Butyl 4-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}-4-{{{1,1-dimethyl-2-[methyl-(phenyl)amino]-2-oxoethyl}amino}carbonyl}piperidine-1-carboxylate* (**18c**; Z-Aib-Pip(Boc)-Aib-N(Ph)Me). tert-*Butyl 4-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}-4-{[methyl(phenyl)amino]carbonyl}piperidine-1-carboxylate* (**15c**). Reaction of **1c** (424 mg, 1.344 mmol) with Z-Aib (332 mg, 1.399 mmol) in MeCN (8 ml) according to *Procedure C*. The colorless precipitate was removed by filtration and dried *i.v.*: 601 mg (81%) of **15c**. Colorless powder. M.p. 215–216°. IR ($CHCl_3$): 3430*m*, 3300*w*, 2980*m*, 2940*w*, 2870*w*, 1670*s*, 1640*m*, 1595*m*, 1490*m*, 1450*m*, 1420*m*, 1370*m*, 1280*m*, 1250*m*, 1155*m*, 1090*m*, 1075*m*, 1030*w*, 1000*w*, 975*w*, 950*w*, 905*w*, 860*w*, 700*w*. ^{1}H-NMR: 7.5–6.95 (*m*, 10 arom. H, 1 NH); 4.80 (*s*, PhC*H*$_2$O); 4.68 (*s*, NH); 3.62 (br. *s*, 2 H$_{eq}$ of CH$_2$(2) and CH$_2$(6)); 3.01 (*s*, MeN); 2.69 (br. '*t*', 2 H$_{ax}$ of CH$_2$(2) and CH$_2$(6)); 1.9–1.8 (*m*, CH$_2$(3), CH$_2$(5)); 1.24 (*s*, Me$_3$C, Me$_2$C). ^{13}C-NMR: 172.9, 171.7 (2*s*, 2 C=O); 155.7, 154.5 (2*s*, 2 OCONH); 144.9, 135.8 (2*s*, 2 arom. C); 129.2, 128.6, 128.4, 128.2, 127.4 (5*d*, 10 arom. CH); 79.5 (*s*, Me$_3$*C*); 66.9 (*t*, PhC*H*$_2$O); 58.7, 57.4 (2*s*, C(4), Me$_2$*C*); 41.3 (*q*, MeN); 39.5, 32.8 (2*t*, 4 CH$_2$); 28.3 (*q*, *Me*$_3$C); 25.5 (*q*, *Me*$_2$C). CI-MS: 553 (40, [*M* + 1]$^+$), 446 (100, [*M* – (PhNMe)]$^+$). Anal. calc. for $C_{30}H_{40}N_4O_6$ (552.67): C 65.20, H 7.30, N 10.14; found: C 64.99, H 7.52, N 9.90.

1-tert-*Butyl 4-Hydrogen 4-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}piperidine-1,4-dicarboxylate* (**16c**). According to *Procedure D*, **15c** (601 mg, 1.087 mmol) in THF (5 ml) at 0° was treated with 6N HCl (5 ml). As soon as the solid had dissolved (2 h), the mixture was extracted with CH_2Cl_2 and the org. layer dried ($MgSO_4$) and evaporated. Recrystallization yielded 170 mg (34%) of **16c**. After neutralization of the aq. layer, 231 mg (59%) of the zwitterion **19** were obtained. To a soln. of **19** (109 mg, 0.300 mmol) in 1N NaOH/dioxan 1:1 (4 ml), di(*tert*-butyl) dicarbonate (107 mg, 0.490 mmol) was added, and the mixture was stirred at 70° (4 h). After addition of 6N HCl until pH 2 was reached, the mixture was extracted twice with AcOEt, the org. phase dried ($MgSO_4$) and evaporated, and the residue purified by FC (CH_2Cl_2/MeOH 10:1): 85 mg (61%) of **16c**. Colorless crystals. M.p. 147–148°. IR: 3400*m* (br.), 2980*m*, 2940*m*, 1670*s* (br.), 1525*m*, 1450*m*, 1430*m*, 1390*m*, 1370*m*, 1280*m*, 1250*s*, 1175*m*, 1155*m*, 1090*m*, 1070*m*, 1020*w*, 960*w*, 860*w*, 740*w*, 700*w*. ^{1}H-NMR (CD_3OD): 7.58 (*s*, NH); 7.35–7.25 (*m*, 5 arom. H); 5.48 (*s*, PhC*H*$_2$O); 3.62 (br. *d*, *J* = 13.5, 2 H$_{eq}$ of CH$_2$(2) and CH$_2$(6)); 2.88 (br. *s*, 2 H$_{ax}$ of CH$_2$(2) and CH$_2$(6)); 2.1–2.0, 1.9–1.75 (2*m*, CH$_2$(3), CH$_2$(5)); 1.47 (*s*, Me$_3$C); 1.43 (*s*, Me$_2$C). ^{13}C-NMR (CD_3OD): 175.6, 174.3 (2*s*, 2 C=O); 155.5, 154.5 (2*s*, 2 OCONH); 136.6 (*s*, 2 arom. C); 127.8, 127.5, 127.4 (3*d*, 5 arom. CH); 79.4 (*s*, Me$_3$C); 65.8 (*t*, PhC*H*$_2$O); 57.3, 56.1 (2*s*, C(4), Me$_2$*C*); 39.4, 31.0 (2*t*, 4 CH$_2$); 27.1 (*q*, *Me*$_3$C); 23.8 (*q*, *Me*$_2$C). ESI-MS: 486 (100, [*M* + Na]$^+$).

