

Chiral Heterospirocyclic 2*H*-Azirin-3-amines as Synthons for 3-Amino-2,3,4,5-tetrahydrofuran-3-carboxylic Acid and Their Use in Peptide Synthesis

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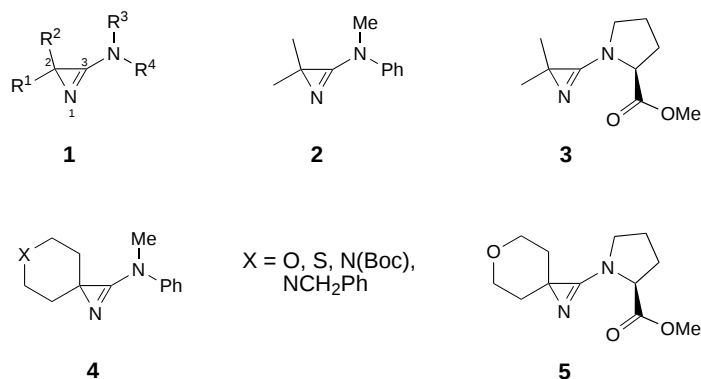
Dedicated to Professor Jack D. Dunitz on the occasion of his 80th birthday

The heterospirocyclic *N*-methyl-*N*-phenyl-5-oxa-1-azaspiro[2.4]hept-1-ene-2-amine (**6**) and *N*-(5-oxa-1-azaspiro[2.4]hept-1-en-2-yl)-(S)-proline methyl ester (**7**) were synthesized from the corresponding heterocyclic thiocarboxamides **12** and **10**, respectively, by consecutive treatment with COCl₂, 1,4-diazabicyclo[2.2.2]octane, and NaN₃ (Schemes 1 and 2). The reaction of these 2*H*-azirin-3-amines with thiobenzoic and benzoic acid gave the racemic benzamides **13** and **14**, and the diastereoisomeric mixtures of the *N*-benzoyl dipeptides **15** and **16**, respectively (Scheme 3). The latter were separated chromatographically. The configurations and solid-state conformations of all six benzamides were determined by X-ray crystallography. With the aim of examining the use of the new synthons in peptide synthesis, the reactions of **7** with Z-Leu-Aib-OH to yield a tetrapeptide **17** (Scheme 4), and of **6** with Z-Ala-OH to give a dipeptide **18** (Scheme 5) were performed. The resulting diastereoisomers were separated by means of MPLC or HPLC. NMR Studies of the solvent dependence of the chemical shifts of the NH resonances indicate the presence of an intramolecular H-bond in **17**. The dipeptides (S,*R*)-**18** and (S,*S*)-**18** were deprotected at the N-terminus and were converted to the crystalline derivatives (S,*R*)-**19** and (S,*S*)-**19**, respectively, by reaction with 4-bromobenzoyl chloride (Scheme 5). Selective hydrolysis of (S,*R*)-**18** and (S,*S*)-**18** gave the dipeptide acids (R,*S*)-**20** and (S,*S*)-**20**, respectively. Coupling of a diastereoisomeric mixture of **20** with H-Phe-O^tBu led to the tripeptides **21** (Scheme 5). X-Ray crystal-structure determinations of (S,*R*)-**19** and (S,*S*)-**19** allowed the determination of the absolute configurations of all diastereoisomers isolated in this series.

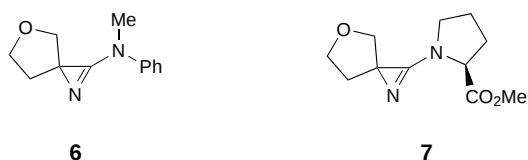
1. Introduction. – Peptides containing α,α -disubstituted α -amino acids are restricted in their conformational freedom [1–12]. As a consequence of the rigidity of the peptide backbone, secondary structures, such as β -turns and helices, are stabilized or even promoted [13][14]. The synthesis of such conformationally restricted peptides is a useful tool in the search for the biologically active conformation of a peptide. A useful method for introducing α,α -disubstituted α -amino acids into peptides is the ‘azirine/oxazolone method’, in which 2*H*-azirin-3-amines **1** are used as amino acid synthons [15][16]. This method has been applied successfully in the synthesis of oligopeptides, endotheiopeptides, cyclic peptides, and cyclic depsipeptides [17] (and refs. cit. therein) [18–21]. Thus, the reaction of 2*H*-azirin-3-amines, e.g., the Aib synthon **2**, with amino or peptide acids leads to peptide amides, the terminal amide bonds of which can be hydrolyzed selectively. Recently, the dipeptide synthon methyl *N*-(2,2-dimethyl-2*H*-azirin-3-yl)-(S)-proline (**3**) [22] has been prepared, and has found application in the synthesis of the peptaibol antibiotics *Trichovirin I 1B* and *I 4A* [22][23]. Furthermore, the heterospirocyclic *N*-methyl-*N*-phenyl-2*H*-azirin-3-amines **4** [24] and the hetero-

¹⁾ Diploma thesis of S. S., Universität Zürich, 2002.

spirocyclic dipeptide synthon *N*-(6-oxa-1-azaspiro[2.5]oct-1-en-2-yl)-(S)-proline methyl ester (**5**) [18] have been synthesized.



In the present paper, we report the synthesis of the amino acid synthon **6** (Thf synthon) and the dipeptide synthon **7** (Thf-Pro synthon). In these new azirine derivatives, a heterocycle is used for the first time as a stereogenic unit in a 2*H*-azirin-3-amine, leading to racemic or diastereoisomeric building blocks **6** and **7**, respectively. Reactions with thiobenzoic and benzoic acid, with an α -amino acid, and with a dipeptide confirmed that these new building blocks are suitable for peptide synthesis.

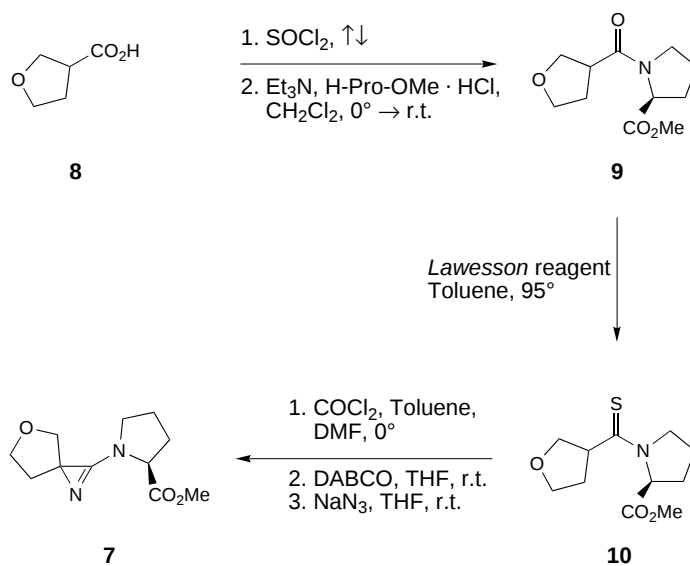


2. Results and Discussion. – 2.1. Synthesis of Heterospirocyclic 2*H*-Azirin-3-amines.

The starting material, 2,3,4,5-tetrahydrofuran-3-carboxylic acid (**8**), was prepared by hydrogenation of commercially available furan-3-carboxylic acid. Consecutive treatment with SOCl_2 and methyl (*S*)-prolinate gave *N*-[(2,3,4,5-tetrahydrofuran-3-yl)carbonyl]-(*S*)-proline methyl ester (**9**; *Scheme 1*). Since the method of *Villalgordo* and *Heimgartner* [19][25], used by *Strässler* [24] for the synthesis of **4**, is limited to *N*-alkyl-*N*-phenyl amides, **9** was converted to **10** by thionation with *Lawesson* reagent. Analogously to the procedure described in [26][27], consecutive treatment of a solution of **10** and catalytic amounts of DMF in CH_2Cl_2 with COCl_2 , evaporation of the solvent, dissolution of the residue in THF, addition of 1,4-diazabicyclo[2.2.2]octane (DABCO), filtration, and reaction with NaN_3 gave, after chromatographic workup, azirine **7** in 63% yield as a pale-yellow oil. It is important that the SiO_2 used for the chromatographic separation of **7** is deactivated with Et_3N , otherwise considerably less product is obtained²⁾.

²⁾ The reaction conditions worked out for the synthesis of **6** (THF/DMF, 8 d, r.t.; *vide infra*) were not optimal in this case.

Scheme 1



The synthesis of **6** by the method of *Villalgordo* and *Heimgartner* [19][25] was unsuccessful, even though **11** is an *N*-alkyl-*N*-phenyl amide (Scheme 2). Therefore, after thionation of **11** to give **12**, **6** was also synthesized according to the procedure described in [26][27], which gives the product in 63% yield. However, after addition of NaN_3 , it was necessary to change the solvent to DMF, otherwise not even traces of **6** could be detected by TLC. *Wipf* [26] has already shown that the rate of reaction of the α -chloro enamine with NaN_3 to give the 2*H*-azirin-3-amine is highly dependent on the solvent. The reaction rate decreases in the order $\text{DMF} > \text{THF} > \text{Et}_2\text{O}$, but, even in DMF, a long reaction time of 8 d was necessary in the case of **6**, which is similar to the reaction time in the synthesis of the carbocyclic *N*-methyl-*N*-phenyl-1-azaspiro[2.4]-hept-1-en-2-amine described by *Sahebi et al.* [28].

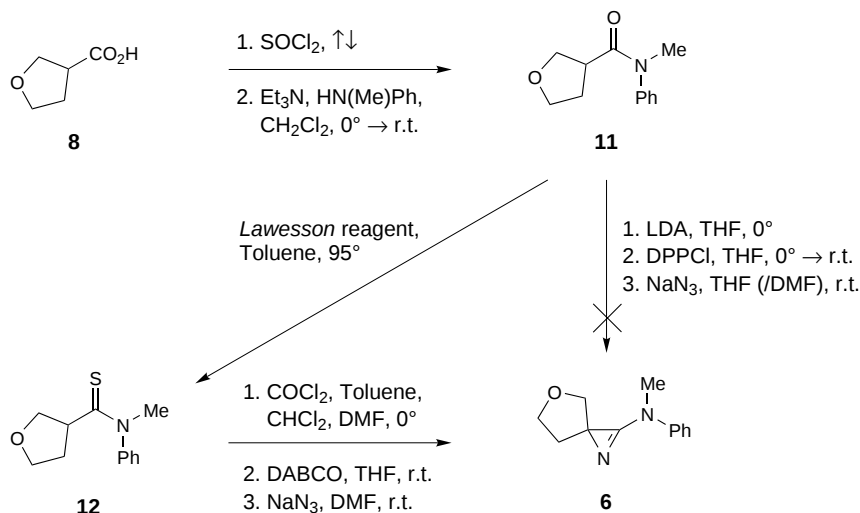
With the aim of showing that **6** and **7** are mixtures of enantiomers and diastereoisomers, respectively, the isomers were separated on a chiral HPLC-column (*Chiracel-OD*). It should also be possible to separate them on a preparative scale into the enantiomerically pure amino acid synthons (*R*)-**6** and (*S*)-**6**, and the diastereoisomerically pure dipeptide synthons (*R,S*)-**7** and (*S,S*)-**7**³⁾.

2.2. Reactions with Thiobenzoic and Benzoic Acid. To examine the reactivity of the new 2*H*-azirin-3-amines **6** and **7**, they were reacted with PhCOSH and PhCOOH (Scheme 3). All reactions gave the products in good to very good yields (87–99%).

The solid-state structures of products **13** and **14**, obtained from the reactions with **6**, were established by X-ray crystallography (Fig. 1). The amide H-atom of **13** forms an intermolecular H-bond with the O-atom of the tetrahydrofuran ring of a neighboring

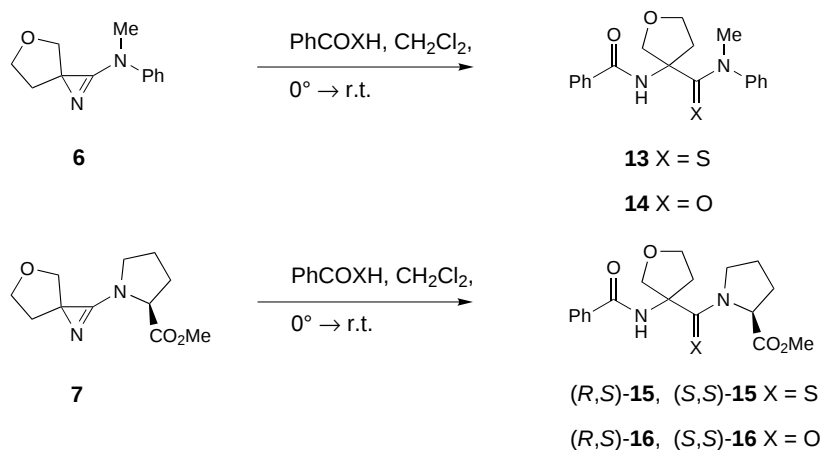
³⁾ All attempts to separate the mixture of diastereoisomers (*R,S*)-**7** and (*S,S*)-**7** on a nonchiral HPLC column failed.

Scheme 2



LDA = Lithium diisopropylamide; DPPCl = diphenylphosphorochloridate; DABCO = 1,4-diazabicyclo[2.2.2]-octane.

Scheme 3



molecule (*Table 1*). This interaction links pairs of molecules across a center of inversion into dimers, which have a graph-set motif [29] of $\text{R}_2^2(10)$ (*Fig. 2*). The conformations of five-membered rings can be described by the puckering parameter ϕ_2 [30], where an ideal envelope conformation has a value for ϕ_2 of $36n^\circ$ (n is an integer), and $\phi_2 = (36n + 18)^\circ$ for an ideal half-chair or twist conformation. The heterocyclic five-membered ring of **13** has an almost perfect envelope conformation ($\phi_2 = 250.7(2)^\circ$)

with C(3)⁴) as the envelope flap. In the case of **14**, there are two symmetry-independent molecules in the asymmetric unit. They differ primarily in the conformation of the five-membered ring and in the orientations of the Ph rings. In molecule B, the Ph rings of the benzamide and secondary amide groups are twisted by *ca.* 30° and 11°, respectively, compared with their orientations in molecule A. In the five-membered ring of molecule B, the O-atom and the adjacent CH₂ group most distant from the spiro-C-atom are disordered over two approximately equally occupied positions, which leads to two different conformations with $\phi_2 = 298(1)^\circ$ and $264.5(5)^\circ$. The former is halfway between a C(46) envelope and a half-chair twisted on C(45a)–C(46), while the latter has a half-chair conformation twisted on O(44b)–C(45b) that is distorted towards an O(44b) envelope. The five-membered ring of molecule A has $\phi_2 = 224.2(4)^\circ$, which is a conformation that lies nearly halfway between a C(13) envelope and a half-chair twisted on C(3)–C(13). The amide H-atom of each molecule acts as a donor for intermolecular H-bonds (*Table 1*). In molecule A, this interaction is with the secondary amide O-atom of a neighboring molecule B. The NH group of molecule B, in turn, interacts with the primary amide O-atom of a different molecule A. The combination of these interactions links the molecules into infinite chains in which both symmetry-independent molecules are incorporated in an alternating ...A...B...A...B... sequence. These chains run parallel to the *x*-axis and have a binary graph-set motif of C₂(9).

