Synthesis of Pseudopeptides with Sulfoximines as Chiral Backbone Modifying Elements

Carsten Bolm,*[a] Guido Moll,[a, b] and Jan D. Kahmann[a, c]

Dedicated to Professor Horst Kessler (TU München) on the occasion of his 60th birthday

Abstract: The synthesis of pseudopeptides with a chiral α-sulfonimidoylcarboxy moiety in the backbone is described. Starting from readily available (S_S)-*S*-methyl *S*-phenyl sulfoximine and various cyclic and acyclic α-amino acids the desired products are obtained in good yields with peptide coupling methodology. Specific secondary structures caused by intramolecular hydrogen bonds may be adopted. Results of NMR studies to reveal conformational preferences will be discussed.

Keywords: amino acids · inhibitors · peptides · pseudopeptides · sulfoximines

Introduction

Much research has focussed on the development of peptide modifications in recent years to find new therapeutic agents.[1] The use of peptides in pharmaceutical applications is often impeded because of their poor bioavailability and rapid degradation.[2] These disadvantages can be reduced by the introduction of peptide mimetics,[3] whilst the specific activity is retained, and in some cases even increased. In general, the following modifications can be carried out on any part of a peptide and they can be applied in any combination:[3–6] amino acids can be deleted, or added/replaced;[7] short-[8] or long-range cyclizations[9] can be used; the bonds of the peptide backbone can be substituted by surrogates;[5] the backbone can be replaced totally by a novel scaffold[1b, 10] or, to achieve a higher bioavailability the peptides can be glycosylated.[11] Most modifications have been made on the amide linkage because it is the primary target for enzymatic degradation, and hence the metabolic stability of the peptides can be increased.[3, 12]

Lucente[13] and Liskamp[14] have reported on the synthesis of derivatives with sulfinamide or sulfonamide moieties as tetrahedral transition state analogues for the hydrolysis of the amide bond.[15] Such compounds may be regarded as new transition-state analogues for peptidase inhibitors,[16–19] besides the known peptidomimetics with a phosphonamidate.[20] The phosphonamidate moiety provides the best mimic for the transition state involved in the hydrolysis of the amide bond both from a steric and an electronic point of view.[14c, d] Owing to the instability of α-amino sulfonamides[15, 21] and sulfinamides[15] only *N*-phthaloyl protected derivatives have been synthesized.[21a] Most of the work in this field has focussed on β-amino sulfonamides[13–15, 22, 23] which provide a peptide bond surrogate with significantly changed polarity, hydrogen-bonding capability, acid/base character, and increased metabolic stability. Oligomeric β-amino sulfonamides have interesting secondary structures owing to specific conformations of the backbone caused by intra- or intermolecular hydrogen bonds.[24] Another interesting variation is the synthesis of vinylogous sulfonamides (vs-peptides): these compounds are, in contrast to peptides with α-sulfonamides, very stable and do not undergo spontaneous fragmentation.[25]

In 1989 Mock et al. introduced sulfoximines[26] and sulfodiimine as analogous transition-state inhibitors for carboxypeptidase A.[27] Those functional groups are chemically stable, and with their sp^3-hybridized[28, 29] sulfur atom they successfully mimic the tetrahedral intermediate in carboxamide addition reactions.[27b] We postulate that the use of such units for backbone modifications could lead to new pseudopeptides with higher stability against enzymatic degradation and thus give rise to potential new enzyme inhibitors. Furthermore, we hoped that the stereogenic center at sulfur

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Supporting information for this contribution is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the author. Spectral characterization (^{1}H NMR, ^{13}C NMR spectra) of pseudotripeptides **20**–**35** (17 pages).

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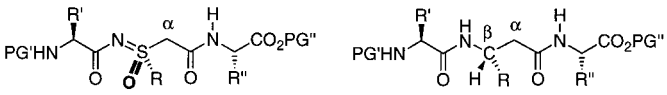
would help to generate compounds with well-defined secondary structures. Conformational preferences could then also be supported by intra- or intermolecular hydrogen bonds with the heteroatoms in these modified peptides. In this article we report on the preparation and structural investigations of pseudopeptides **1** with a chiral α-sulfonimidoyl carboxy unit[30, 31] in the backbone.