4-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}piperidine-4-carboxylic Acid (**19**). To a suspension of **15c** (436 mg, 0.789 mmol) in THF (5 ml) at 0°, 6N HCl (5 ml) was added. After stirring for 14 h, the solvent was evaporated, the residue dissolved in a few ml of 2N HCl and extracted with AcOEt and CH_2Cl_2. The aq. layer was neutralized with 4N NaOH. Crystallization from H_2O yielded 251 mg (88%) of **19**. M.p. 170–171°. IR: 3320*m*, 3290*s*, 3170*m*, 3000*w*, 2980*m*, 1710*s*, 1670*s*, 1615*m*, 1570*s*, 1530*s*, 1495*w*, 1470*m*, 1455*m*, 1445*w*, 1390*s*, 1370*s*, 1330*s*, 1300*m*, 1260*m*, 1235*m*, 1210*m*, 1190*m*, 1170*w*, 1080*w*, 1050*s*, 1030*w*, 990*m*, 960*w*, 920*w*, 880*w*, 800*m*, 780*m*, 750*m*, 700*m*, 650*m*. ^{1}H-NMR (CD_3OD): 7.35–7.25 (*m*, 5 arom. H); 5.08 (*s*, PhC*H*$_2$O); 3.4–3.3, 3.15–3.1, 2.55–2.5, 2.1–1.95 (4*m*, 4 CH$_2$); 1.44 (*s*, Me$_2$C). ^{13}C-NMR (CD_3OD): 178.5, 176.6 (2*s*, 2 C=O); 157.3 (*s*, OCONH); 138.2 (*s*, 1 arom. C); 129.5, 129.0, 128.7 (3*d*, 10 arom. CH); 67.3 (*t*, PhC*H*$_2$O); 58.1 (*s*, C(4), Me$_2$*C*); 42.1, 29.7 (2*t*, 4 CH$_2$); 25.6 (*q*, *Me*$_2$C). CI-MS: 364 (9, [*M* + 1]$^+$), 256 (49, [*M* – (PhCH$_2$O)]$^+$), 230 (100).

Ester **18c**. According to *Procedure C*, **16c** (150 mg, 0.324 mmol) and **17** (64 mg, 0.367 mmol) in MeCN (10 ml) yielded 183 mg (89%) of **18c**. Colorless crystals. M.p. 89–90°. IR ($CHCl_3$): 3420*w*, 3350*w*, 3000*m*, 2940*w*, 2860*w*, 1715*m*, 1680*s*, 1640*m*, 1595*m*, 1510*m*, 1495*s*, 1455*m*, 1430*m*, 1390*m*, 1370*m*, 1280*m*, 1210*m*, 1245*m*, 1170*m*, 1150*m*, 1120*w*, 1090*m*, 1075*m*, 1015*w*, 960*w*, 700*m*. ^{1}H-NMR: 7.43 (*s*, NH); 7.3–7.15 (*m*, 10 arom. H); 5.48 (*s*, NH); 5.03 (*s*, PhC*H*$_2$O); 3.82 (br. *s*, 2 H$_{eq}$ of CH$_2$(2) and CH$_2$(6)); 3.20 (*s*, MeN); 2.71 (br. '*t*', 2 H$_{ax}$ of CH$_2$(2) and CH$_2$(6)); 2.0–1.85 (*m*, CH$_2$(3) and CH$_2$(5)); 1.40, 1.35, 1.30 (3*s*, *Me*$_3$C, 2 *Me*$_2$C). ^{13}C-NMR: 173.7, 173.5, 172.1 (3*s*, 3 C=O); 155.7, 154.4 (2*s*, 2 OCONH); 145.2, 136.0 (2*s*, 2 arom. C); 129.1, 128.6, 128.4, 127.9, 127.7, 127.2 (6*d*, 10 arom. CH); 79.7 (*s*, Me$_3$*C*); 67.0 (*t*, PhC*H*$_2$O); 58.2, 57.8, 57.6 (3*s*, C(4), Me$_2$*C*); 40.6 (*q*, MeN); 39.4, 38.7, 31.8, 30.9 (4*t*, 4 CH$_2$); 28.4, 25.8, 25.4 (3*q*, *Me*$_3$C, 2 *Me*$_2$C). ESI-MS: 660 (100, [*M* + Na]$^+$). Anal. calc. for $C_{34}H_{47}N_5O_7$ (637.77): C 64.03, H 7.43, N 10.98; found: C 63.99, H 7.17, N 10.94.