Table 1. *H-Bonding parameters for 13, 14, (R,S)-15, (S,S)-15, (R,S)-16, (S,S)-16, (S,R)-19, and (S,S)-19*

	D–H...A ^{a)}	D–H [Å]	H...A [Å]	D...A [Å]	D–H...A [°]
13	N(4)–H(4)...O(14 ⁱ)	0.81(1)	2.37(1)	3.136(2)	160(1)
14	N(4)–H(4)...O(32 ⁱⁱ)	0.84(2)	2.05(3)	2.877(3)	168(2)
	N(34)–H(34)...O(5)	0.87(3)	2.24(3)	3.092(3)	163(2)
<i>(R,S)</i> - 15	N(7)–H(7)...S(5 ⁱⁱⁱ)	0.82(2)	2.84(2)	3.628(1)	164(1)
<i>(S,S)</i> - 15	N(7)–H(7)...S(5 ⁱⁱⁱ)	0.86(1)	2.76(1)	3.590(1)	161(1)
<i>(R,S)</i> - 16	N(7)–H(7)...O(5 ^{iv})	0.86(2)	2.10(2)	2.933(2)	163(2)
<i>(S,S)</i> - 16	N(7)–H(7)...O(5 ^v)	0.82(2)	2.17(2)	2.974(2)	167(2)
<i>(S,R)</i> - 19	N(4)–H(4)...O(28 ^{vi})	0.79(3)	2.07(3)	2.847(2)	170(2)
	N(7)–H(7)...O(2 ^{vii})	0.86(2)	2.21(2)	3.049(2)	168(2)
	O(27)–H(27)...O(8)	0.91(4)	1.81(4)	2.723(2)	176(4)
	O(28)–H(28)...O(27)	0.83(4)	1.87(4)	2.680(3)	162(3)
<i>(S,S)</i> - 19	N(4)–H(4)...O(27 ^{viii})	0.81(2)	2.00(2)	2.810(2)	173(2)
	N(7)–H(7)...O(2 ^{ix})	0.85(2)	2.22(2)	3.056(2)	169(2)
	O(27)–H(27)...O(28)	0.95	1.72	2.664(2)	172
	O(28)–H(28)...O(8)	0.95	1.80	2.737(2)	171

^{a)} Symmetry operators: ⁱ 1 – *x*, 1 – *y*, 1 – *z*; ⁱⁱ – 1 + *x*, *y*, *z*; ⁱⁱⁱ 1 – *x*, 1/2 + *y*, 3/2 – *z*; ^{iv} 1 – *x*, – 1/2 + *y*, 1/2 – *z*; ^v 2 – *x*, – 1/2 + *y*, 1 – *z*; ^{vi} – *x*, – 1/2 + *y*, 1 – *z*; ^{vii} – *x*, 1/2 + *y*, – *z*; ^{viii} 2 – *x*, – 1/2 + *y*, – *z*; ^{ix} 2 – *x*, 1/2 + *y*, 1 – *z*.

The reactions with **7** resulted in mixtures of diastereoisomers, *i. e.*, *(R,S)/(S,S)*-**15** and *(R,S)/(S,S)*-**16**, which could be separated by means of MPLC. The X-ray crystal-structure determinations of all four compounds were carried out (*Fig. 3*), and the absolute configurations of *(R,S)*-**15**, *(S,S)*-**15**, and *(S,S)*-**16** were determined inde-

⁴⁾ The atom numbering used in crystal-structure determinations was chosen arbitrarily.

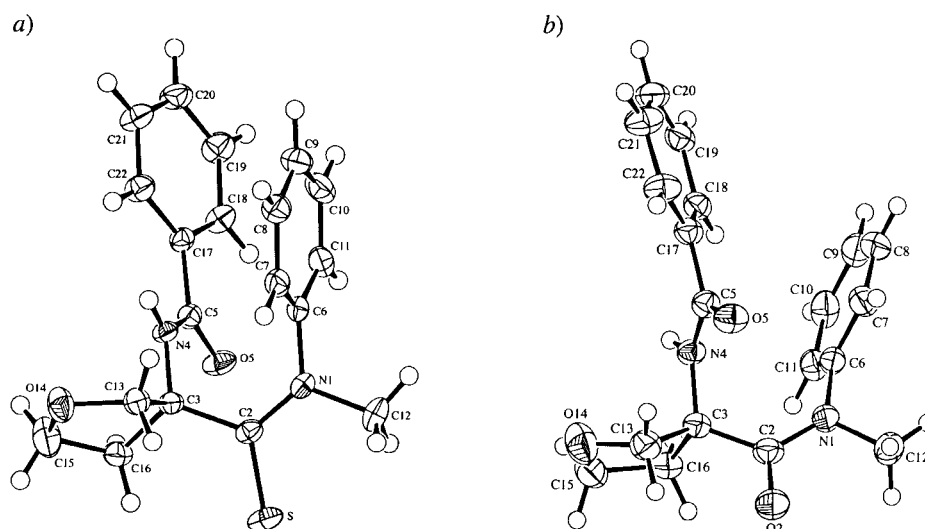


Fig. 1. ORTEP Plots [31] of the molecular structures of a) **13** and b) molecule A of **14** (50% probability ellipsoids; arbitrary numbering of atoms)

pendently by the diffraction experiment, whereas, for (*R,S*)-**16**, the (*R*)-configuration at the spiro-C(6)-atom⁴ was determined relative to the known (*S*)-configuration of the proline moiety. The pyrrolidine ring of (*R,S*)-**15** has a half-chair conformation ($\phi_2 = 97.2(2)^\circ$) twisted on C(10)–C(11), but distorted significantly towards a C(11) envelope, while the tetrahydrofuran ring has a C(6) envelope conformation ($\phi_2 = 258.8(2)^\circ$) distorted towards a half-chair twisted on C(6)–C(16). The NH group forms an intermolecular H-bond with the S-atom of a neighboring molecule (Table 1). This interaction links the molecules into infinite chains that run parallel to the *y*-axis and have a graph-set motif of C(5) (Fig. 4). Both five-membered rings of the diastereoisomeric (*S,S*)-**15** have slightly distorted half-chair conformations. The pyrrolidine ring ($\phi_2 = 94.6(2)^\circ$) is twisted on C(10)–C(11), while the tetrahydrofuran ring ($\phi_2 = 164.7(2)^\circ$) is twisted on O(14)–C(15). The intermolecular H-bonding pattern is analogous to that of (*R,S*)-**15** (Table 1).

The pyrrolidine rings of (*R,S*)-**16** and (*S,S*)-**16** have nearly ideal half-chair conformations ($\phi_2 = 91.4(3)$ and $92.9(3)^\circ$, resp.) twisted on C(10)–C(11)⁴. The tetrahydrofuran rings also have half-chair conformations ($\phi_2 = 270.1(3)$ and $168.5(3)^\circ$, resp.) twisted on C(6)–C(16) and O(14)–C(15), respectively, although the latter is somewhat distorted towards an O(14) envelope conformation. In both cases, the amide NH group forms an intermolecular H-bond with the O(5)-atom of the central amide group of a neighboring molecule (Table 1). These interactions link the molecules into infinite chains that run parallel to the *y*-axis and have a graph-set motif of C(5) (Figs. 5 and 6). The asymmetric unit of (*S,S*)-**16** contains one molecule of the peptide and one CDCl₃ molecule.

2.3. Reactions with Amino Acids and Peptides. To examine the use of the new synthons in peptide synthesis, **7** was reacted with Z-Leu-Aib-OH to give the

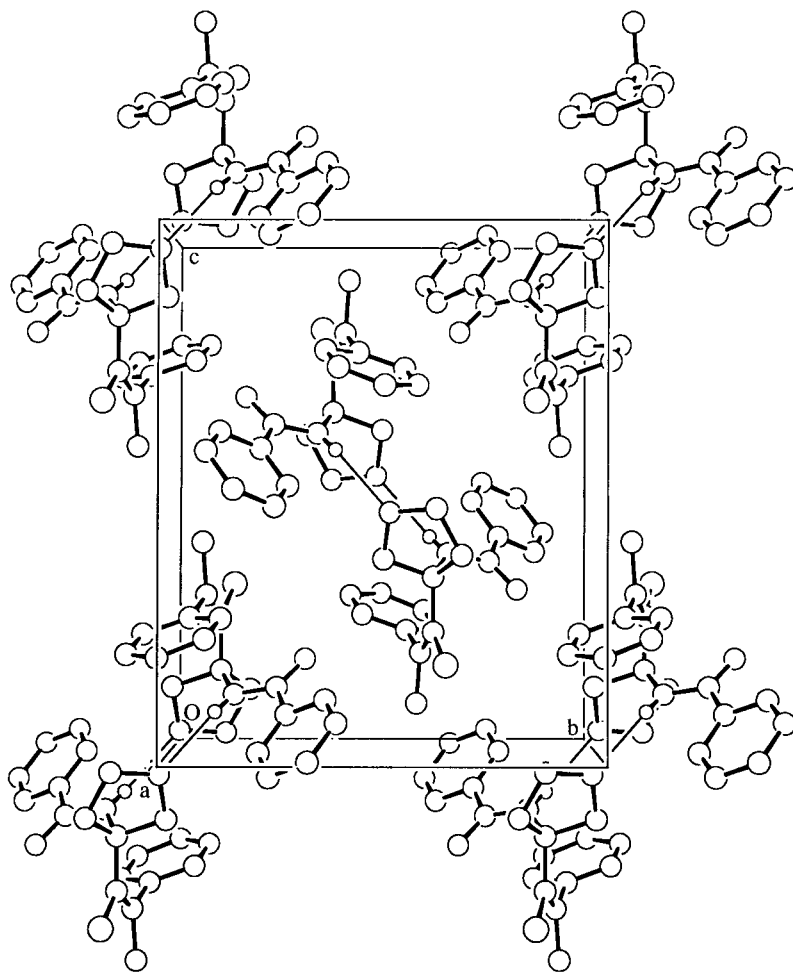


Fig. 2. Crystal packing of **13**, projected down the *a*-axis showing the *H*-bonding interactions (uninvolved H-atoms omitted for clarity)

tetrapeptides **17a** and **17b** (Scheme 4), while **6** was reacted with Z-Ala-OH to yield the dipeptides (*S,R*)-**18** and (*S,S*)-**18** (Scheme 5). The resulting mixtures of diastereoisomers were separated by means of MPLC ((*S,R*)-**18** and (*S,S*)-**18**) and HPLC (**17a** and **17b**).

In the case of the dipeptides (*S,R*)-**18** and (*S,S*)-**18**, it was shown that both the N- and the C-termini can be deprotected selectively by standard methods. After hydrogenolysis of the dipeptides (*S,R*)-**18** and (*S,S*)-**18** and reaction with 4-bromobenzoyl chloride, the crystalline derivatives (*S,R*)-**19** and (*S,S*)-**19**, respectively, were obtained. Their structures were established by X-ray crystallography (Fig. 7), and the absolute configurations of the two molecules were determined independently by the diffraction experiment. This confirmed the expected (*S*)-configurations of the proline

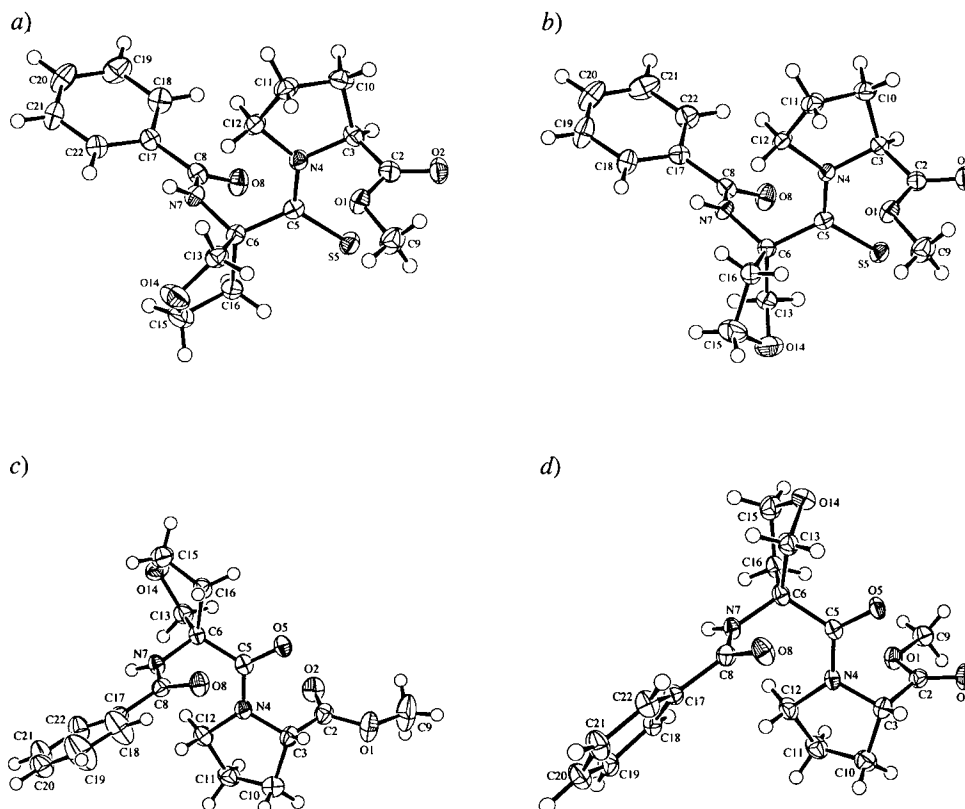
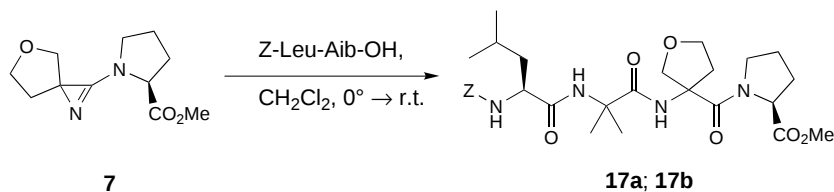


Fig. 3. ORTEP Plots [31] of the molecular structures of a) (R,S)-**15**, b) (S,S)-**15**, c) (R,S)-**16**, and d) (S,S)-**16** (50% probability ellipsoids; arbitrary numbering of atoms; the CDCl_3 molecule in (S,S)-**16** is not shown)

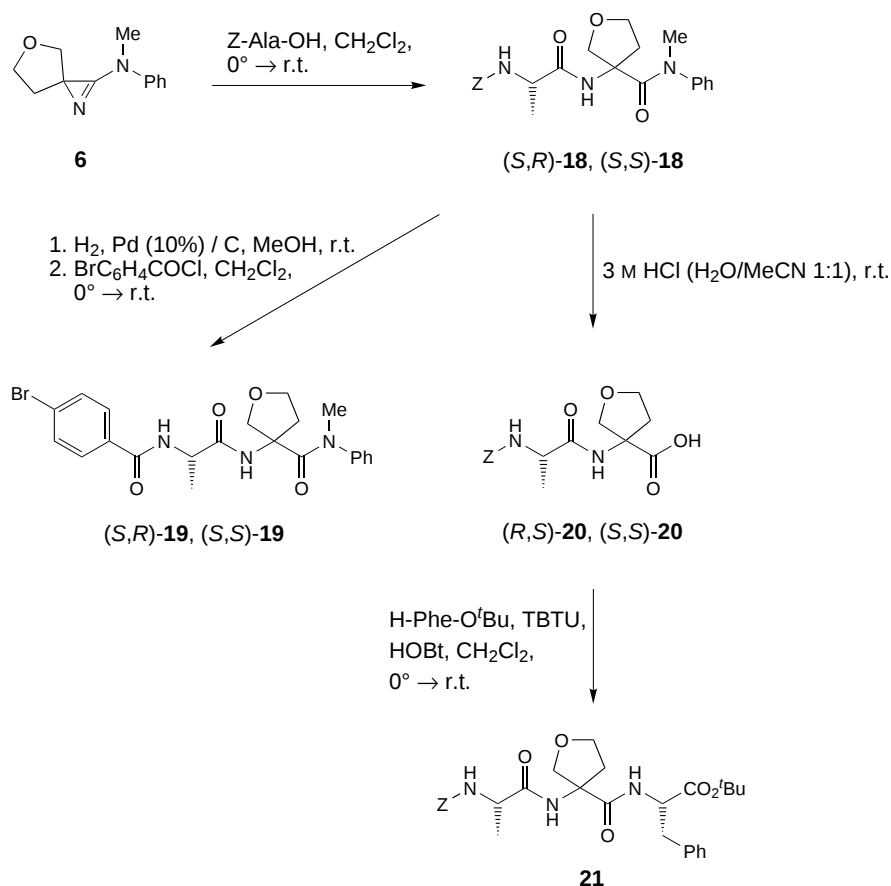
Scheme 4



residue, and the (*R*)- and (*S*)-configurations, respectively, at C(6)⁴). The knowledge of the absolute configurations of (*S,R*)-**19** and (*S,S*)-**19** allowed the assignment of the absolute configurations of all diastereoisomers isolated in this series (Scheme 5).