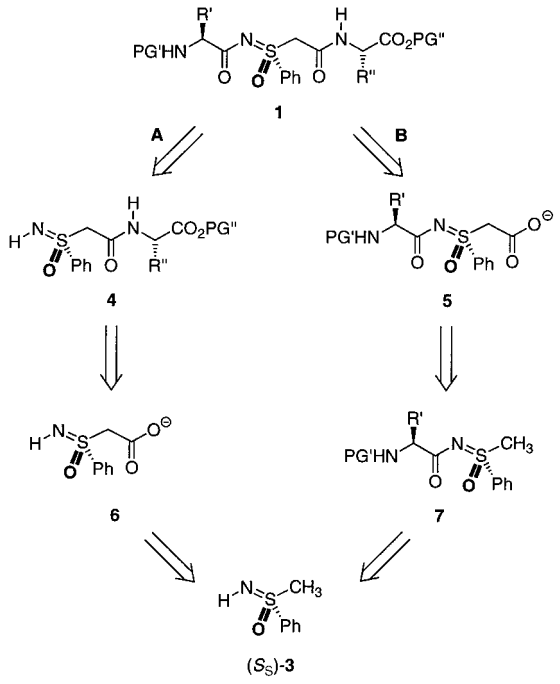
As depicted in its structure, sulfoximine-containing pseudopeptides **1** have a structural relationship with peptide **2**, which has a β-amino acid. Modifications with β-amino acids are of interest because they can lead to compounds with an enhanced stability towards hydrolysis and proteolytic cleavage by normal proteases. The construction of peptides containing exclusively β-amino acids leads to structurally well-defined β-peptides of which some are very biologically active compounds.[32, 33]



1 **2**

Results and Discussion

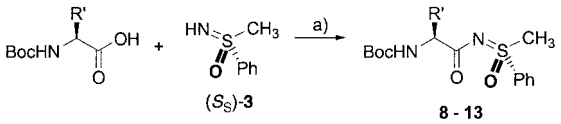
In order to synthesize target compounds **1** we chose (S_S)-*S*-methyl *S*-phenyl sulfoximine [(S_S)-**3**] as the starting material because both enantiomers are readily available with a high enantiomeric excess using well-established literature procedures.[26, 30c, 34–37] Two general synthetic strategies are considered in Scheme 1.



Scheme 1. Retrosynthetic analysis for sulfoximines.

Following route A, a pseudodipeptide **4** with a free sulfoximine nitrogen is required. This compound could be synthesized starting from (S_S)-**3** through β-amino acid analogue **6** by coupling with a protected amino acid. Alternatively (route B), a pseudodipeptide carboxylate **5** had to be synthesized, which could be prepared by selective carboxylation of **7**. The latter compound should be available by coupling (S_S)-**3** with an appropriate *N*-protected amino acid. In principle both reaction pathways lead to the desired pseudotripeptides **1**, but as shown previously,[38, 39] route B proved advantageous with higher yields owing to fewer protection/deprotection steps and better performance of the coupling reactions.

Amino acid–sulfoximine couplings: According to route B, (S_S)-**3** was treated with a number of *N*-Boc protected amino acids[40, 41] following standard peptide coupling protocols.[42] By means of a combination of HOBt and DCC[43] products **8**–**13** were obtained in good to high yields (Scheme 2, Table 1).



Scheme 2. Synthesis of compounds **8**–**13**: a) DCC/HOBt, CH_2Cl_2, 0 °C.

Table 1. Couplings of amino acids with sulfoximine (S_S)-**3**.[a]

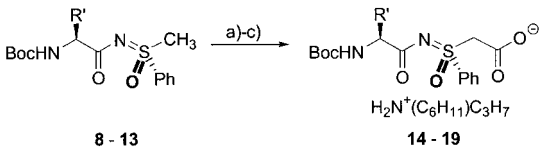
Entry	Amino acid	Product	Yield [%][b]
1	*N*-Boc-alanine	**8**	92
2	*N*-Boc-valine	**9**	97
3	*N*-Boc-leucine	**10**	97
4	*N*-Boc-isoleucine	**11**	93
5	*N*-Boc-*tert*-leucine	**12**	79
6	*N*-Boc-proline	**13**	91

[a] Reaction conditions: 1 equiv HOBt, 1.03 equiv DCC, CH_2Cl_2. [b] After column chromatography.

The lower yield in the coupling reaction using *tert*-leucine is probably caused by steric hindrance of the bulky *tert*-butyl group.