4.6. *Benzyl {2-{{1-(Benzyloxycarbonyl)-4-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}-carbonyl}piperidin-4-yl}amino}-1,1-dimethyl-2-oxoethyl}carbamate* (**18d**; Z-Aib-Pip(Z)-Aib-N(Ph)Me). *1-(Benzyloxycarbonyl)-4-{{2-[(benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}piperidine-4-carboxylic Acid* (**16d**). To a soln. of **19** (431 mg, 1.186 mmol) in 1N NaOH/dioxan 1:1 (10 ml) at 0°, (benzyloxy)carbonyl chloride (Z–Cl; 325 mg, 1.905 mmol) was added and the soln. was stirred at r.t. (16 h). Then, 6N HCl was added until pH 2 was reached. Extraction with AcOEt (twice), drying of the org. layer ($MgSO_4$), evaporation, and FC (CH_2Cl_2/ MeOH 10:1) yielded 450 mg (76%) of **16d**. Colorless solid. M.p. 75–76°. IR: 3420*m*, 3300*m*, 3000*m*, 2870*w*, 1690*s*, 1510*m*, 1500*m*, 1450*m*, 1435*m*, 1385*w*, 1370*w*, 1355*w*, 1280*m*, 1250*s*, 1160*m*, 1135*w*, 1090*m*, 1010*w*, 955*w*, 905*w*, 860*w*, 700*m*. ^{1}H-NMR (CD_3OD): 7.35–7.15 (*m*, 10 arom. H); 5.13, 5.03 (2*s*, 2 PhCH_2O); 3.76 (*d*, J = 13.6, 2 H_{eq} of CH_2(2′) and CH_2(6′)); 2.87 (*t*, J = 13.5, 2 H_{ax} of CH_2(2′) and CH_2(6′)); 2.05 (*d*, J = 13.5, 2 H_{eq} of CH_2(3′) and CH_2(5′)); 1.83 (‘*t*’, 2 H_{ax} of CH_2(3′) and CH_2(5′)); 1.43 (*s*, Me_2C). ^{13}C-NMR (CD_3OD): 176.0, 175.8 (2*s*, 2 C=O); 155.6, 155.1 (2*s*, 2 OCONH); 136.6, 136.0 (2*s*, 2 arom. C); 128.8, 128.7, 128.4, 128.3, 128.3, 128.2 (6*d*, 10 arom. CH); 66.8, 65.9 (2*t*, 2 PhCH_2O); 57.2, 56.2 (2*s*, C(4), Me_2C); 39.3, 31.0 (2*t*, 4 CH_2); 24.0 (*q*, Me_2C). CI-MS: 497 (15, $[M - OH + NH_3]^+$), 346 (100, $[M - PhCH_2OCO]^+$).

Carbamate **18d**. According to *Procedure C*, **16d** (100 mg, 0.201 mmol) and **17** (45 mg, 0.258 mmol) in MeCN (3 ml) yielded 103 mg (76%) of **18d**. Colorless crystals. M.p. 162–164°. IR ($CHCl_3$): 3420*m*, 3360*m*, 3060*w*, 3030*w*, 3000*m*, 2940*w*, 2860*w*, 1690*s*, 1640*m*, 1595*m*, 1495*s*, 1470*m*, 1450*m*, 1430*m*, 1390*m*, 1365*m*, 1280*m*, 1245*s*, 1170*m*, 1150*m*, 1090*m*, 1015*w*, 975*w*, 960*w*, 910*w*, 860*w*, 700*m*. ^{1}H-NMR: 7.51 (*s*, NH); 7.35–7.2 (*m*, 15 arom. H); 6.43 (*s*, NH); 5.61 (*s*, OCONH); 5.12, 5.08 (2*s*, 2 PhCH_2O); 4.0–3.85 (*m*, 2 H_{eq} of CH_2(2′) and CH_2(6′)); 3.26 (*s*, MeN); 2.88 (*t*, J = 11.8, 2 H_{ax} of CH_2(2′) and CH_2(6′)); 2.1–1.85 (*m*, CH_2(3′), CH_2(5′)); 1.46, 1.41 (2*s*, Me_2C). ^{13}C-NMR: 172.5, 172.4, 170.7 (3*s*, 3 C=O); 154.7, 154.0 (2*s*, 2 OCONH); 144.1, 135.6, 135.0 (3*s*, 3 arom. C); 129.1, 128.6, 128.4, 128.3, 127.9, 127.8, 127.8, 127.7, 127.2 (9*d*, 15 arom. CH); 66.2 (*t*, 2 PhCH_2O); 57.1, 56.8, 56.7 (3*s*, C(4′), 2 Me_2C); 39.7 (*q*, MeN); 38.3 (*t*, C(2′), C(6′)); 30.5, 29.9 (2*t*, C(3′), C(5′)); 24.8, 24.5 (2*q*, 2 Me_2C). ESI-MS: 694 (100, $[M + Na]^+$). Anal. calc. for $C_{37}H_{45}N_5O_7$ (671.79): C 65.15, H 6.75, N 10.42; found: C 65.90, H 6.61, N 10.15.