The asymmetric units of both (*S,R*)-**19** and (*S,S*)-**19** contain one peptide molecule plus two molecules of MeOH. In the five-membered ring of (*S,R*)-**19**, the O-atom and the adjacent CH_2 group most distant from the spiro-C-atom are disordered. Two positions were defined for each of the disordered atoms, and the model was refined

Scheme 5



successfully, although restraints were required in order to maintain sensible behavior of the disordered region. The major conformation exists in *ca.* 68% of the molecules that clearly have the (*R*)-configuration at C(3)⁴). However, from a purely crystallographic point of view, it is not entirely unequivocal whether the minor conformation also has the (*R*)-configuration, and the disorder is due simply to conformational disorder of the ring, or whether the minor conformation actually has the (*S*)-configuration at C(3), and the disorder is the result of there being a mixture of diastereoisomers in the crystal. If the disordered model is refined as a mixture of diastereoisomers without bond-length restraints, the resultant geometric parameters are slightly better than when the model is treated as a single diastereoisomer. However, the anisotropic displacement parameters for the disordered atoms are better in the latter case. The *R*-factors for the two models are essentially identical. The crystallographic results probably favor the model representing a single diastereoisomer very slightly, but the evidence is weak. Nevertheless, this conclusion is in agreement with the NMR evidence obtained from

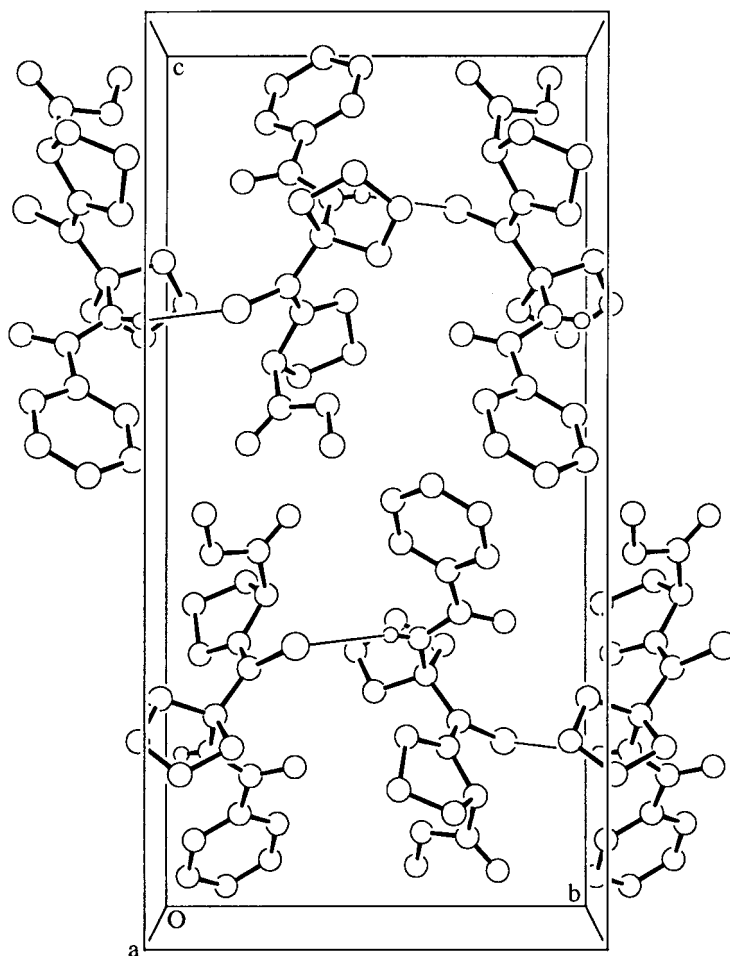


Fig. 4. Crystal packing of (R,S)-**15**, projected down the *a*-axis showing the H-bonding interactions (uninvolved H-atoms omitted for clarity)

a solution made from the crystalline material, which shows that the batch from which the crystal was taken contains only a single diastereoisomer. The two conformations of the disordered tetrahydrofuran ring in (*S,R*)-**19** have C(18a) and C(19) envelope conformations ($\phi_2 = 329.9(6)$ and $332(2)^\circ$, resp.) that are distorted towards half-chair conformations twisted on O(17a)–C(18a) and O(3)–C(19), respectively. The O-atom of the tetrahydrofuran ring of (*S,S*)-**19** is also disordered over two orientations with the major conformation being occupied in *ca.* 80% of the molecules. This leads to two conformations of the ring ($\phi_2 = 150.6(3)$ and $222.4(6)^\circ$) that represent C(18) and C(16) envelopes distorted towards half-chair conformations twisted on O(17a)–C(18) and C(16)–O(17b), respectively.

In both diastereoisomers, the central amide NH group of the peptide molecule forms an intermolecular H-bond with the O-atom of an adjacent MeOH molecule. The

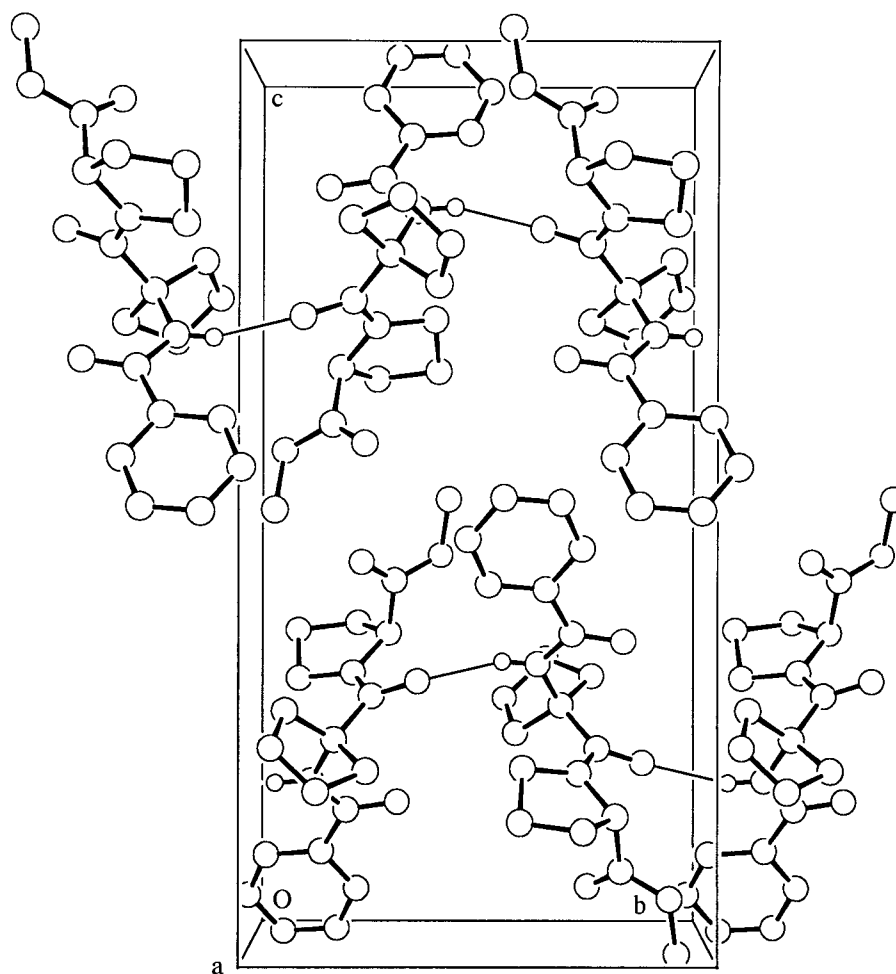


Fig. 5. Crystal packing of (R,S)-**16**, projected down the *a*-axis showing the H-bonding interactions (uninvolved H-atoms omitted for clarity)

latter then forms an intermolecular H-bond with the O-atom of the other symmetry-independent MeOH molecule, which, in turn, forms another intermolecular H-bond with the O-atom of the bromobenzamide group of a second peptide molecule (*Table 1*). The combination of these interactions generates infinite zig-zag chains containing the $\cdots$ peptide $\cdots$ MeOH(1) $\cdots$ MeOH(2) $\cdots$ peptide $\cdots$ sequence (*Fig. 8*). These chains run parallel to the [010] direction and have a ternary graph-set motif of $C_3^3(11)$. An additional intermolecular H-bond between the bromobenzamide NH and the O-atom at the opposite end of an adjacent peptide molecule links just the peptide molecules into additional infinite chains, which also run parallel to the [010] direction and have a graph-set motif of $C(8)$. The combination of all H-bonding interactions links the peptide and MeOH molecules together into an infinite two-dimensional

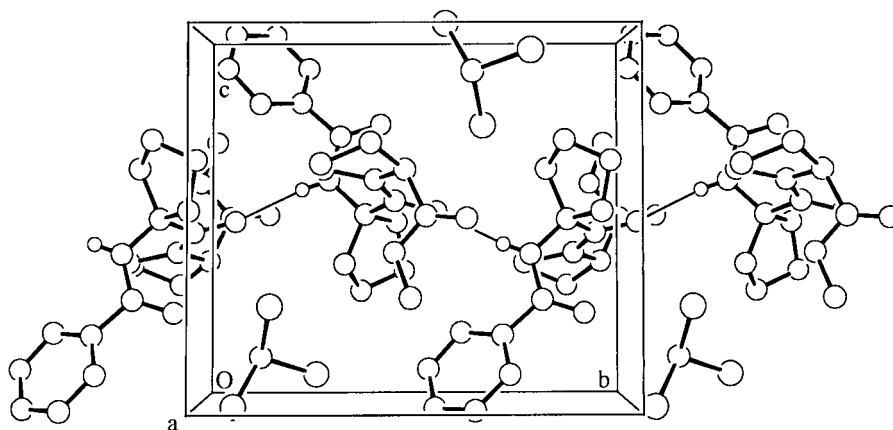


Fig. 6. Crystal packing of (S,S)-**16**, projected down the *a*-axis showing the H-bonding interactions (uninvolved H-atoms omitted for clarity)

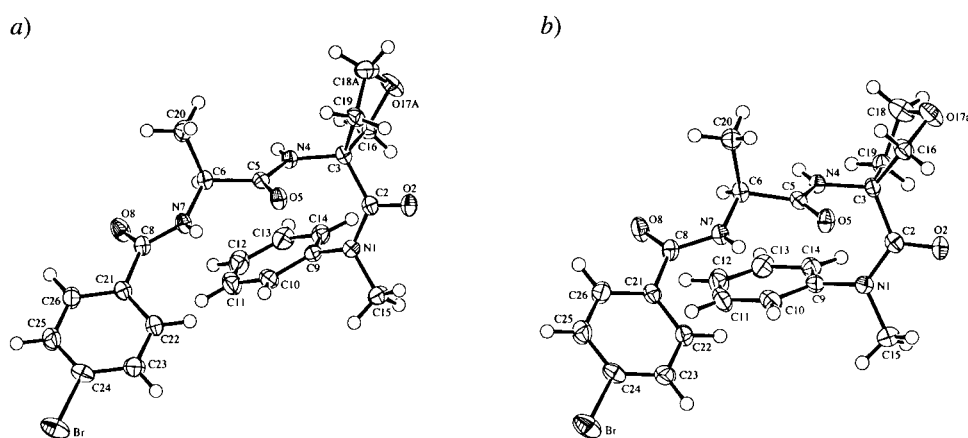


Fig. 7. ORTEP Plots [31] of the molecular structures of a) (S,R)-**19** and b) (S,S)-**19** (50% probability ellipsoids; arbitrary numbering of atoms; only one of the disordered conformations is shown; the MeOH molecules are not shown)

network that lies parallel to the (100) plane. Overall, aside from the inverse configuration at the spiro-C-atom, the structures of (S,R)-**19** and (S,S)-**19** are extremely similar in terms of molecular conformation, crystal packing, H-bond properties, and unit-cell dimensions.

Selective hydrolysis of (S,R)-**18** and (S,S)-**18** with 3M HCl in H₂O/MeCN 1:1 at room temperature gave the dipeptide acids (R,S)-**20** and (S,S)-**20**, respectively, in 75 and 84% yield (*Scheme 5*). A mixture of these two diastereoisomers was coupled with H-Phe-O^tBu using TBTU/HOBt, which led to the tripeptide **21** as a mixture of diastereoisomers.

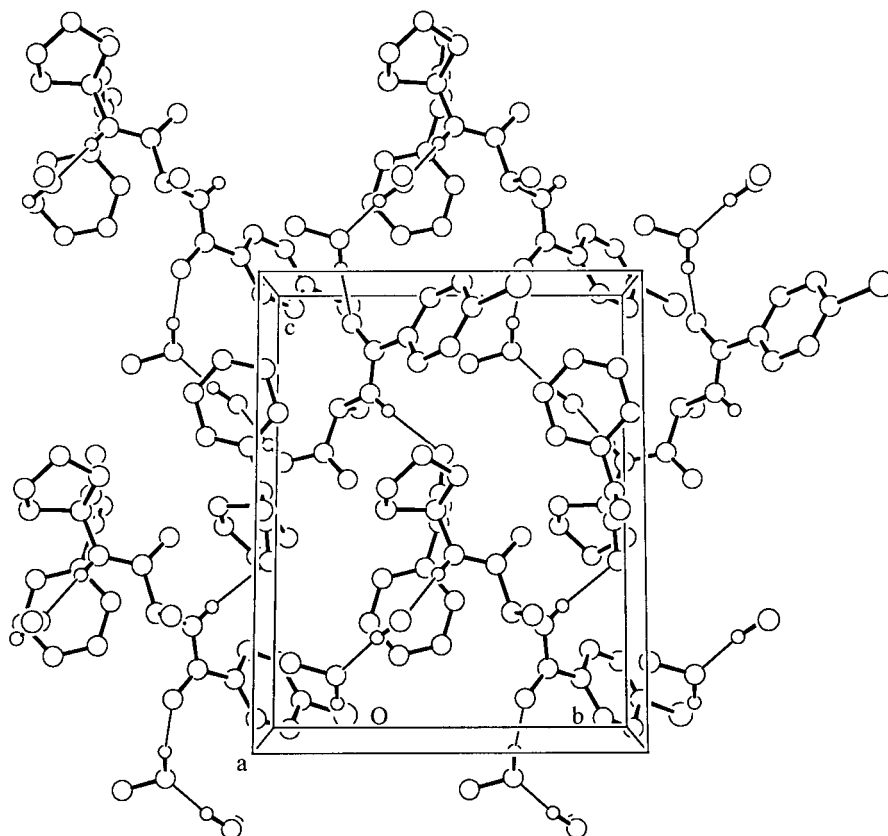
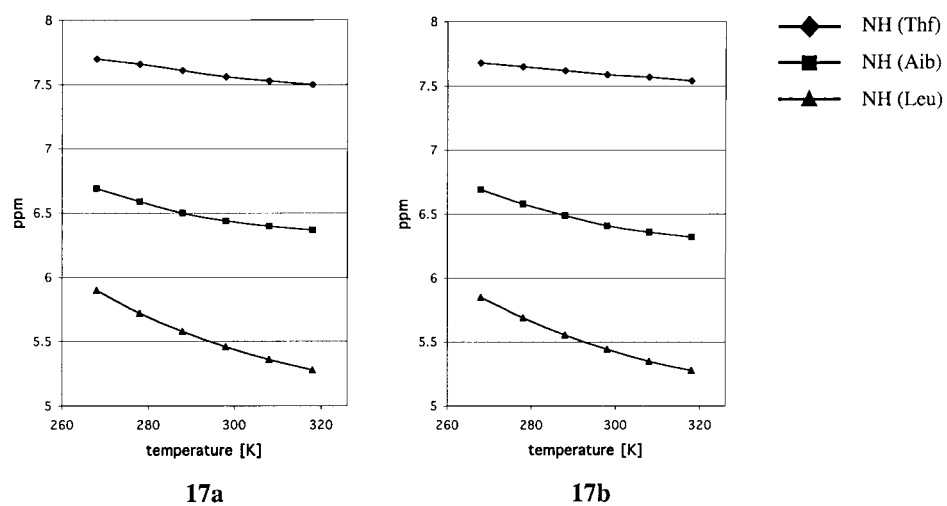


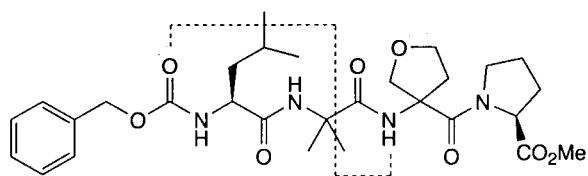
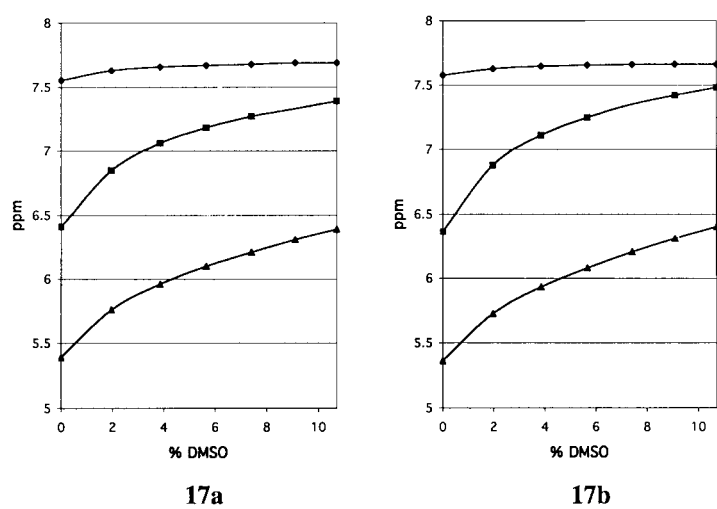
Fig. 8. Crystal packing of (S,S)-**19**, projected down the *a*-axis showing the H-bonding interactions (uninvolved H-atoms omitted for clarity)

No crystals suitable for an X-ray crystal-structure determination were obtained from **17a** and **17b**. Therefore, the conformations of **17a** and **17b** were examined in solution by NMR methods. To determine which of the NH groups of **17a** and **17b** are involved in intramolecular H-bonds, the chemical shifts of the NH resonances were measured in different CDCl₃/(D₆)DMSO mixtures (solvent-titration experiment) and at different temperatures (Fig. 9). The NH groups involved in intramolecular H-bonds should show a very small dependence, whereas the chemical shifts of solvent-exposed NH groups are influenced more significantly [32][33]. For the assignment of the NH resonances, 2D-NMR experiments were performed. Surprisingly, no significant differences could be observed in the temperature dependence of the NH shifts. However, significant differences were observed in the solvent-titration experiment: the very small dependency of the NH(Thf) resonance on the CDCl₃/(D₆)DMSO ratio, compared with the other NH resonances, strongly indicates the presence of an intramolecular H-bond. Most likely, the acceptor is the O-atom of the urethane group, as this interaction leads to the formation of a ten-membered ring, *i.e.*, a β -turn (Fig. 9; *cf.* also [34][35]).

a)



b)

Fig. 9. a) Solvent and b) temperature dependence of the NH shifts of **17a** and **17b**

However, because all attempts to determine the crystal structure failed, and NOE measurements concerning the configuration at the spiro-C-atom brought no clear results, the configurations of **17a** and **17b** still remain in doubt.

2.4. Favored Torsion Angles of the Thf Residue. The torsion angles ϕ , ψ , and ω (Fig. 10) of the synthesized peptides containing the Thf residue are listed in Table 2; the data come from the X-ray crystal-structure determinations. The values of the torsion angles ϕ_i and ψ_i of **13**, **14**, (S,S)-**16**, (S,R)-**19**, and (S,S)-**19**, correspond to the values expected for a β -turn of type I' or III' (I or III for molecule A of **14**). In (R,S)-**15**, (S,S)-**15**, and (R,S)-**16**, they correspond to the values expected for a left-handed α -helix. Such short sequences containing proline as a 'helix-breaking' amino acid do not allow exact classifications. However, it is clear that the amino acid Thf prefers helical conformations (a β -turn of type III or III', respectively, corresponds to a part of a 3_{10} helix), as expected for α,α -disubstituted amino acids. The amide bonds are almost planar as the torsion angles ω show. As mentioned above, the formation of a β -turn has also been observed for **17a** and **17b** in solution.

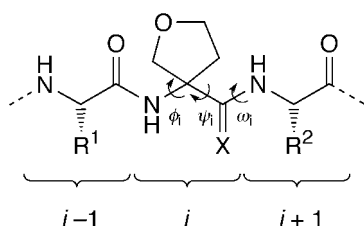


Fig. 10. Torsion angles of the Thf residue in a peptide backbone

Table 2. Torsion Angles [$^{\circ}$] within the Backbone of **13**, **14**, (R,S)-**15**, (S,S)-**15**, (R,S)-**16**, (S,S)-**16**, (S,R)-**19**, and (S,S)-**19**

	ϕ_{i-1}	ψ_{i-1}	ω_{i-1}	ϕ_i	ψ_i	ω_i	ϕ_{i+1}	ψ_{i+1}
13				58.4(2)	37.1(2)	174.6(1) ^a		
14A				– 61.7(3)	– 24.9(3)	176.9(2) ^a		
14B				60.0(3)	37.3(3)	174.0(2) ^a		
(R,S)- 15				63.5(2)	49.0(2)	174.1(1)	– 60.7(2)	– 30.4(2)
(S,S)- 15				66.3(2)	47.4(2)	175.5(1)	– 60.6(2)	– 32.2(2)
(R,S)- 16				54.8(2)	46.1(2)	180.0(1)	– 67.7(2)	156.9(1)
(S,S)- 16				62.2(2)	37.5(3)	176.0(2)	– 61.2(2)	– 40.1(2)
(S,R)- 19	– 149.03(17)	151.11(15)	176.22(15)	56.4(2)	29.2(2)	– 178.66(16) ^a		
(S,S)- 19	– 150.1(2)	147.5(2)	177.0(2)	56.7(3)	30.9(3)	178.8(2) ^a		

^a) Torsion angle C(3)–C(2)–N(1)–(Me).

3. Conclusions. – We have shown that 2*H*-azirin-3-amines **6** and **7** can be prepared and, in principle, separated into stereochemically pure compounds. These azirines are Thf and Thf-Pro building blocks, which can be introduced conveniently into a peptide chain by the 'azirine/oxazolone method'. The conformational characteristics of Thf within peptide backbones are comparable with those of other α,α -disubstituted α -amino acids.

We thank the analytical sections of our institute for spectra and elemental analyses, especially Miss *Nadja Walch* for numerous NMR measurements, and Miss *Jovita Cavegn* for her assistance with the determination of the crystal structures. Financial support of the *Swiss National Science Foundation* and *F. Hoffmann-La Roche AG*, Basel, is gratefully acknowledged.

Experimental Part

1. *General*. Solvents were purified by standard procedures. TLC: *Merck* TLC aluminum sheets, silica gel 60 F_{254} . Prep. TLC: *Merck* PLC plates (glass), silica gel 60 F_{254} , 2 mm. Column chromatography (CC): *Uetikon-Chemie*, silica gel C-560 (0.04–0.063 mm, 230–400 mesh). Medium-pressure liquid chromatography (MPLC): *Merck LiChroprep Si 60*, 15–25 μm ; column: *Kron-Lab 4/98 – PRO*, 480 $\times$ 30 mm or *Labomatic*, 380 $\times$ 20 mm. High-performance liquid chromatography (HPLC): column: *Chiracel-OD*, 250 $\times$ 4.6 mm, 5 μm or *Macherey-Nagel Nucleosil 100-7*, 250 $\times$ 4.6 mm, 7 μm ; or (reversed phase) *Macherey-Nagel Nucleosil 100-7 C8*, 250 $\times$ 4.6 mm, 7 μm ; detection (DAD) at $\lambda = 220$ nm. Prep. HPLC: column: *Macherey-Nagel Nucleosil 100-7*, 250 $\times$ 21 mm, 7 μm ; detection (DAD) at $\lambda = 254$ nm. M. p.: *Büchi Melting Point B-450* apparatus; uncorrected. IR Spectra: *Perkin-Elmer, Spectrum one FT-IR* spectrophotometer; in KBr unless otherwise stated; absorptions in cm^{-1} . NMR Spectra: *Bruker AC-300* (^1H , ^{13}C , DEPT) at 300 and 75 MHz, resp., or *Bruker DRX-600* (^1H , ^{13}C , HSQC, HMBC, COSY, NOESY) at 600 and 150 MHz, resp., in CDCl_3 at 300 K unless otherwise stated; δ in ppm, coupling constants J in Hz; ^{13}C -signal multiplicity from DEPT spectra. MS: *Finnigan MAT-90* (EI, CI), *Finnigan SSQ-700* (EI, CI), or *Finnigan TSQ-700* instrument (ESI); m/z (rel. %). GC/MS: *Hewlett Packard HP-5890 Series II* (GC) / *Hewlett Packard HP-5971 Series* (EI-MS).

2. *Synthesis of the 2H-Azirin-3-amines*. 2.1. *N-Methyl-N-phenyl-5-oxa-1-azaspiro[2.4]hept-1-en-2-amine (6)*. 2,3,4,5-Tetrahydrofuran-3-carboxylic acid (**8**). To a soln. of furan-3-carboxylic acid (5.006 g, 44.67 mmol) in 100% AcOH (60 ml), Pd/C (10%, 0.308 g) was added. The mixture was shaken for 1 d at r.t. in a hydrogenation apparatus (3.5 atm H_2), then left standing for additional 1.5 d. The suspension was filtered over *Celite*, and the filtrate was concentrated. Short-path distillation yielded **8** (4.902 g, 95%). Colorless liquid. GC/MS: t_R 4.29 min, m/z 116. IR (film): 2984vs, 2884vs, 2647vs, 1956w, 1732vs, 1712vs, 1454s, 1417vs, 1371s, 1327vs, 1285vs, 1212vs, 1064vs, 965s, 904vs, 679s. ^1H -NMR (300 MHz): 9.35 (br. s, COOH); 4.04–3.80 (*m*, 2 CH_2O); 3.19–3.09 (*m*, CH); 2.30–2.11 (*m*, $\text{CH}_2\text{CH}_2\text{O}$). ^{13}C -NMR (75 MHz): 179.4 (*s*, CO_2H); 70.0, 68.1 (2*t*, 2 CH_2O); 43.5 (*d*, CH); 29.3 (*t*, $\text{CH}_2\text{CH}_2\text{O}$). CI-MS (NH_3): 135 (**6**), 134 (100, $[M + \text{NH}_4]^+$).

2,3,4,5-Tetrahydro-N-methyl-N-phenylfuran-3-carboxamide (**11**). A mixture of **8** (2.003 g, 17.25 mmol) and SOCl_2 (1.9 ml, 26.11 mmol) was heated under reflux for 1 h. Then, excess SOCl_2 was removed by distillation (50°/20 mbar). The residue was dissolved in CH_2Cl_2 (20 ml), and Et_3N (2.7 ml, 19.34 mmol) and *N*-methylaniline (2.1 ml, 19.30 mmol) were added at 0°. The mixture was slowly warmed to r.t., stirred for 3 h, and then concentrated. The residue was dispersed in Et_2O , filtered, and the filtrate was concentrated. CC (hexane/AcOEt 5:1) yielded **11** (2.764 g, 78%). An almost colorless liquid. TLC (hexane/AcOEt 1:2): R_f 0.27 (UV₂₅₄). GC/MS: t_R 9.69 min, m/z 205. B.p. 125°/10^{–2} mbar. IR (film): 3563w, 3503w, 3296w, 3061m, 2977s, 2948s, 2869s, 1968w, 1734w, 1660vs, 1596vs, 1496vs, 1453s, 1424vs, 1391vs, 1336s, 1320m, 1290s, 1264s, 1210w, 1174w, 1125vs, 1068vs, 919s, 776s, 703vs. ^1H -NMR (300 MHz): 7.47–7.34 (*m*, 3 arom. H); 7.19–7.15 (*m*, 2 arom. H); 3.91–3.69 (*m*, 2 CH_2O); 3.28 (*s*, Me); 2.93 (*quint.*, $J = 8.1$, CH); 2.27–2.16, 1.88–1.80 (2*m*, $\text{CH}_2\text{CH}_2\text{O}$). ^{13}C -NMR (75 MHz): 173.2 (*s*, CO); 143.7 (*s*, 1 arom. C); 129.8, 127.9, 127.3 (3*d*, 5 arom. CH); 71.3, 68.5 (2*t*, 2 CH_2O); 42.0 (*d*, CH); 37.5 (*q*, Me); 30.9 (*t*, $\text{CH}_2\text{CH}_2\text{O}$). CI-MS (NH_3): 207 (12), 206 (100, $[M + \text{H}]^+$). Anal. calc. for $\text{C}_{12}\text{H}_{13}\text{NO}_2$ (205.25): C 70.22, H 7.37, N 6.82; found: C 69.94, H 7.24, N 6.74.

2,3,4,5-Tetrahydro-N-methyl-N-phenylfuran-3-thiocarboxamide (**12**). A suspension of Lawesson reagent (dried *i.v.*, 1.780 g, 4.401 mmol) and **11** (1.502 g, 7.318 mmol) in toluene (15 ml) was heated at 95° (oilbath) for 1 h. After cooling to r.t., the mixture was filtered, and the solvent was evaporated. CC (hexane/AcOEt 5:1) yielded **12** (1.356 g, 84%). Yellow oil. TLC (hexane/AcOEt 5:1): R_f 0.18 (UV₂₅₄, 'Schlittler'). IR (film): 3055w, 2975w, 2867w, 1594w, 1493vs, 1469vs, 1385vs, 1364w, 1338w, 1317w, 1274w, 1215w, 1180w, 1171w, 1103m, 1073m, 1049m, 1002w, 806w, 912w, 774m, 701s. ^1H -NMR (300 MHz): 7.51–7.39 (*m*, 3 arom. H); 7.16–7.14 (*m*, 2 arom. H); 4.02–3.94, 3.94–3.69 (2*m*, 2 CH_2O); 3.73 (*s*, Me); 3.23 (*quint.*, $J = 8.3$, CH); 2.50–2.39, 1.96–1.87 (2*m*, $\text{CH}_2\text{CH}_2\text{O}$). ^{13}C -NMR (75 MHz): 206.4 (*s*, CS); 145.6 (*s*, 1 arom. C); 130.1, 128.6, 125.5 (3*d*, 5 arom. CH); 75.8, 68.8 (2*t*, 2 CH_2O); 49.3 (*d*, CH); 45.8 (*q*, Me); 35.4 (*t*, $\text{CH}_2\text{CH}_2\text{O}$). CI-MS (NH_3): 224 (**6**), 223 (15), 222 (100, $[M + \text{H}]^+$). Anal. calc. for $\text{C}_{12}\text{H}_{15}\text{NOS}$ (221.32): C 65.12, H 6.83, N 6.33, S 14.49; found: C 65.42, H 6.88, N 6.59, S 14.27.

Compound **6**. A COCl_2 soln. in toluene (20%, 7.5 ml, 14.18 mmol) was added to a soln. of **12** (1.255 g, 5.671 mmol) and 3 drops of DMF in CH_2Cl_2 (20 ml) at 0° , the mixture was stirred for 2 h at 0° , then the volatiles were removed under reduced pressure. The residue was dissolved in THF (15 ml), DABCO (0.640 g, 5.705 mmol) was added, and the mixture was stirred at r.t. for 20 min. The solid was removed by filtration under N_2 and washed with THF. To the filtrate, NaN_3 (1.106 g, 17.01 mmol) and DMF (30 ml) were added, and the THF was removed by distillation. The mixture was stirred at r.t. for 8 d. After addition of Et_2O , the resulting suspension was filtered over a *Celite* pad, and the solvent was removed *i.v.* CC (hexane/AcOEt 1:1) yielded a mixture of **6** and **11** (11%). The yield of pure **6** (pale yellow oil), considering 11% **11**, was 0.717 g (63%). Pure **6** for analysis was obtained by means of MPLC (hexane/AcOEt 1:2). TLC (hexane/AcOEt 1:1): R_f 0.18 (UV_{254} , $\text{Ce}(\text{SO}_4)_2$). HPLC (*Chiracel OD*, hexane/*i*-PrOH 25:1, 1 ml/min; enantiomers): $t_R(\text{A})$ 13.9 min; $t_R(\text{B})$ 15.4 min. IR (film): 3480w, 3064w, 3046w, 2958m, 2921m, 2855s, 1761vs ($\nu(\text{C}=\text{N})$), 1647m, 1600s, 1502s, 1459m, 1421m, 1361w, 1333s, 1285s, 1221m, 1188m, 1156m, 1110s, 1078s, 1056s, 1034s, 1004s, 990m, 962m, 913m, 756s, 693s, 674s. $^1\text{H-NMR}$ (300 MHz): 7.42–7.04 (m, 5 arom. H); 4.18–4.03 (m, $\text{CH}_2\text{CH}_2\text{O}$); 3.83, 3.58 (AB, $J=10.3$, CH_2O); 3.47 (s, Me); 2.26–2.16, 1.88–1.80 (2m, $\text{CH}_2\text{CH}_2\text{O}$). $^{13}\text{C-NMR}$ (75 MHz): 158.6 (s, C(2)); 142.2 (s, 1 arom. C); 129.7, 123.6, 116.2 (3d, 5 arom. CH); 72.4, 68.3 (2t, 2 CH_2O); ca. 52 (br., C(3)); 34.9 (t, $\text{CH}_2\text{CH}_2\text{O}$); ca. 34 (br., Me). CI-MS (NH_3): 204 (14), 203 (100, $[M+H]^+$). Anal. calc. for $\text{C}_{12}\text{H}_{14}\text{N}_2\text{O}$ (202.25): C 71.26, H 6.98, N 13.85; found: C 70.99, H 6.75, N 13.87.