4.7. *Benzyl {2-{{1-{{{1,1-Dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}carbonyl}cyclohexyl}amino}-1,1-dimethyl-2-oxoethyl}carbamate* (**18e**; Z-Aib-Ach-Aib-N(Ph)Me). *Benzyl {1,1-Dimethyl-2-{{1-{[methyl(phenyl)-amino]carbonyl}cyclohexyl}amino}-2-oxoethyl}carbamate* (**15e**). Reaction of **1e** (240 mg, 1.120 mmol) with Z-Aib (295 mg, 1.243 mmol) in CH_2Cl_2 (3 ml) according to *Procedure C*. Purification by FC yielded 412 mg (81%) of **15e**. Colorless crystals. M.p. 166–167°. IR ($CHCl_3$): 3430*m*, 3060*w*, 3020*m*, 3000*s*, 2930*m*, 2860*m*, 1705*s*, 1670*s*, 1635*s*, 1595*m*, 1510*s*, 1495*s*, 1460*m*, 1450*m*, 1420*w*, 1380*m*, 1370*m*, 1350*w*, 1285*m*, 1250*s*, 1180*m*, 1130*w*, 1090*m*, 1075*m*, 1030*m*, 1000*w*, 950*w*, 930*w*, 900*w*, 700*m*. ^{1}H-NMR: 7.35–7.05 (*m*, 10 arom. H); 6.70 (*s*, NH); 4.95 (*s*, PhCH_2O); 4.86 (*s*, NH); 3.13 (*s*, MeN); 2.04 (*d*, $J \approx$ 13.6, 2H); 1.77 (*t*, $J \approx$ 12.9, 2H); 1.55–1.45 (*m*, 3H); 1.37 (*s*, Me_2C); 1.3–1.1 (*m*, 3H). ^{13}C-NMR: 172.9, 172.6 (2*s*, 2 C=O); 155.4 (*s*, OCONH); 145.4, 136.1 (2*s*, 2 arom. C); 129.0, 128.5, 128.2, 128.1, 127.4, 127.1 (6*d*, 10 arom. CH); 66.6 (*t*, PhCH_2O); 60.4, 57.3 (2*s*, C(4′), Me_2C); 41.3 (*q*, MeN); 32.9 (*t*, 2 CH_2); 25.4 (*q*, Me_2C); 25.0, 21.4 (2*t*, 3 CH_2). ESI-MS: 474 (100, $[M + Na]^+$). Anal. calc. for $C_{26}H_{33}N_3O_4$ (451.57): C 69.16, H 7.37, N 9.31; found: C 69.08, H 7.21, N 9.33.

1-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}cyclohexane-1-carboxylic Acid (**16e**). According to *Procedure D*, **15e** (154 mg, 0.341 mmol) in THF (2 ml) at 0° was treated with 6N HCl (2 ml, 4 h). FC and recrystallization yielded 106 mg (86%) of **16e**. Colorless crystals. M.p. 157–159°. IR: 3430*m*, 3300*m*, 3030*m*, 3000*m*, 2970*m*, 2920*m*, 2860*m*, 1720*s*, 1700*s*, 1660*s*, 1530*s*, 1505*s*, 1470*m*, 1450*m*, 1420*m*, 1380*m*, 1360*w*, 1290*m*, 1260*m*, 1250*s*, 1215*w*, 1170*m*, 1080*s*, 1030*w*, 1015*w*, 965*m*, 940*w*, 920*w*, 870*w*, 780*w*, 750*m*, 700*m*. ^{1}H-NMR: 7.35–7.25 (*m*, 5 arom. H); 6.97, 5.49 (2*s*, 2 NH); 5.10 (*s*, PhCH_2O); 2.05–2.0, 1.85–1.7, 1.6–1.55 (3*m*, 7H); 1.52 (*s*, Me_2C); 1.4–1.25 (*m*, 3H). ^{13}C-NMR: 177.2, 174.8 (2*s*, 2 C=O); 155.8 (*s*, OCONH); 136.1 (*s*, 1 arom. C); 128.6, 128.3, 128.1 (3*d*, 5 arom. CH); 67.0 (*t*, PhCH_2O); 59.0, 57.3 (2*s*, C(4), Me_2C); 31.9 (*t*, 2 CH_2); 25.4 (*q*, Me_2C); 25.1, 21.2 (2*t*, 3 CH_2). CI-MS: 380 (31, $[M + 1 + NH_3]^+$), 363 (100, $[M + 1]^+$), 345 (83, $[M - OH]^+$), 272 (57, $[M - PhCH_2]^+$). Anal. calc. for $C_{19}H_{26}N_2O_5$ (362.43): C 62.97, H 7.23, N 7.73; found: C 63.20, H 7.26, N 7.80.