2.2. N-(5-Oxa-1-azaspiro[2.4]hept-1-en-2-yl)-(S)-proline Methyl Ester (**7**). N-[(2,3,4,5-Tetrahydrofuran-3-yl)carbonyl]-(S)-proline Methyl Ester (**9**). A mixture of **8** (4.013 g, 34.55 mmol) and SOCl_2 (3.8 ml, 52.22 mmol) was heated under reflux for 75 min. Then, excess SOCl_2 was removed by distillation ($40^\circ/20$ mbar). The residue was dissolved in CH_2Cl_2 (30 ml), and Et_3N (10.6 ml, 76.16 mmol) and H-Pro-OMe·HCl (6.314 g, 38.12 mmol) were added at 0° . The mixture was slowly warmed to r.t., stirred for 18 h, and then concentrated. The residue was dispersed in Et_2O , filtered, and the filtrate was concentrated. CC (AcOEt) yielded **9** (5.558 g, 71%). An almost colorless oil. TLC (AcOEt): R_f 0.17 (KMnO_4). GC/MS: t_R 10.69 min, m/z 227. IR (film): 3577w, 3488w, 2956s, 2876m, 1746vs, 1647vs, 1435vs, 1366m, 1339m, 1314m, 1281m, 1199vs, 1176vs, 1092m, 1066m, 1028w, 999w, 970w, 919m, 721w. $^1\text{H-NMR}$ (300 MHz; diastereoisomers): 4.53–4.47 (m, CH(α)(Pro)); 4.12–3.78 (m, 2 $\text{CH}_2\text{O}(\text{Thf})$); 3.73, 3.72 (s, MeO); 3.71–3.53 (m, $\text{CH}_2(\delta)(\text{Pro})$); 3.22–3.15, 2.98–2.86 (m, CH(Thf)); 2.29–1.91 (m, $\text{CH}_2(\beta)(\text{Pro})$, $\text{CH}_2(\gamma)(\text{Pro})$, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$). $^{13}\text{C-NMR}$ (75 MHz; diastereoisomers): 172.8, 172.7, 172.0, 171.9 (4s, 2 CO); 70.4, 70.2, 68.6, 68.4 (4t, 2 $\text{CH}_2\text{O}(\text{Thf})$); 59.4, 58.9 (2d, CH(α)(Pro)); 52.2 (q, MeO); 47.0 (t, $\text{CH}_2(\delta)(\text{Pro})$); 43.0 (d, CH(Thf)); 30.0, 29.6 (2t, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 29.1 (t, $\text{CH}_2(\beta)(\text{Pro})$); 24.8 (t, $\text{CH}_2(\gamma)(\text{Pro})$). CI-MS (NH_3): 229 (13), 228 (100, $[M+H]^+$), 203 (12). Anal. calc. for $\text{C}_{11}\text{H}_{17}\text{NO}_4$ (227.26): C 58.14, H 7.54, N 6.16; found: C 58.44, H 7.42, N 6.29.

N-[(2,3,4,5-Tetrahydrofuran-3-yl)thiocarbonyl]-(S)-proline Methyl Ester (**10**). A suspension of Lawesson reagent (dried *i.v.*, 5.882 g, 14.54 mmol) and **9** (5.493 g, 24.17 mmol) in toluene (30 ml) was heated at 95° (oil-bath) for 1 h. After cooling to r.t., the mixture was filtered, and the solvent was evaporated. CC (hexane/AcOEt 1:2) yielded **10** (4.910 g, 84%). Yellow oil. TLC (hexane/AcOEt 1:2; diastereoisomers): $R_f(\text{A})$ 0.28, $R_f(\text{B})$ 0.35 ('*Schlittler*'). GC/MS (diastereoisomers): $t_R(\text{A})$ 12.99 min, m/z 243, $t_R(\text{B})$ 12.95 min, m/z 243. IR (film): 3593w, 3470w, 2977s, 2953s, 2875s, 1744vs, 1465vs, 1445vs, 1350s, 1272vs, 1205vs, 1130m, 1087s, 1054s, 1002m, 973m, 914m, 885w, 848w, 791w, 747w. $^1\text{H-NMR}$ (300 MHz; diastereoisomers): 5.08–5.04, 4.81–4.72 (2m, CH(α)(Pro)); 4.17–3.76 (m, $\text{CH}_2(\delta)(\text{Pro})$, 2 $\text{CH}_2\text{O}(\text{Thf})$); 3.74, 3.73 (2s, MeO); 3.53–3.45, 3.30–3.18 (2m, CH(Thf)); 2.54–2.03 (m, $\text{CH}_2(\beta)(\text{Pro})$, $\text{CH}_2(\gamma)(\text{Pro})$, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$). $^{13}\text{C-NMR}$ (75 MHz; diastereoisomers): 203.2 (s, CS); 170.8 (s, CO); 73.6, 73.2, 68.7, 68.4 (4t, 2 $\text{CH}_2\text{O}(\text{Thf})$); 65.4 (d, CH(α)(Pro)); 52.2 (q, MeO); 50.8 (t, $\text{CH}_2(\delta)(\text{Pro})$); 49.4, 49.3 (2d, CH(Thf)); 33.8, 33.4 (2t, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 28.7 (t, $\text{CH}_2(\beta)(\text{Pro})$); 24.6 (t, $\text{CH}_2(\gamma)(\text{Pro})$). CI-MS (NH_3): 246 (6), 245 (14), 244 (100, $[M+H]^+$), 225 (10). Anal. calc. for $\text{C}_{11}\text{H}_{17}\text{NO}_3\text{S}$ (243.32): C 54.30, H 7.04, N 5.76, S 13.18; found: C 54.24, H 7.25, N 5.60, S 13.34.

Compound **7**. A COCl_2 soln. in toluene (20%, 6.5 ml, 12.29 mmol) was added to a soln. of **10** (1.196 g, 4.917 mmol) and 3 drops of DMF in CH_2Cl_2 (16 ml) at 0° , the mixture was stirred for 45 min at 0° , and then the volatiles were removed under reduced pressure. The residue was dissolved in THF (15 ml), DABCO (0.562 g, 5.010 mmol) was added, and the mixture was stirred at r.t. for 20 min. The solid was removed by filtration under N_2 and washed with THF. To the filtrate, NaN_3 (0.973 g, 14.97 mmol) was added, and the resulting mixture was stirred at r.t. for 72 h. After addition of Et_2O , the resulting suspension was filtered over a *Celite* pad, and the solvent removed *i.v.* CC (SiO_2 ; inactivated with Et_3N , AcOEt/ Et_3N 100:1) yielded **7** (0.697 g, 63%). Pale yellow oil. TLC (AcOEt): R_f 0.16 ('*Schlittler*'). HPLC (*Chiracel OD*, hexane/*i*-PrOH 12:1, 1 ml/min; diastereoisomers): $t_R(\text{A})$ 14.4 min; $t_R(\text{B})$ 17.6 min; HPLC (normal phase, $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}/\text{MeOH}$ 70:30:0.5, 1 ml/min; diastereoisomers): $t_R(\text{A})$ 11.3 min; $t_R(\text{B})$ 11.7 min; HPLC (reversed phase, $\text{MeCN}/\text{H}_2\text{O}$ 10:90, 1 ml/min; diastereoisomers): $t_R(\text{A})$ 23.5 min; $t_R(\text{B})$ 24.2 min. IR (film): 3468w, 2955m, 2876m, 2856m, 1780vs, 1744vs,

1665w, 1437m, 1418w, 1364m, 1346m, 1327w, 1282m, 1214vs, 1175vs, 1092w, 1077w, 1052s, 998w, 963w, 913m, 867w, 759w, 730w. ¹H-NMR (300 MHz; diastereoisomers): 4.34 (br. s, CH(α)(Pro)); 4.10–4.02, 3.96–3.92 (2m, 2 H of CH₂(δ)(Pro), 2 CH₂O(Thf)); 3.75 (s, MeO); 3.72–3.44 (m, 4 H of CH₂(δ)(Pro), 2 CH₂O(Thf)); 2.37–2.00, 1.77–1.69 (2m, CH₂(β)(Pro), CH₂(γ)(Pro), CH₂CH₂O (Thf)). ¹³C-NMR (75 MHz; diastereoisomers): 172.2 (s, CO), 156.7 (s, C(2)); 72.2, 68.3, 68.2 (3t, 2 CH₂O(Thf)); 60.9 (d, CH(α)(Pro)); 52.5 (q, MeO); 48.2 (s, C(3)); 47.1 (d, CH₂(δ)(Pro)); 34.6, 34.5 (2t, CH₂CH₂O (Thf)); 30.3 (t, CH₂(β)(Pro)); 24.1 (t, CH₂(γ)(Pro)). EI-MS: 224 (22, M^+), 195 (80, $[M - \text{CH}_2\text{O} + \text{H}]^+$), 165 (41, $[M - \text{CO}_2\text{Me}]^+$), 122 (22), 70 (100, [pyrrolidine – H]⁺), 68 (27), 55 (50), 41 (29). Anal. calc. for C₁₁H₁₆N₂O₃ (224.26): C 58.91, H 7.19, N 12.49; found: C 59.06, H 7.33, N 12.40.

3. Reactions of **6** and **7** with PhCOSH and PhCOOH. 3.1. Reactions of **6**. N-(2,3,4,5-Tetrahydro-3-[(methyl)(phenyl)amino]thiocarbonyl)furan-3-yl)benzamide (**13**). A soln. of PhCOSH (28 mg, 0.203 mmol) in CH₂Cl₂ (3 ml) was added to a soln. of **6** (36 mg, 0.176 mmol) in CH₂Cl₂ (2 ml) at 0°. The mixture was stirred at r.t. for 19 h, the solvent was evaporated, and the yellow, powdery crude product was purified by prep. TLC (hexane/AcOEt 1:1). Recrystallization from CHCl₃/Et₂O yielded **13** (61 mg, 99%) as colorless prisms, which were suitable for X-ray crystal-structure determination. TLC (hexane/AcOEt 1:1): R_f 0.29 (UV₂₅₄, 'Schlittler'). M.p. 200–201°. IR: 3370s, 3057w, 2974w, 2921w, 2876w, 1657vs, 1593m, 1582m, 1526vs, 1490vs, 1466vs, 1432s, 1377vs, 1289s, 1248m, 1168w, 1129m, 1101vs, 1074m, 1051s, 1024w, 977w, 925w, 899w, 805w, 774m, 707vs, 691m. ¹H-NMR (300 MHz): 7.50–7.04 (m, 10 arom. H); 5.71 (br. s, NH); 4.52 (part of AB, $J = 9.4$, 1 H of CH₂O); 4.04–3.86 (m, CH₂CH₂O, 1 H of CH₂O); 3.72 (s, Me); 3.44–3.34, 2.36–2.04 (2m, CH₂CH₂O). ¹³C-NMR (75 MHz): 202.7 (s, CS); 165.7 (s, CO); 147.0, 133.3 (2s, 2 arom. C); 131.7, 129.5, 128.3, 128.0, 126.8, 125.4 (6d, 10 arom. CH); 80.0 (t, CH₂O); 71.8 (s, C(α)(Thf)); 67.8 (t, CH₂O); 50.0 (q, Me); 42.9 (t, CH₂CH₂O). CI-MS (NH₃): 342 (23), 341 (100, $[M + \text{H}]^+$), 220 (26, $[M - \text{PhCONH}]^+$), 139 (15). Anal. calc. for C₁₉H₂₀N₂O₂S (340.44): C 67.03, H 5.92, N 8.23, S 9.42; found: C 67.07, H 5.91, N 8.08, S 9.47.

N-(2,3,4,5-Tetrahydro-3-[(methyl)(phenyl)amino]carbonyl)furan-3-yl)benzamide (**14**). A soln. of PhCO₂H (53 mg, 0.434 mmol) in CH₂Cl₂ (3 ml) was added to a soln. of **6** (71 mg, 0.352 mmol) in CH₂Cl₂ (2 ml) at 0°. The mixture was stirred at r.t. overnight, and the solvent was evaporated. Prep. TLC (hexane/AcOEt 1:2) yielded **14** (110 mg, 95%) as a colorless powder. Suitable crystals for the X-ray crystal-structure determination were grown from CHCl₃/Et₂O. TLC (hexane/AcOEt 1:2): R_f 0.18 (UV₂₅₄, Ce(SO₄)₂). M.p. 166–167°. IR: 3356w, 3280m, 3062w, 2971w, 2946w, 2862w, 1646vs, 1594vs, 1528vs, 1496vs, 1449m, 1380s, 1291m, 1220w, 1166w, 1100m, 1075m, 1065m, 1028w, 969w, 802w, 930w, 776w, 703s. ¹H-NMR (300 MHz): 7.50–7.03 (m, 10 arom. H); 5.63 (br. s, NH); 4.26 (part of AB, $J = 9.5$, 1 H of CH₂O); 3.98–3.86 (m, CH₂CH₂O, 1 H of CH₂O); 3.28 (s, Me); 3.11–3.01, 2.24–2.16 (2m, CH₂CH₂O). ¹³C-NMR (75 MHz): 169.3, 166.2 (2s, 2 CO); 144.0, 133.2 (2s, 2 arom. C); 131.7, 129.4, 128.2, 127.5, 126.9, 128.8 (6d, 10 arom. CH); 77.2, 67.5 (2t, 2 CH₂O); 67.2 (s, C(α)(Thf)); 40.4 (q, Me); 38.9 (t, CH₂CH₂O). CI-MS (NH₃): 326 (22), 325 (100, $[M + \text{H}]^+$), 218 (32, $[M - \text{N}(\text{Me})\text{Ph}]^+$), 108 (35, $[\text{H}_2\text{N}(\text{Me})\text{Ph}]^+$). Anal. calc. for C₁₉H₂₀N₂O₃ (324.37): C 70.35, H 6.21, N 8.64; found: C 70.50, H 6.33, N 8.58.

3.2. Reactions of **7**. N-[(R)-3-(Benzoylamino)-2,3,4,5-tetrahydrofuran-3-yl]thiocarbonyl)-(S)-proline Methyl Ester ((R,S)-**15**) and N-[(S)-3-(Benzoylamino)-2,3,4,5-tetrahydrofuran-3-yl]thiocarbonyl)-(S)-proline Methyl Ester ((S,S)-**15**). A soln. of PhCOSH (68 mg, 0.492 mmol) in CH₂Cl₂ (2 ml) was added to a soln. of **7** (101 mg, 0.450 mmol) in CH₂Cl₂ (3 ml) at 0°. The mixture was stirred at r.t. for 52 h, and the solvent was evaporated. Prep. TLC (AcOEt/Et₃N 100:3) yielded **15** (147 mg (90%)) as a colorless foam. The diastereoisomers were separated by MPLC (CH₂Cl₂/MeOH 40:1). Suitable crystals for the X-ray crystal-structure determination of both diastereoisomers were grown from CH₂Cl₂/CHCl₃/(i-Pr)₂O.

Data of (R,S)-**15**. TLC (CH₂Cl₂/MeOH 40:1): R_f 0.34 (UV₂₅₄, 'Schlittler'). M.p. 181–183°. IR: 3325m, 3056w, 2975m, 2951m, 2876m, 1742vs, 1643vs, 1602m, 1579m, 1524vs, 1487s, 1427vs, 1345s, 1287s, 1201vs, 1152s, 1086m, 1064s, 1001w, 970w, 927w, 914w, 804w, 717s, 695m. ¹H-NMR (300 MHz): 7.83–7.81 (m, 2 arom. H); 7.55–7.41 (m, 3 arom. H, NH); 5.30–5.14 (m, CH(α)(Pro)); 4.33–4.10, 4.04–3.96 (2m, CH₂(δ)(Pro), 2 CH₂O(Thf)); 3.57 (s, MeO); 3.20–3.09, 2.67–2.59, 2.27–2.11, 2.07–1.99 (4m, CH₂(β)(Pro), CH₂(γ)(Pro), CH₂CH₂O(Thf)). ¹³C-NMR (75 MHz): 200.3 (s, CS); 170.9 (s, O=C=O); 166.2 (s, Ph-C=O); 133.8 (s, 1 arom. C); 131.8, 128.6, 126.9 (3d, 5 arom. CH); 75.8 (t, CH₂O(Thf)); 71.4 (s, C(α)(Thf)); 68.5 (t, CH₂O(Thf)); 68.4 (d, CH(α)(Pro)); 52.6 (t, CH₂(δ)(Pro)); 52.1 (q, MeO); 40.3 (t, CH₂CH₂O(Thf)); 27.9 (t, CH₂(β)(Pro)); 25.7 (CH₂(γ)(Pro)). ESI-MS: 747 (24, $[2M + \text{Na}]^+$), 390 (29), 385 (100, $[M + \text{Na}]^+$), 363 (27, $[M + \text{H}]^+$).

Data of (S,S)-**15**. TLC (CH₂Cl₂/MeOH 40:1): R_f 0.29 (UV₂₅₄, 'Schlittler'). M.p. 132–135°. IR: 3316m, 2979m, 2952m, 2878m, 1742vs, 1643vs, 1602m, 1579m, 1524vs, 1488s, 1427vs, 1346s, 1289s, 1246s, 1201vs, 1151s, 1060s, 1027w, 1001m, 968m, 927w, 889w, 805w, 717m, 695m. ¹H-NMR (300 MHz): 7.82–7.78 (m, 2 arom. H); 7.53–7.39 (m, 3 arom. H); 7.31 (br. s, NH); 5.30–5.10 (m, CH(α)(Pro)); 4.65, 4.29 (AB, $J = 9.7$, CH₂O(Thf));

4.24–4.07, 4.01–3.95 (2*m*, CH₂CH₂O(Thf), CH₂(δ)(Pro)); 3.73 (*s*, MeO); 2.65–2.59, 2.25–2.14, 2.07–1.95 (3*m*, CH₂(β)(Pro), CH₂(γ)(Pro), CH₂CH₂O(Thf)). ¹³C-NMR (75 MHz): 200.1 (*s*, CS); 170.9 (*s*, O=C=O); 166.3 (*s*, Ph–C=O); 133.7 (*s*, 1 arom. C); 131.8, 128.6, 127.0 (3*d*, 5 arom. CH); 78.9 (*t*, CH₂O(Thf)); 70.6 (*s*, C(α)(Thf)); 68.0 (*t*, CH₂O(Thf)); 67.8 (*d*, CH(α)(Pro)); 52.9 (*t*, CH₂(δ)(Pro)); 52.1 (*q*, MeO); 37.8 (*t*, CH₂CH₂O(Thf)); 27.9 (*t*, CH₂(β)(Pro)); 25.7 (CH₂(γ)(Pro)). CI-MS (NH₃): 364 (21), 363 (100, [M + H]⁺), 331 (34, [M – MeO]⁺).

N-[[*(R)*-3-(Benzoylamino)-2,3,4,5-tetrahydrofuran-3-yl]carbonyl]-(*S*)-proline Methyl Ester ((*R,S*)-**16**) and N-[[*(S)*-3-(Benzoylamino)-2,3,4,5-tetrahydrofuran-3-yl]carbonyl]-(*S*)-proline Methyl Ester ((*S,S*)-**16**). A soln. of PhCO₂H (60 mg, 0.491 mmol) in CH₂Cl₂ (3 ml) was added to a soln. of **7** (98 mg, 0.437 mmol) in CH₂Cl₂ (3 ml) at 0°. The mixture was stirred at r.t. for 16 h, and the solvent was evaporated. Then, AcOEt was added to the residue, and the resulting precipitate was filtered, to yield **16** (132 mg, 87%). Colorless powder. The diastereoisomers were separated by MPLC (CH₂Cl₂/MeOH 40:1). Suitable crystals for the X-ray crystal-structure determination of both diastereoisomers were grown from CHCl₃/Et₂O ((*R,S*)-**16**) and CDCl₃ ((*S,S*)-**16**), resp.

Data of (*R,S*)-**16**. TLC (AcOEt): *R*_f 0.18 (UV₂₅₄, 'Schlittler'). M.p. 223–225°. IR: 3324*s*, 3047*w*, 2980*w*, 2954*m*, 2885*w*, 2871*m*, 1745*vs*, 1654*vs*, 1620*vs*, 1579*m*, 1530*vs*, 1491*s*, 1433*s*, 1370*m*, 1297*s*, 1218*s*, 1204*s*, 1179*s*, 1157*m*, 1091*w*, 1059*m*, 1039*w*, 912*w*, 899*w*, 768*w*, 731*m*, 719*m*, 695*m*. ¹H-NMR (300 MHz): 7.83–7.79 (*m*, 2 arom. H); 7.53–7.39 (*m*, 3 arom. H, NH); 4.62–4.58 (*m*, CH(α)(Pro)); 4.26–4.01, 3.78–3.57 (2*m*, CH₂(δ)(Pro), 2 CH₂O(Thf)); 3.71 (*s*, MeO); 3.03–2.93, 2.37–2.29, 2.14–1.90 (3*m*, CH₂(β)(Pro), CH₂(γ)(Pro), CH₂CH₂O(Thf)). ¹³C-NMR (75 MHz): 172.8, 169.3 (2*s*, 2 CO); 166.4 (*s*, PhCO); 133.5 (*s*, 1 arom. C); 131.8, 128.5, 127.0 (3*d*, 5 arom. CH); 74.1, 68.4 (2*t*, 2 CH₂O(Thf)); 67.0 (*s*, C(α)(Thf)); 60.7 (*d*, CH(α)(Pro)); 52.0 (*q*, MeO); 47.5 (*t*, CH₂(δ)(Pro)); 37.2 (*t*, CH₂CH₂O(Thf)); 27.8 (*t*, CH₂(β)(Pro)); 25.5 (*t*, CH₂(γ)(Pro)). ESI-MS: 715 (11, [2M + Na]⁺), 385 (10, [M + K]⁺), 374 (91, [(M – Pro-OMe) + (M – PhCONH(Thf))]⁺), 369 (100, [M + Na]⁺), 366 (41), 347 (48, [M + H]⁺), 130 (31), 102 (38). Anal. calc. for C₁₈H₂₂N₂O₅ (346.38): C 62.42, H 6.40, N 8.09; found: C 62.45, H 6.57, N 8.08.

Data of (*S,S*)-**16**. TLC (AcOEt): *R*_f 0.16 (UV₂₅₄, 'Schlittler'). M.p. 225–226°. IR: 3324*s*, 3064*w*, 2983*m*, 2951*m*, 2876*m*, 2854*m*, 1748*vs*, 1659*vs*, 1615*vs*, 1580*m*, 1525*vs*, 1488*s*, 1447*s*, 1421*vs*, 1364*s*, 1307*s*, 1210*vs*, 1197*s*, 1178*vs*, 1067*s*, 936*w*, 927*w*, 747*w*, 731*m*, 696*m*. ¹H-NMR (300 MHz): 7.84–7.81 (*m*, 2 arom. H); 7.56–7.38 (*m*, 3 arom. H, NH); 4.59–4.54 (*m*, CH(α)(Pro), 1 H of CH₂(β)(Pro), 2 CH₂O(Thf)); 4.22–4.10, 4.09–3.95, 3.88–3.95 (3*m*, 4 H of CH₂(δ)(Pro), 2 CH₂O(Thf)); 3.70 (*s*, MeO); 3.58–3.50 (*m*, 1 H of CH₂(δ)(Pro), 2 CH₂O(Thf)); 2.59–2.44, 2.09–1.86 (2*m*, CH₂(β)(Pro), CH₂(γ)(Pro), CH₂CH₂O(Thf)). ¹³C-NMR (75 MHz): 172.8, 169.8 (2*s*, 2 CO); 166.5 (*s*, PhCO); 133.3 (*s*, 1 arom. C); 131.8, 128.5, 127.1 (3*d*, 5 arom. CH); 76.1, 67.7 (2*t*, 2 CH₂O(Thf)); 66.0 (*s*, C(α)(Thf)); 60.5 (*d*, CH(α)(Pro)); 52.0 (*q*, MeO); 47.6 (*t*, CH₂(δ)(Pro)); 36.2 (*t*, CH₂CH₂O(Thf)); 27.8 (*t*, CH₂(β)(Pro)); 25.3 (*t*, CH₂(γ)(Pro)). ESI-MS: 715 (6, [2M + Na]⁺), 374 (100, [(M – Pro-OMe) + (M – PhCONH(Thf))]⁺), 369 (54, [M + Na]⁺), 366 (17), 347 (16, [M + H]⁺), 130 (14), 102 (66). Anal. calc. for C₁₈H₂₂N₂O₅ (346.38): C 62.42, H 6.40, N 8.09; found: C 62.21, H 6.64, N 7.98.

4. Synthesis of Model Peptides. 4.1. Reactions of **6**. Benzyl N-[(*S*)-2-[(*R*)-2,3,4,5-Tetrahydro-3-[(methyl)(phenyl)amino]carbonyl]furan-3-yl]amino]-1-methyl-2-oxoethyl]carbamate ((*S,R*)-**18**) and Benzyl N-[(*S*)-2-[(*S*)-2,3,4,5-Tetrahydro-3-[(methyl)(phenyl)amino]carbonyl]furan-3-yl]amino]-1-methyl-2-oxoethyl]carbamate ((*S,S*)-**18**). To a soln. of **6** (233 mg, 1.100 mmol) in CH₂Cl₂ (8 ml) at 0°, Z-Ala-OH (309 mg, 1.384 mmol) in CH₂Cl₂ (7 ml) was added. The mixture was stirred at r.t. for 68 h, and the solvent was evaporated. CC (hexane/AcOEt 1:2) yielded **18** (465 mg, 97%). Colorless foam. A second CC separated the diastereoisomers, with the exception of a small mixed fraction.

Data of (*S,R*)-**18**. TLC(hexane/AcOEt 1:2): *R*_f 0.15 (UV₂₅₄, Ce(SO₄)₂). IR: 3295*s*, 3063*m*, 3034*m*, 2980*m*, 2939*m*, 2876*m*, 1963*w*, 1716*vs*, 1664*vs*, 1637*vs*, 1594*vs*, 1529*vs*, 1496*vs*, 1454*vs*, 1375*s*, 1287*s*, 1244*vs*, 1156*m*, 1098*s*, 1070*vs*, 1027*s*, 972*w*, 917*w*, 774*m*, 751*m*, 701*vs*. ¹H-NMR (300 MHz): 7.39–7.27 (*m*, 8 arom. H); 7.09–7.06 (*m*, 2 arom. H); *ca.* 5.78 (br. *s*, NH(Thf)); 5.20 (*d*, *J* = 7.3, NH(Ala)); 5.09 (*s*, PhCH₂); 4.11–4.08, 3.92–3.84, 3.78–3.67 (3*m*, CH(α)(Ala), 2 CH₂O(Thf)); 3.25 (*s*, MeN); 2.97–2.87, 2.08–2.00 (2*m*, CH₂CH₂O(Thf)); 1.22 (*d*, *J* = 7.0, Me(Ala)). ¹³C-NMR (75 MHz): 171.0, 169.0 (2*s*, 2 CO); 155.7 (*s*, CO(carbamate)); 144.0, 136.1 (2*s*, 2 arom. C); 129.5, 128.5, 128.2, 127.9, 126.7 (5*d*, 10 arom. CH); 76.8, 67.4 (2*t*, 2 CH₂O(Thf)); 66.9 (*t*, PhCH₂ and C(α)(Thf)); 49.9 (*d*, CH(α)(Ala)); 40.4 (*q*, MeN); 38.4 (*t*, CH₂CH₂O(Thf)); 18.0 (*q*, Me(Ala)). CI-MS (NH₃): 427 (27), 426 (100, [M + H]⁺), 320 (9), 319 (50, [M – N(Me)Ph]⁺), 318 (17, [M – PhCH₂O]⁺), 241 (13), 108 (11, [H₂N(Me)Ph]⁺). Anal. calc. for C₂₃H₂₇N₃O₅ (425.48): C 64.93, H 6.40, N 9.88; found: C 64.99, H 6.70, N 9.65.

Data of (S,S)-18. TLC (hexane/AcOEt 1:2): R_f 0.10 (UV₂₅₄, Ce(SO₄)₂). IR: 3311s, 3063m, 3035m, 2980m, 2940m, 2876m, 1958w, 1720vs, 1672vs, 1651vs, 1594vs, 1526vs, 1496vs, 1454vs, 1376vs, 1249vs, 1157m, 1098s, 1070vs, 1028s, 972w, 924w, 848w, 775m, 741m, 701vs. ¹H-NMR (300 MHz): 7.39–7.27 (*m*, 8 arom. H); 7.10–7.07 (*m*, 2 arom. H); *ca.* 5.97 (br. *s*, NH (Thf)); 5.25 (*d*, *J* = 6.0, NH(Ala)); 5.10, 5.04 (*AB*, *J* = 12.3, PhCH₂); 4.24 (part of *AB*, *J* = 9.5, 1 H of CH₂O(Thf)); 4.12–3.70 (*m*, CH(α)(Ala), CH₂CH₂O(Thf), 1 H of CH₂O(Thf)); 3.24 (*s*, MeN); 2.78–2.71, 1.96–1.92 (*2m*, CH₂CH₂O(Thf)); 1.23 (*d*, *J* = 7.0, Me(Ala)). ¹³C-NMR (75 MHz): 171.1, 169.3 (2s, 2 CO); 155.7 (*s*, CO (carbamate)); 144.0, 136.0 (2s, 2 arom. C); 129.5, 128.5, 128.2, 127.9, 127.8, 126.8 (6d, 10 arom. CH); 77.0, 67.2 (2t, 2 CH₂O(Thf)); 66.9 (*t*, PhCH₂); 66.6 (*s*, C(α)(Thf)); 49.9 (*d*, CH(α)(Ala)); 40.3 (*q*, MeN); 38.9 (*t*, CH₂CH₂O(Thf)); 18.0 (*q*, Me(Ala)). CI-MS (NH₃): 427 (27), 426 (100, [M + H]⁺), 320 (7), 319 (42, [M – N(Me)Ph]⁺), 318 (42, [M – PhCH₂O]⁺), 108 (6, [H₂N(Me)Ph]⁺). Anal. calc. for C₂₃H₂₇N₃O₅ (425.48): C 64.93, H 6.40, N 9.88; found: C 64.78, H 6.68, N 9.58.