Carbamate **18e**. According to *Procedure C*, **16e** (420 mg, 1.159 mmol) and **17** (245 mg, 1.406 mmol) in THF (5 ml) yielded 475 mg (76%) of **18e**. Colorless crystals. M.p. 190–192°. IR ($CHCl_3$): 3420*m*, 3360*m*, 3060*w*, 3040*m*, 3000*s*, 2940*m*, 2860*m*, 1715*s*, 1680*s*, 1640*s*, 1595*m*, 1495*s*, 1455*s*, 1390*m*, 1365*m*, 1240*s*, 1170*m*, 1120*w*, 1090*s*, 1075*m*, 1030*w*, 1015*w*, 1000*w*, 975*w*, 950*w*, 925*w*, 900*w*, 700*m*. ^{1}H-NMR: 7.42 (*s*, NH); 7.35–7.2 (*m*, 10 arom. H); 6.20, 5.58 (2*s*, 2 NH); 5.10 (*s*, PhCH_2O); 3.28 (*s*, MeN); 2.0–1.95, 1.9–1.8, 1.6–1.55 (3*m*, 7 H); 1.48, 1.43 (2*s*, 2 Me_2C); 1.25–1.2 (*m*, 3 H). ^{13}C-NMR: 173.6, 173.4, 173.1 (3*s*, 3 C=O); 155.9 (*s*, OCONH); 145.7, 136.4 (2*s*, 2 arom. C); 128.9, 128.6, 128.3, 127.7, 127.6, 126.7 (6*d*, 10 arom. CH); 66.8 (*t*, PhCH_2O); 59.9, 57.6, 57.4 (3*s*, C(4′), 2 Me_2C); 40.3 (*q*, MeN); 31.6 (*t*, 2 CH_2); 25.9, 25.4 (2*q*, 2 Me_2C); 25.1, 21.3 (2*t*, 3 CH_2). ESI-MS:

559 (100, $[M + Na]^+$), 537 (21, $[M + 1]^+$). Anal. calc. for $C_{30}H_{40}N_4O_5$ (536.67): C 67.14, H 7.51, N 10.44; found: C 67.05, H 7.25, N 10.67.

5. *Deprotection of Tripeptides Z-Aib-Xaa-Aib-N(Ph)Me.* 5.1. *General Procedure E: Hydrogenolysis.* To a soln. of **18** in MeOH, 10% of the catalyst (10% Pd/C) was added, and the suspension was stirred under H_2 at r.t. until **18** disappeared (DC). Filtration through a *Celite* pad, evaporation, and drying *i.v.* or crystallization yielded the corresponding tripeptide amide **21**.

5.2. *4-[(2-Amino-2-methylpropanoyl)amino]-*N*-{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}tetrahydro-2*H*-pyran-4-carboxamide* (**21a**). According to *Procedure E*, **18a** (116 mg, 0.215 mmol) in MeOH (3 ml) was hydrogenated: 87 mg (99%) of **21a**. Colorless solid. IR ($CHCl_3$): 3350*m* (br.), 2960*m*, 2920*m*, 2860*m*, 1650*s* (br.), 1590*m*, 1500*s*, 1470*m*, 1450*m*, 1390*m*, 1360*m*, 1290*m*, 1250*m*, 1215*m*, 1200*m*, 1145*w*, 1110*m*, 1090*m*, 1070*m*, 980*w*, 920*w*, 830*w*, 770*m*, 705*m*. ^{1}H-NMR (CD_3OD): 8.55 (*s*, NH); 7.4–7.3 (*m*, 5 arom. H); 3.85–3.75, 3.65–3.55 (2*m*, CH_2(2), CH_2(6)); 3.35 (*s*, MeN); 2.1–2.0 (*m*, CH_2(3), CH_2(5)); 1.43, 1.33 (2*s*, 2 Me_2C). ^{13}C-NMR (CD_3OD): 178.4, 173.8, 173.2 (3*s*, 3 C=O); 144.9 (*s*, arom. C); 128.9, 127.3 (2*d*, 5 arom. CH); 62.8 (*t*, C(2), C(6)); 57.3, 56.7, 54.5 (3*s*, C(4), 2 Me_2C); 31.5 (*t*, C(3), C(5)); 27.0, 24.8 (2*q*, 2 Me_2C). CI-MS: 406 (21), 405 (100, $[M + 1]^+$), 298 (40).