4-Bromo-N-[(S)-2-[(R)-2,3,4,5-tetrahydro-3-[(methyl)(phenyl)amino]carbonyl]furan-3-yl)amino]-2-oxoethyl]benzamide ((S,R)-19). To a soln. of (S,R)-18 (100 mg, 0.235 mmol) in MeOH (5 ml), Pd/C (10%, 21 mg) was added, and the mixture was stirred at r.t. under H₂ for 20 h. The suspension was filtered through *Celite*, and the filtrate was concentrated. The residue was dissolved in CH₂Cl₂ (2 ml), and an Et₃N soln. (0.3 ml, 1.2M in CH₂Cl₂) and 4-bromobenzoyl chloride (58 mg, 0.289 mmol) were added at 0°. The mixture was then stirred at r.t. for 16 h, and the solvent was evaporated. CC (CH₂Cl₂/MeOH 50:1) yielded (S,R)-19 (96 mg, 86%). Colorless powder. Suitable crystals for the X-ray crystal-structure determination were grown from MeOH/Et₂O. TLC (CH₂Cl₂/MeOH 10:1): R_f 0.48 (UV₂₅₄, 'Schlittler'). IR: 3297s, 3061w, 2979w, 2936w, 2873w, 1643vs, 1593vs, 1534vs, 1495vs, 1482vs, 1450s, 1376s, 1269m, 1170w, 1110m, 1070s, 1027w, 1011m, 970w, 938w, 845w, 774w, 756m, 703m. ¹H-NMR (300 MHz): 7.67–7.59, 7.38–7.31, 7.09–7.06 (*3m*, 9 arom. H); 6.82 (*d*, *J* = 7.1, NH(Ala)); *ca.* 6.00 (br. *s*, NH(Thf)); 4.10–3.75 (*m*, CH(α)(Ala), 2 CH₂O(Thf)); 3.27 (*s*, MeN); 3.02–2.95, 2.15–2.06 (*2m*, CH₂CH₂O(Thf)); 1.32 (*d*, *J* = 7.0, Me(Ala)). ¹³C-NMR (75 MHz): 171.3, 169.0, 165.7 (3s, 3 CO); 143.9, 132.4 (2s, 2 arom. C); 131.9, 129.5, 128.5, 127.9, 126.8 (5d, 9 arom. CH); 126.7 (*s*, 1 arom. CBr); 76.6, 67.4 (2t, 2 CH₂O(Thf)); 67.0 (*s*, C(α)(Thf)); 48.8 (*d*, CH(α)(Ala)); 40.3 (*q*, MeN); 38.3 (*t*, CH₂CH₂O(Thf)); 18.5 (*q*, Me(Ala)). CI-MS (NH₃): 477 (25), 476 (100, [M(⁸¹Br) + H]⁺), 475 (25), 474 (100, [M(⁷⁹Br) + H]⁺), 396 (11), 370 (14), 369 (82, [M(⁸¹Br) – N(Me)Ph]⁺), 368 (14), 367 (83, [M(⁷⁹Br) – N(Me)Ph]⁺), 289 (12), 228 (19), 108 (95, [H₂N(Me)Ph]⁺). Anal. calc. for C₂₂H₂₄BrN₃O₄ · 0.5 MeOH (490.37): C 55.11, H 5.34, N 8.57; found: C 55.11, H 5.11, N 8.67.

4-Bromo-N-[(S)-2-[(S)-2,3,4,5-tetrahydro-3-[(methyl)(phenyl)amino]carbonyl]furan-3-yl)amino]-2-oxoethyl]benzamide ((S,S)-19). To a soln. of (S,S)-18 (60 mg, 0.141 mmol) in MeOH (5 ml), Pd/C (10%, 12 mg) was added, and the mixture was stirred at r.t. under H₂ for 8 h. The suspension was filtered through *Celite*, and the filtrate was concentrated. The residue was dissolved in CH₂Cl₂ (2 ml), and an Et₃N soln. (0.3 ml, 0.8M in CH₂Cl₂) and 4-bromobenzoyl chloride (37 mg, 0.184 mmol) were added at 0°. The mixture was then stirred at r.t. for 8 h, and the solvent was evaporated. CC (CH₂Cl₂/MeOH 50:1) yielded (S,S)-19 (61 mg, 92%). Colorless powder. Suitable crystals for the X-ray crystal-structure determination were grown from MeOH/CHCl₃. TLC (CH₂Cl₂/MeOH 10:1): R_f 0.43 (UV₂₅₄, 'Schlittler'). IR: 3439w, 3326m, 3062w, 2978w, 2932w, 2857w, 1691s, 1657vs, 1641vs, 1593vs, 1523vs, 1496vs, 1481vs, 1448s, 1382s, 1359s, 1268m, 1166m, 1108m, 1072s, 1012m, 963w, 933w, 843m, 778w, 755m, 705m. ¹H-NMR (300 MHz): 7.67–7.58, 7.38–7.25, 7.18–7.08 (*3m*, 9 arom. H); 6.94 (*d*, *J* = 7.3 NH(Ala)); *ca.* 6.32 (br. *s*, NH(Thf)); 4.31 (part of *AB*, *J* = 9.5, 1 H of CH₂O(Thf)); 4.22–4.13, 3.94–3.77 (*2m*, CH(α)(Ala), CH₂CH₂O(Thf), 1 H of CH₂O(Thf)); 3.26 (*s*, MeN); 2.83–2.71, 2.02–1.94 (*2m*, CH₂CH₂O(Thf)); 1.34 (*d*, *J* = 6.9, Me(Ala)). ¹³C-NMR (75 MHz): 171.4, 169.4, 165.8 (3s, 3 CO); 143.9, 132.4 (2s, 2 arom. C); 131.8, 129.4, 128.6, 127.7, 126.9 (5d, 9 arom. CH); 126.6 (*s*, 1 arom. CBr); 76.9, 67.2 (2t, 2 CH₂O(Thf)); 66.7 (*s*, C(α)(Thf)); 48.8 (*d*, CH(α)(Ala)); 40.2 (*q*, MeN); 38.8 (*t*, CH₂CH₂O(Thf)); 18.4 (*q*, Me(Ala)). CI-MS (NH₃): 493 (8, [M(⁸¹Br) + NH₄]⁺), 491 (8, [M(⁷⁹Br) + NH₄]⁺), 477 (25), 476 (100, [M(⁸¹Br) + H]⁺), 475 (25), 474 (99, [M(⁷⁹Br) + H]⁺), 411 (10), 396 (26), 369 (12, [M(⁸¹Br) – N(Me)Ph]⁺), 367 (13, [M(⁷⁹Br) – N(Me)Ph]⁺), 108 (13, [H₂N(Me)Ph]⁺). Anal. calc. for C₂₂H₂₄BrN₃O₄ (474.35): C 55.70, H 5.10, N 8.86; found: C 55.41, H 5.12, N 8.80.

(R)-3-[(S)-2-[(Benzoyloxy)carbonyl]amino]-1-oxopropyl]amino]-2,3,4,5-tetrahydrofuran-3-carboxylic Acid ((R,S)-20). A soln. of (S,R)-18 (106 mg, 0.249 mmol) and aq. HCl (2 ml, 6M) in MeCN (2 ml) was stirred at r.t. for 88 h. After removal of the solvent, the crude product was purified by prep. TLC (CH₂Cl₂/MeOH 10:1) to yield (R,S)-20 (63 mg, 75%). Colorless powder. TLC (CH₂Cl₂/MeOH 10:1): R_f stretched spot at the start, yellow, with bromocresol green. IR: 3312s, 3065m, 3035m, 2980m, 2882m, 1707vs, 1664vs, 1607vs, 1517vs, 1454s, 1399vs, 1357s, 1342s, 1259vs, 1156w, 1072s, 1052s, 1029s, 973w, 917w, 826w, 777w, 740m, 698s. ¹H-NMR (300 MHz, CD₃OD): 7.37–7.26 (*m*, 5 arom. H); 5.09–5.04 (*m*, PhCH₂); 4.18–4.11 (*m*, 2 H of CH(α)(Ala), 2 CH₂O(Thf)); 3.99–3.94 (*m*, 3 H of CH(α)(Ala), 2 CH₂O(Thf)); 2.43–2.40, 2.26–2.22 (*2m*, CH₂CH₂O(Thf)); 1.34 (*d*, *J* = 7.1,

Me(Ala)). ^{13}C -NMR (75 MHz, CD_3OD): 178.8, 174.6 (2s, 2 CO); 158.2 (s, CO(carbamate)); 138.2 (s, 1 arom. C); 129.4, 129.0, 128.8 (3d, 5 arom. CH); 77.2, 69.4, 67.7 (3t, 2 $\text{CH}_2\text{O}(\text{Thf})$, PhCH_2); 68.0 (s, C(α)(Thf)); 52.2 (d, CH(α)(Ala)); 38.5 (t, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 18.3 (Me(Ala)). ESI-MS: 739 (24), 717 (12), 359 (100, $[M + \text{Na}]^+$).

(S)-3-[(S)-2-[(Benzyloxy)carbonyl]amino]-1-oxopropyl]amino]-2,3,4,5-tetrahydrofuran-3-carboxylic Acid ((S,S)-**20**). A soln. of (S,S)-**18** (101 mg, 0.237 mmol) and aq. HCl (2 ml, 6M) in MeCN (2 ml) was stirred at r.t. for 88 h. After removal of the solvent, the crude product was purified by prep. TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) to yield (S,S)-**20** (67 mg, 84%). Colorless powder. TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1): R_f : stretched spot at the start, yellow, with bromocresol green. IR: 3394s, 3316s, 3064m, 3035m, 2980m, 2881m, 1707vs, 1659vs, 1597vs, 1536vs, 1514vs, 1454s, 1396vs, 1357s, 1259vs, 1154w, 1097m, 1070s, 1056s, 1029s, 973w, 917w, 827w, 774w, 737m, 698s. ^1H -NMR (300 MHz, CD_3OD): 7.37–7.26 (m, 5 arom. H); 5.09 (s, PhCH_2); 4.19–4.11 (m, 2 H of CH(α)(Ala), 2 $\text{CH}_2\text{O}(\text{Thf})$); 3.98–3.85 (m, 3 H of CH(α)(Ala), 2 $\text{CH}_2\text{O}(\text{Thf})$); 2.43–2.39, 2.26–2.15 (2m, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 1.34 (d, $J = 7.1$, Me(Ala)). ^{13}C -NMR (75 MHz, CD_3OD): 178.7, 174.8 (2s, 2 CO); 158.2 (s, CO(carbamate)); 138.2 (s, 1 arom. C); 129.6, 129.1, 129.0 (3d, 5 arom. CH); 77.2, 69.4, 67.9 (3t, 2 $\text{CH}_2\text{O}(\text{Thf})$, PhCH_2); 67.7 (s, C(α)(Thf)); 52.4 (d, CH(α)(Ala)); 38.5 (t, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 18.5 (q, Me(Ala)). ESI-MS: 739 (16), 717 (12), 359 (100, $[M + \text{Na}]^+$), 209 (11).

tert-Butyl (S)-2-[(R)- and (S)-3-[(S)-2-[(Benzyloxy)carbonyl]amino]-1-oxopropyl]amino]-2,3,4,5-tetrahydrofuran-3-yl]carbonyl]amino]-3-phenylpropanoate (**21**). At 0°, EtN(i-Pr)₂ (0.1 ml, 0.584 mmol) was added to a mixture of (R,S)-**20**/(S,S)-**20** (67 mg, 0.199 mmol, mixture of diastereoisomers), H-Phe-O'Bu·HCl (57 mg, 0.221 mmol), TBTU (64 mg, 0.199 mmol), and HOBt hydrate (12% H_2O , 31 mg, 0.202 mmol) in CH_2Cl_2 (5 ml), whereupon the soln. turned clear for a short time. The mixture was stirred at r.t. for 5 d, and washed twice with aq. 5% KHSO_4 soln., aq. 5% NaHCO_3 soln., and sat. aq. NaCl soln. The aq. layers were extracted twice with CH_2Cl_2 , then all combined org. layers were filtered through cotton and concentrated. CC (hexane/AcOEt 2:1) yielded **21** (80 mg, 74%). Colorless powder. TLC (hexane/AcOEt 2:1): R_f 0.17 (UV₂₅₄, 'Schlittler'). M.p. 152–158°. IR: 3377m, 3308s, 3065w, 3035m, 2980m, 2936m, 2880w, 1726vs, 1707vs, 1682vs, 1651vs, 1546vs, 1456s, 1393m, 1367s, 1317s, 1257vs, 1227s, 1160vs, 1117m, 1074s, 1029s, 847w, 740m, 701s. ^1H -NMR (300 MHz; diastereoisomers): 7.34–7.13 (m, 10 arom. H); 7.08, 7.06 (2s, NH); 6.91, 6.88 (2s, NH); 5.33, 5.30 (2s, NH); 5.13, 5.07 (AB, $J = 12.3$, $\text{PhCH}_2(\text{Z})$); 4.69–4.66 (m, CH(α)(Phe)); 4.19–3.85 (m, CH(α)(Ala), 2 $\text{CH}_2\text{O}(\text{Thf})$); 3.15–3.01 (m, $\text{CH}_2(\text{Phe})$); 2.38–2.05 (m, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 1.42, 1.41 (2s, Me_3C); 1.34 (d, $J = 6.6$, Me(Ala)). ^{13}C -NMR (125 MHz; diastereoisomers): 172.4, 172.1, 172.1, 170.2 (4s, 3 CO); 156.0 (s, CO(carbamate)); 136.2, 136.1, 136.0 (3s, 2 arom. C); 129.3, 129.3, 128.5, 128.4, 128.2, 128.0, 127.0 (7d, 10 arom. CH); 82.4, 82.3 (2s, Me_3C); 73.7, 73.4, 67.7, 67.6, 67.1 (5t, 2 $\text{CH}_2\text{O}(\text{Thf})$, PhCH_2); 64.8 (s, C(α)(Thf)); 53.8, 53.8, 50.8 (3d, CH(α)(Ala), CH(α)(Phe)); 37.8, 37.7 (2t, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 36.1, 36.0 (2t, $\text{CH}_2(\text{Phe})$); 27.9 (q, Me_3C); 18.2 (q, Me(Ala)). ESI-MS: 837 (27), 562 (100, $[M + \text{Na}]^+$), 540 (31, $[M + \text{H}]^+$), 484 (94). Anal. calc. for $\text{C}_{29}\text{H}_{37}\text{N}_3\text{O}_7$ (539.62): C 64.55, H 6.91, N 7.79; found: C 64.33, H 7.03, N 7.68.

4.2. Reaction of **7**. N-[(R)- and (S)-3-[(S)-2-[(Benzyloxy)carbonyl]amino]-4-methyl-1-oxopentyl]-amino]-2-methyl-1-oxopropyl]amino]-2,3,4,5-tetrahydrofuran-3-yl]carbonyl]-(S)-proline Methyl Ester (**17a** and **17b**, resp.). To a soln. of **7** (81 mg, 0.361 mmol) in CH_2Cl_2 (3 ml) at 0°, Z-Leu-Aib-OH (138 mg, 0.394 mmol) in CH_2Cl_2 (3 ml) was added. The mixture was stirred at r.t. for 2 d, and the solvent was evaporated. Prep. TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1) yielded **17** (172 mg (83%)). Colorless foam. The diastereoisomers were separated by prep. HPLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1).

Data of **17a**. TLC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 10:1): R_f 0.31 (UV₂₅₄, 'Schlittler'). HPLC (normal phase, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1, 1 ml/min): t_R 17.2 min. Prep. HPLC (normal phase, $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1, 12 ml/min): t_R 44.2 min. IR: 3319vs, 3033w, 2956s, 2873m, 1745vs, 1680vs, 1629vs, 1526vs, 1469s, 1454s, 1435vs, 1384s, 1363s, 1265vs, 1221vs, 1174vs, 1118m, 1092m, 1060s, 1044s, 923w, 741m, 699m. ^1H -NMR (600 MHz): 7.57 (s, NH(Thf)); 7.37–7.31 (m, 5 arom. H); 6.44 (s, NH(Aib)); 5.45 (d, $J = 3.9$, NH(Leu)); 5.12 (s, PhCH_2); 4.54 (dd, $J = 8.9$, $J = 3.5$, CH(α)(Pro)); 4.16–4.14 (m, 1 H of $\text{CH}_2\text{O}(\text{Thf})$); 3.98–3.90 (m, CH(α)(Leu), 3 H of $\text{CH}_2\text{O}(\text{Thf})$); 3.69 (s, MeO); 3.66–3.62 (m, 1 H of $\text{CH}_2(\delta)(\text{Pro})$); 3.43 (br. s, 1 H of $\text{CH}_2(\delta)(\text{Pro})$); 2.95–2.91 (m, 1 H of $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 2.12–2.04 (m, 1 H of $\text{CH}_2(\beta)(\text{Pro})$, 1 H of $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 1.95–1.89 (m, $\text{CH}_2(\gamma)(\text{Pro})$); 1.87–1.85 (m, 1 H of $\text{CH}_2(\beta)(\text{Pro})$); 1.69–1.62 (m, 1 H of $\text{CH}_2(\beta)(\text{Leu})$, CH(γ)(Leu)); 1.55–1.49 (m, 1 H of $\text{CH}_2(\beta)(\text{Leu})$); 1.52, 1.46 (2s, 2 Me(Aib)); 0.96–0.93 (m, 2 Me(Leu)). ^{13}C -NMR (150 MHz): 173.5, 173.0, 171.9, 168.8 (4s, 4 CO); 156.7 (s, CO(carbamate)); 135.9 (s, 1 arom. C); 128.6, 128.4, 127.9 (3d, 5 arom. CH); 74.1, 68.1 (2t, 2 $\text{CH}_2\text{O}(\text{Thf})$); 67.2 (t, PhCH_2); 66.9 (s, C(α)(Thf)); 60.3 (d, CH(α)(Pro)); 57.4 (s, C(α)(Aib)); 54.7 (d, CH(α)(Leu)); 52.0 (q, MeO); 47.1 (t, $\text{CH}_2(\delta)(\text{Pro})$); 40.2 (t, $\text{CH}_2(\beta)(\text{Leu})$); 36.9 (t, $\text{CH}_2\text{CH}_2\text{O}(\text{Thf})$); 28.0 (t, $\text{CH}_2(\beta)(\text{Pro})$); 26.2 (q, Me(Aib)); 25.4 (t, $\text{CH}_2(\gamma)(\text{Pro})$); 24.7 (d, CH(γ)(Leu)); 24.5 (q, Me(Aib)); 22.9, 21.8 (2q, 2 Me(Leu)). ESI-MS: 597 (50, $[M + \text{Na}]^+$), 575 (10, $[M + \text{H}]^+$), 446 (100, $[M - \text{Pro-OMe}]^+$), 333 (46,