5.3. tert-*Butyl 4-[(2-Amino-2-methylpropanoyl)amino]-4-{{{1,1-dimethyl-2-[methyl(phenyl)amino]-2-oxoethyl}amino}carbonyl}piperidine-1-carboxylate* (**21c**). According to *Procedure E*, **18c** (105 mg, 0.164 mmol) in MeOH (5 ml) was hydrogenated: 80 mg (97%) of **21c**. Colorless crystals. M.p. 70–72°. IR ($CHCl_3$): 3300*m*, 3020*m*, 2920*w*, 2860*w*, 1680*s*, 1595*m*, 1490*m*, 1450*m*, 1430*m*, 1390*m*, 1370*m*, 1280*m*, 1250*m*, 1245*m*, 1170*m*, 1150*m*, 1120*w*, 1090*w*, 1070*w*. ^{1}H-NMR: 8.13, 7.99 (2*s*, 2 NH); 7.4–7.2 (*m*, 5 arom. H); 3.90 (br. *d*, $J = 12.0$, 2 H_{eq} of CH_2(2) and CH_2(6)); 3.26 (*s*, MeN); 2.91 (br. *t*, $J = 11.2$, 2 H_{ax} of CH_2(2) and CH_2(6)); 2.1–1.9 (*m*, CH_2(3), CH_2(5)); 1.45 (*s*, Me_3C); 1.30, 1.35 (2*s*, 2 Me_2C). ^{13}C-NMR: 178.1, 173.5, 171.6 (3*s*, 3 C=O); 154.5 (*s*, OCONH); 144.5 (*s*, 1 arom. C); 129.2, 128.2, 127.7 (3*d*, 5 arom. CH); 79.6 (*s*, Me_3C); 58.0, 55.2 (2*s*, C(4), 2 Me_2C); 41.2 (*q*, MeN); 38.8 (*t*, C(2), C(6)); 31.2 (*t*, C(3), C(5)); 28.8, 28.3, 25.5 (3*q*, Me_3C, 2 Me_2C). ESI-MS: 526 (17, $[M + Na]^+$), 504 (100, $[M + 1]^+$), 397 (44).

5.4. *2-{{{4-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}tetrahydro-2*H*-pyran-4-yl}carbonyl}-amino}-2-methylpropanoic Acid* (**20a**). According to *Procedure D*, **18a** (100 mg, 0.186 mmol) was hydrolyzed in THF/6N HCl 1:1 (4 ml) for 4 h. FC (CH_2Cl_2/MeOH 10:1) yielded, 82 mg (98%) of **20a**. Colorless crystals. M.p. 135–137°. IR ($CHCl_3$): 3440*w*, 3420*w*, 3340*m*, 3300*m*, 2980*m*, 2940*m*, 2840*w*, 1710*s*, 1650*s*, 1530*s*, 1490*s*, 1455*m*, 1385*m*, 1370*m*, 1305*m*, 1270*s*, 1225*m*, 1180*m*, 1110*m*, 1020*m*, 970*m*, 930*m*, 910*m*. ^{1}H-NMR (CD_3OD): 7.66, 7.43 (2*s*, 2 NH); 7.45–7.25 (*m*, 5 arom. H); 5.12 (*s*, PhCH_2O); 3.8–3.7, 3.6–3.5 (2*m*, CH_2(2'), CH_2(6')); 2.15–2.05 (*m*, 2 H_{ax} of CH_2(3') and CH_2(5')); 1.90 (*d*, $J = 13.8$, 2 H_{eq} of CH_2(3') and CH_2(5')); 1.47, 1.44 (2*s*, 2 Me_2C). ^{13}C-NMR (CD_3OD): 178.3, 176.7, 175.0 (3*s*, 3 C=O); 157.9 (*s*, OCONH); 138.2 (*s*, 1 arom. C); 129.6, 129.2, 128.9 (3*d*, 5 arom. CH); 67.7, 64.4 (2*t*, PhCH_2O, C(2'), C(6')); 58.4, 58.1, 57.3 (3*s*, C(4'), 2 Me_2C); 33.1 (*t*, C(3'), C(5')); 25.7, 25.2 (2*q*, 2 Me_2C). CI-MS: 450 (31, $[M + 1]^+$), 359 (66), 358 (52), 342 (100), 316 (62). Anal. calc. for $C_{22}H_{31}N_3O_7$ (449.50): C 58.79, H 6.95, N 9.35; found: C 58.70, H 6.95, N 9.19.

5.5. *2-{{{4-{{2-[(Benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}tetrahydro-2*H*-thiopyran-4-yl}carbonyl}amino}-2-methylpropanoic Acid* (**20b**). According to *Procedure D*, **18b** (150 mg, 0.270 mmol) was hydrolyzed in THF/6N HCl 1:1 (4 ml) for 4 h. FC (CH_2Cl_2/MeOH 10:1) yielded 109 mg (87%) of **20b**. Colorless crystals. M.p. 183°. IR: 3300*s* (br.), 3030*m*, 2980*m*, 2940*m*, 1745*s*, 1700*s*, 1660*s*, 1585*w*, 1530*s*, 1520*s*, 1510*s*, 1470*m*, 1455*m*, 1440*m*, 1390*m*, 1365*m*, 1315*s*, 1280*m*, 1260*s*, 1225*m*, 1170*m*, 1080*m*, 1030*w*, 1020*w*, 975*w*, 945*w*, 920*w*, 900*w*, 870*w*, 820*w*, 790*w*, 740*m*, 695*m*. ^{1}H-NMR ((D$_6$)DMSO): 7.55 (*s*, NH); 7.4–7.3 (*m*, 5 arom. H); 7.26, 7.19 (2*s*, 2 NH); 5.07 (*s*, PhCH_2O); 2.7–2.65, 2.5–2.45, 2.35–2.3, 1.95–1.85 (4*m*, 4 CH_2); 1.35, 1.29 (2*s*, 2 Me_2C). ^{13}C-NMR ((D$_6$)DMSO): 175.4, 173.4, 172.6 (3*s*, 3 C=O); 155.4 (*s*, OCONH); 136.7 (*s*, 1 arom. C); 128.3, 127.8, 127.6 (3*d*, 5 arom. CH); 65.4 (*t*, PhCH_2O); 57.6, 56.4, 54.7 (3*s*, C(4'), 2 Me_2C); 32.3 (*t*, C(3'), C(5')); 25.0, 24.4 (2*q*, 2 Me_2C); 22.4 (*t*, C(2'), C(6')). ESI-MS: 488 (100, $[M + Na]^+$).

5.6. *2-{{{1-(Benzyloxycarbonyl)-4-{{2-[(benzyloxycarbonyl)amino]-2-methylpropanoyl}amino}piperidin-4-yl}carbonyl}amino}-2-methylpropanoic Acid* (**20d**). According to *Procedure D*, **18d** (122 mg, 0.182 mmol) was hydrolyzed in THF/6N HCl 1:1 (4 ml) for 4 h. FC (CH_2Cl_2/MeOH/AcOH 100:5:1) yielded 92 mg (87%) of **20d**. Colorless solid. M.p. 142–145°. IR: 3350*m* (br.), 3020*w*, 2980*w*, 2920*m*, 1700*s*, 1670*s*, 1590*m*, 1530*s*, 1470*w*, 1450*s*, 1385*m*, 1365*m*, 1280*m*, 1250*s*, 1160*w*, 1090*m*, 1075*m*, 1025*w*, 975*w*. ^{1}H-NMR (CD_3OD): 7.70 (*s*, NH); 7.35–7.2 (*m*, 10 arom. H); 5.12, 5.08 (2*s*, 2 PhCH_2O); 3.83 (br. *d*, $J \approx 13.7$, 2 H_{eq} of CH_2(2') and CH_2(6')); 3.00 (*t*, 2 H_{ax} of CH_2(2') and CH_2(6')); 2.05–1.9 (*m*, CH_2(3'), CH_2(5')); 1.45, 1.44 (2*s*, 2 Me_2C). ^{13}C-NMR (CD_3OD): 175.7, 173.2 (2*s*, 3 C=O); 156.1, 155.2 (2*s*, 2 OCONH); 136.6, 136.5 (2*s*, 2 arom. C); 128.1, 128.0, 127.1, 127.5 (4*d*, 10 arom. CH); 66.9, 66.2 (2*t*, 2 PhCH_2O); 57.8, 57.0, 56.6 (3*s*, C(4'), 2 Me_2C); 39.2 (*t*, C(2'), C(6')); 30.9 (*t*, C(3'), C(5')); 24.3, 23.9 (2*q*, 2 Me_2C). ESI-MS: 605 (100, $[M + Na]^+$).

6. *Solvent Dependence of the Chemical Shifts of the NH Groups of the Tripeptides Z-Aib-Xaa-Aib-N(Ph)Me* **18** (see *Fig. 6*). The tripeptides **18a–e** were dissolved in $CDCl_3$ ($c \approx 0.2$M) and the chemical shifts of the NH groups determined at *ca.* 30°. Then, using a syringe, 2, 4, 6, 8, 10, and 12% (*v/v*) of (D_6)DMSO were added, and after each addition, the chemical shifts were determined again.

7. *Crystal-Structure Determination of* **18a–e** *and* **20a** (see *Table 4* and *Figs. 1–3, 5, 7,* and *8*)[4]). All measurements were made on a *Rigaku AFC5R* diffractometer using graphite-monochromated MoK_α radiation (λ 0.71069 Å) and a 12 kW rotating anode generator. The intensities were corrected for *Lorentz* and polarization effects, but not for absorption. Data collection and refinement parameters are listed in *Table 5*, views of the molecules and packing diagrams are shown in *Figs. 1–3, 7,* and *5* and *8*, resp. The structures were solved by direct methods using *SHELXS86* [49], which revealed the positions of all non-H atoms. For **18a–e**, the non-H atoms were refined anisotropically. All of the H-atoms were located in difference electron density maps, and their positions were allowed to refine together with individual isotropic displacement parameters. For **20a**, the asymmetric unit contains a rotationally disordered $CHCl_3$ molecule, but it was difficult to model the disorder adequately. Two positions with relative occupation factors of 3:1 were defined for one Cl-atom only, and the remaining atoms were retained as single entities. All non-H-atoms were refined anisotropically. The amide and hydroxy H-atoms were fixed in the positions indicated by a difference electron density map, while all other H-atoms were fixed in geometrically calculated positions (d(C–H) = 0.95 Å). Each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of the atom to which it was bonded. Refinements of the structures were carried out on F using full-matrix least-squares procedures which minimized the function $\sum w(|F_o| - |F_c|)^2$ where $w = [\sigma^2(F_o) + (0.005\ F_o)^2]^{-1}$. A correction for secondary extinction was applied in the cases of **18a**, **18b**, and **18d**. Neutral atom scattering factors for non-H-atoms were taken from [50a] and the scattering factors for H-atoms from [51]. Anomalous dispersion effects were included in F_c [52]; the values for f' and f'' were those of [50b]. All calculations were performed using the TEXSAN crystallographic software package [53].