Table 3. Crystallographic Data of Compounds **13**, **14**, (R,S)-**15**, (S,S)-**15**, (R,S)-**16**, (S,S)-**16**, (S,R)-**19**, and (S,S)-**19**

	13	14	(R,S)- 15	(S,S)- 15
Crystallized from	CDCl ₃ /Et ₂ O	CHCl ₃ /Et ₂ O	i-Pr ₂ O/CHCl ₃ / CH ₂ Cl ₂	CHCl ₃ /i-Pr ₂ O
Empirical formula	C ₁₉ H ₂₀ N ₂ O ₂ S	C ₁₉ H ₂₀ N ₂ O ₃	C ₁₈ H ₂₂ N ₂ O ₄ S	C ₁₈ H ₂₂ N ₂ O ₄ S
Formula weight [g mol ⁻¹]	340.44	324.38	362.44	362.44
Crystal color, habit	colorless, prism	colorless, needle	colorless, needle	colorless, prism
Crystal dimensions [mm]	0.20 × 0.25 × 0.30	0.05 × 0.05 × 0.30	0.07 × 0.10 × 0.25	0.20 × 0.25 × 0.25
Temp. [K]	160(1)	160(1)	160(1)	160(1)
Crystal system	monoclinic	monoclinic	orthorhombic	orthorhombic
Space group	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ / <i>c</i>	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>Z</i>	4	8	4	4
Reflections for cell determination	2711	5981	2378	2407
2 θ range for cell determination [°]	4–60	4–50	4–55	4–55
Unit-cell parameters <i>a</i> [Å]	9.6138(1)	10.9181(1)	7.4749(1)	7.5237(1)
<i>b</i> [Å]	12.1775(2)	29.1337(3)	10.8981(2)	10.9586(1)
<i>c</i> [Å]	14.6489(2)	10.9614(1)	21.9857(4)	21.9085(3)
β [°]	90.9387(6)	108.2256(5)	90	90
<i>V</i> [Å ³]	1714.75(4)	3311.74(6)	1791.00(5)	1806.34(4)
<i>D_x</i> [g cm ⁻³]	1.319	1.301	1.344	1.333
μ (MoK α) [mm ⁻¹]	0.202	0.0887	0.206	0.204
Transmission factors [min; max]	0.844; 0.962	–	–	–
Scan type	ϕ and ω	ϕ and ω	ϕ and ω	ϕ and ω
2 θ_{max} [°]	60	50	55	55
Total reflections measured	44650	50909	37878	38672
Symmetry-independent reflections	4999	5850	4092	4151
Reflections with <i>I</i> > 2 σ (<i>I</i>)	3895	4276	3280	3633
Reflections used in refinement	3895	5845	3280	3633
Parameters refined	222	463 (30 restraints)	232	232
<i>R</i> (on <i>F</i> ; <i>I</i> > 2 σ (<i>I</i>) reflections)	0.0453	0.0508	0.0374	0.0375
<i>wR</i> (on <i>F</i> ; <i>I</i> > 2 σ (<i>I</i>) reflections)	0.0446	–	0.0331	0.0375
<i>wR</i> (on <i>F</i> ² ; all indept. reflections)	–	0.1357	–	–
Weighting parameter [<i>p</i>] ^a)	0.005	–	0.010	0.007
Weighting parameters [<i>a</i> , <i>b</i>] ^b)	–	0.0609; 1.9374	–	–
Goodness-of-fit	3.011	1.017	1.492	2.240
Secondary extinction coefficient	1.8(3) × 10 ⁻⁶	0.0053(8)	1.0(1) × 10 ⁻⁶	7(2) × 10 ⁻⁷
Final $\Delta_{\text{max}}/\sigma$	0.0004	0.001	0.0005	0.001
$\Delta\rho$ (max; min) [e Å ⁻³]	0.33; 0.23	0.47; –0.45	0.22; –0.22	0.38; –0.24

^a) $w^{-1} = \sigma^2(F_o) + (pF_o)^2$. ^b) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, where $P = (F_o^2 + 2 F_c^2)/3$.

[*M* – Thf-Pro-OMe]⁺). Anal. calc. for C₂₉H₄₂N₄O₈ · 0.4 H₂O (581.88): C 59.86, H 7.41, N 9.63; found: C 59.96, H 7.33, N 9.56.

Data of **17b**. TLC (CH₂Cl₂/MeOH 10:1): *R_f* 0.31 (UV₂₅₄, 'Schlittler'). HPLC (normal phase, CH₂Cl₂/MeOH 40:1, 1 ml/min): *t_R* 20.1 min. Prep. HPLC (normal phase, CH₂Cl₂/MeOH 40:1, 12 ml/min): *t_R* 52.5 min. IR: 3320vs, 3033m, 2956vs, 2873m, 1745vs, 1692vs, 1665vs, 1628vs, 1525vs, 1453s, 1437s, 1384s, 1362s, 1264vs, 1221vs, 1173vs, 1119m, 1093w, 1062s, 973w, 924w, 741m, 698m. ¹H-NMR (600 MHz): 7.59 (s, NH(Thf)); 7.38–7.31 (m, 5 arom. H); 6.41 (s, NH(Aib)); 5.43 (d, *J* = 4.3, NH(Leu)); 5.13, 5.08 (AB, *J* = 12.3, PhCH₂); 4.54–4.50

Table 3 (cont.)

	(<i>R,S</i>)- 16	(<i>S,S</i>)- 16	(<i>S,R</i>)- 19	(<i>S,S</i>)- 19
Crystallized from	CHCl ₃ /Et ₂ O	CDCl ₃	MeOH/Et ₂ O	MeOH/CHCl ₃
Empirical formula	C ₁₈ H ₂₂ N ₂ O ₃	C ₁₈ H ₂₂ N ₂ O ₅ · CDCl ₃	C ₂₂ H ₂₄ BrN ₃ O ₄ · 2 CH ₃ OH	C ₂₂ H ₂₄ BrN ₃ O ₄ · 2 CH ₃ OH
Formula weight [g mol ⁻¹]	346.38	466.76	538.43	538.43
Crystal color, habit	colorless, needle	colorless, needle	colorless, plate	colorless, plate
Crystal dimensions [mm]	0.05 × 0.07 × 0.22	0.04 × 0.05 × 0.22	0.07 × 0.22 × 0.22	0.05 × 0.15 × 0.25
Temp. [K]	160(1)	160(1)	160(1)	160(1)
Crystal system	orthorhombic	monoclinic	monoclinic	monoclinic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁	<i>P</i> 2 ₁
<i>Z</i>	4	2	2	2
Reflections for cell determination	1829	2585	26729	22646
2θ range for cell determination [°]	4–50	4–55	4–60	4–55
Unit-cell parameters <i>a</i> [Å]	7.8381(1)	9.3887(2)	9.3610(1)	9.1378(1)
<i>b</i> [Å]	10.8238(2)	11.5550(2)	10.5163(1)	10.6355(1)
<i>c</i> [Å]	20.8005(4)	9.8990(2)	13.3600(2)	13.3132(2)
β [°]	90	94.3998(9)	102.8138(5)	100.6612(6)
<i>V</i> [Å ³]	1764.67(5)	1070.74(4)	1282.45(3)	1271.51(3)
<i>D</i> _x [g cm ⁻³]	1.304	1.445	1.394	1.406
μ(MoK _α) [mm ⁻¹]	0.0956	0.460	1.650	1.664
Transmission factors [min; max]	–	–	0.671; 0.858	0.726; 0.920
Scan type	ω	φ and ω	φ and ω	φ and ω
2θ _(max) [°]	50	55	60	55
Total reflections measured	19865	24423	42259	33790
Symmetry-independent reflections	3117	4882	7459	5802
Reflections with <i>I</i> > 2σ(<i>I</i>)	2806	4040	6091	5076
Reflections used in refinement	2806	4040	7458	5076
Parameters refined	230	267	347 (30 restraints)	325
<i>R</i> (on <i>F</i> ; <i>I</i> > 2σ(<i>I</i>) reflections)	0.0371	0.0378	0.0354	0.0330
<i>wR</i> (on <i>F</i> ; <i>I</i> > 2σ(<i>I</i>) reflections)	0.0366	0.0368	–	0.0303
<i>wR</i> (on <i>F</i> ² ; all indept. reflections)	–	–	0.0762	–
Weighting parameter [<i>p</i>] ^a)	0.005	0.013	–	0.005
Weighting parameters [<i>a</i> , <i>b</i>] ^b)	–	–	0.0334; 0.2605	–
Goodness-of-fit	2.124	1.370	1.016	1.625
Secondary extinction coefficient	–	2.5(3) × 10 ⁻⁶	0.008(1)	2.3(1) × 10 ⁻⁶
Final Δ _{max} /σ	0.0003	0.0005	0.002	0.0006
Δρ (max; min) [e Å ⁻³]	0.16; –0.21	0.29; –0.32	0.26; –0.34	0.31; –0.31

^a) $w^{-1} = \sigma^2(F_o) + (pF_o)^2$. ^b) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$, where $P = (F_o^2 + 2F_c^2)/3$.

(*m*, CH(*α*)(Pro), 1 H of CH₂O(Thf)); 4.03–3.92 (*m*, 1 H of CH₂CH₂O(Thf)); 3.91–3.90 (*m*, CH(*α*)(Leu), 1 H of CH₂CH₂O(Thf)); 3.85–3.84 (*m*, 1 H of CH₂O(Thf)); 3.70 (*s*, MeO); 3.67–3.65 (*m*, 1 H of CH₂(*δ*)(Pro)); 3.51 (br. *s*, 1 H of CH₂(*δ*)(Pro)); 2.37–2.35 (*m*, CH₂CH₂O(Thf)); 2.08–2.04 (*m*, 1 H of CH₂(*β*)(Pro)); 1.95–1.93 (*m*, CH₂(*γ*)(Pro)); 1.87–1.85 (*m*, 1 H of CH₂(*β*)(Pro)); 1.67–1.62 (*m*, 1 H of CH₂(*β*)(Leu), CH(*γ*)(Leu)); 1.55–1.52 (*m*, 1 H of CH₂(*β*)(Leu)); 1.54, 1.44 (2*s*, 2 Me(Aib)); 0.96–0.93 (*m*, 2 Me(Leu)). ¹³C-NMR (150 MHz): 173.6, 173.2, 172.0, 169.4 (4*s*, 4 CO); 156.8 (*s*, CO(carbamate)); 135.9 (*s*, 1 arom. C); 128.7, 128.4, 127.8 (3*d*, 5 arom. CH); 76.2 (*t*, CH₂O(Thf)); 67.4 (*t*, CH₂CH₂O(Thf)); 67.2 (*t*, PhCH₂); 65.8 (*s*, C(*α*)(Thf)); 60.1 (*d*, CH(*α*)(Pro)); 57.5 (*s*, C(*α*)(Aib)); 54.8 (*d*, CH(*α*)(Leu)); 52.0 (*q*, MeO); 47.2 (*t*, CH₂(*δ*)(Pro)); 40.2 (*t*,

CH₂(β)(Leu)); 35.7 (*t*, CH₂CH₂O(Thf)); 28.1 (*t*, (CH₂(β)(Pro))); 26.7 (*q*, Me(Aib)); 25.4 (*t*, CH₂(γ)(Pro)); 24.8 (*d*, CH(β)(Leu)); 24.2 (*q*, Me(Aib)); 22.9, 21.9 (2*q*, 2 Me(Leu)). ESI-MS: 597 (100, [*M* + Na]⁺), 575 (26, [*M* + H]⁺), 446 (50, [*M* – Pro-OMe]⁺), 333 (7, [*M* – Thf-Pro-OMe]⁺). Anal. calc. for C₂₉H₄₂N₄O₈ · 0.2 H₂O (578.27): C 60.23, H 7.39, N 9.73; found: C 60.17, H 7.20, N 9.62.

5. *X-Ray Crystal-Structure Determination of 13, 14, (R,S)-15, (S,S)-15, (R,S)-16, (S,S)-16, (S,R)-19 and (S,S)-19*, (see Table 3 and Figs. 1–8⁵). All measurements were made at low temp. on a *Nonius Kappa CCD* area-detector diffractometer [36] with graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in Table 3, and views of the molecules are shown in Figs. 1–8. Data reduction was performed with *HKL Denzo* and *Scalepack* [37]. The intensities were corrected for *Lorentz* and polarization effects. In the case of **13**, an absorption correction based on the multi-scan method [38] was applied, while a numerical absorption correction [39] was applied for (*S,R*)-**19** and (*S,S*)-**19**. Each structure was solved by direct methods with *SIR92* [40], which revealed the positions of all non-H-atoms. The non-H-atoms were refined anisotropically. The amide H-atoms in each structure, as well as the OH H-atoms of the MeOH molecules in (*S,R*)-**19**, were placed in the positions indicated by difference-electron-density maps, and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms were placed in geometrically calculated positions, and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2*U*_{eq} of its parent atom (1.5*U*_{eq} for the Me groups of **14** and (*S,R*)-**19**). The orientations of the idealized O–H vectors in the MeOH molecules in (*S,S*)-**19** were aligned to correspond with peaks in a difference electron-density map.

Except for **14** and (*S,R*)-**19**, each structure was refined on *F* using full-matrix least-squares procedures, which minimized the function $\sum w(|F_o| - |F_c|)^2$. For **14** and (*S,R*)-**19**, the refinement was carried out on *F*² by minimizing the corresponding function based on *F*². Corrections for secondary extinction were applied, except for (*R,S*)-**16**. Between one and five low-angle reflections were omitted from the final refinement of each structure because their observed intensities were much lower than the calculated values as a result of being partially obscured by the beam stop. Refinement of the absolute structure parameter [41] in the cases of (*R,S*)-**15**, (*S,S*)-**15**, (*S,S*)-**16**, (*S,R*)-**19**, and (*S,S*)-**19** yielded values of –0.06(5), –0.08(4), –0.05(4), –0.017(5), and –0.013(4), respectively, which confidently confirmed that the refined coordinates represent the true enantiomorph.

The structure of **14** has two symmetry-independent molecules in the asymmetric unit, but significant differences in their conformations preclude the possibility of a relationship from a higher-symmetry space group. Two atoms in the five-membered ring of molecule B are disordered, and two equally occupied positions were defined for each of these atoms. The disordered model could be refined satisfactorily, but only by applying quite strong bond-length restraints to all bonds involving the disordered atoms, as well as strong approximate isotropic restraints to the anisotropic atomic displacement parameters of the disordered atoms. In the structures of (*S,R*)-**19** and (*S,S*)-**19**, the asymmetric unit contains one peptide molecule plus two MeOH molecules. Two atoms in the five-membered ring of (*S,R*)-**19** are disordered, and two positions were defined for each of these molecules. The disordered model was refined in an analogous way to that described for **14**. The site occupation factors of the two conformations refined to 0.68(2) and 0.32(2), resp. In the case of (*S,S*)-**19**, the O-atom of the five-membered ring is disordered, and two positions were defined for this atom. The disordered model could be refined satisfactorily without bond-length restraints, and the best results were obtained when the site-occupation factors of the two conformations were set to 0.80 and 0.20, resp.

Neutral atom scattering factors for non-H-atoms were taken from [42a], and 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 for **14** and (*S,R*)-**19** were performed using SHELXL97 [45], while the teXsan crystallographic software package [46] was used for the remaining structures.

⁵) CCDC-201305–201312 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk)).

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