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[4]) Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication no. CCDC-10/52. Copies of the data can be obtained, free of charge, on application to the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: + 44-(0)1223-336033, or e-mail: teched@ccdc.cam.ac.uk).

Table 4. *Crystallographic Data of Compounds* **18a–e** *and* **20a**

	18a	**18b**	**18c**	**18d**	**18e**	**20a**
Crystallized from	MeCN	MeCN	MeCN	MeCN	$CHCl_3$/hexane	$CHCl_3$/hexane
Empirical formula	$C_{29}H_{38}N_4O_6$	$C_{29}H_{38}N_4O_5S$	$C_{34}H_{47}N_5O_7 \cdot H_2O$	$C_{37}H_{45}N_5O_7$	$C_{30}H_{40}N_4O_5$	$C_{22}H_{31}N_3O_7 \cdot CHCl_3$
Formula weight	538.64	554.70	655.79	671.79	536.67	568.88
Crystal color, habit	colorless, prism	colorless, prism	colorless, prism	colorless, prism	colorless, prism	colorless, plate
Crystal dimensions [mm]	$0.23 \times 0.38 \times 0.40$	$0.20 \times 0.40 \times 0.45$	$0.25 \times 0.38 \times 0.40$	$0.33 \times 0.38 \times 0.50$	$0.23 \times 0.38 \times 0.45$	$0.12 \times 0.40 \times 0.43$
Temperatur [K]	173(1)	173(1)	173(1)	173(1)	173(1)	173(1)
Crystal system	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P2_1/n$	$P2_1/n$	$P2_1/n$	$P2_1/c$	$P2_1/n$	$P2_1/c$
Z	4	4	4	4	4	4
Reflections for cell determination	25	25	25	25	25	25
2θ range for cell determination [°]	37–40	24–26	38–40	39–40	33–40	29–37
Unit cell parameters a [Å]	17.461(3)	11.963(4)	12.645(3)	9.830(6)	11.949(2)	13.008(3)
b [Å]	16.576(6)	18.122(3)	17.200(4)	22.12(1)	18.230(3)	19.063(4)
c [Å]	9.741(3)	14.133(4)	16.974(2)	16.259(5)	14.130(2)	11.813(4)
β [°]	92.60(2)	106.39(2)	102.66(1)	90.24(4)	106.71(1)	101.75(2)
V [Å^3]	2816(1)	2939(1)	3602(1)	3535(3)	2948.1(8)	2868(2)
D_x [g cm^{-3}]	1.270	1.253	1.209	1.262	1.209	1.317
$\mu(MoK_\alpha)$ [mm^{-1}]	0.0890	0.154	0.0865	0.0880	0.0830	0.363
Scan type	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$	$\omega/2\theta$
$2\theta_{(max)}$ [Å]	55	50	55	60	60	50
Total reflections measured	6904	5624	8929	10878	9221	5475
Symmetry-independent reflections	6465	5172	8269	10293	8594	5036
Reflections used [$I > 2\sigma(I)$]	3937 [$I > 3\sigma(I)$]	3696	4797	6509 [$I > 3\sigma(I)$]	4984	2802
Parameters refined	505	505	620	623	512	334
Final R	0.0416	0.0463	0.0493	0.0493	0.0510	0.0760
wR	0.0379	0.0451	0.0382	0.0464	0.0417	0.0707
Goodness of fit	1.757	2.056	1.724	2.176	1.594	2.953
Secondary extinction coefficient	$3.80 \cdot 10^{-7}$	$3.64 \cdot 10^{-7}$	–	$1.84 \cdot 10^{-7}$	–	–
Final Δ_{max}/σ	0.0003	0.0003	0.0003	0.0003	0.0004	0.004
$\Delta\rho$(max; min) [e Å^{-3}]	0.20; −0.23	0.25; −0.26	0.27; −0.23	0.31; −0.34	0.27; −0.19	0.45; −0.49
Range of $\sigma(d(C-C))$ [Å]	0.003–0.004	0.004–0.005	0.003–0.005	0.002–0.003	0.002–0.004	0.008–0.01

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