The couplings can also be performed using PyBOP[43] and DIEA, however, the yields are lower. DCC and DMAP as coupling agents gave the products in very high yields, but in the case of valine racemization at the α-carbon occurred as detected by ^{1}H NMR spectroscopy. Thus, integration of the two doublets of the methylene group indicated about 17% racemization.[44]

Synthesis of pseudotripeptides: On the basis of the impressive work by Seebach on regio- and stereoselective reactions of lithiated peptides,[45] we decided to attempt a selective carboxylation at the acidic methyl group of the sulfoximine to generate a carboxylate which could be used in a subsequent coupling with a carboxy-protected amino acid. Metalation of **8**–**13** with lithium cyclohexyl(isopropyl)amide (LCHIPA)[46, 47] followed by reaction of the resulting anion with dried gaseous CO_2[48] at −78 °C in absolute THF[49] and subsequent aqueous workup gave the corresponding ammonium carboxylates **14**–**19** in good crude yields[50] (Scheme 3, Table 2). No epimerization was detected by NMR spectroscopy.



8 - 13 **14 - 19**

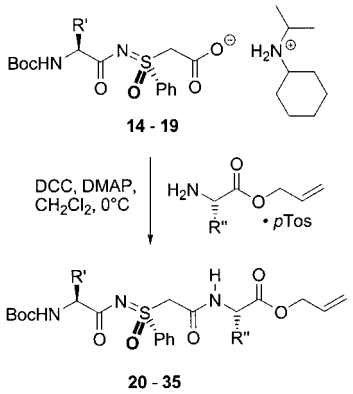
Scheme 3. Synthesis of compounds **14**–**19**: a) LCHIPA, 0 °C; b) CO_2 (g), −78 °C; c) aqueous workup.

Table 2. Synthesis of ammonium carboxylates.[a]

Entry	Starting material	Product	Yield [%][b]
1	**8**	**14**	54
2	**9**	**15**	85
3	**10**	**16**	81
4	**11**	**17**	82
5	**12**	**18**	76
6	**13**	**19**	82

[a] Reaction conditions: i) LCHIPA, 0 °C; ii) CO_2 (g), −78 °C. [b] Crude yield.

A clear indication that the reaction had proceeded well could be deduced from the ^{1}H NMR spectra of **14**–**19**. Typical AB-systems between $\delta = 4.1$ and 4.5 for the diastereotopic protons at the methylene group next to the sulfur were observed. Because the ammonium carboxylates **14**–**19** were prone to decarboxylation, no further purification was performed at this stage,[50] and the reactions with the allyl-protected amino acids were carried out directly after workup using DMAP and DCC as coupling reagents. After purification by column chromatography the desired Boc- and allyl-protected pseudotripeptides **20**–**35** were obtained in moderate to good yields as diastereomerically pure products (Scheme 4, Table 3).

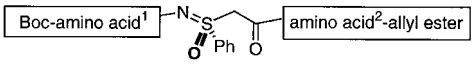


14 - 19 **20 - 35**

Scheme 4. Synthesis of pseudopeptides **20**–**35** with sulfoximines.

With tetrakis(triphenylphosphine)palladium(0) and morpholine, the allylic ester can be selectively cleaved to generate pseudotripeptides with a free carboxy group.[51, 52] Treatment with TFA leads to Boc deprotection.[51] Benzyl esters could also be used in the couplings with the ammonium carboxylates but hydrogenolysis under various conditions to liberate the carboxy terminus of the corresponding pseudotripeptides remained unsuccessful.[38, 39] With methyl ester, free acids under basic hydrolysis were generated but due to the acidic hydrogens at the α-carbon next to the sulfur about 30% fragmentation of the pseudotripeptide was observed yielding products of the type **7**.[51]

Table 3. Synthesis of pseudotripeptides.[a]



Entry	Amino acid[1]	Amino acid[2]	Product	Yield [%][b]
1	alanine	valine	**20**	56
2	alanine	leucine	**21**	66
3	alanine	isoleucine	**22**	55
4	valine	valine	**23**	82
5	valine	leucine	**24**	70
6	valine	isoleucine	**25**	63
7	leucine	leucine	**26**	76
8	leucine	valine	**27**	54
9	leucine	isoleucine	**28**	52
10	isoleucine	isoleucine	**29**	68
11	isoleucine	valine	**30**	48
12	isoleucine	leucine	**31**	55
13	*tert*-leucine	valine	**32**	66
14	*tert*-leucine	leucine	**33**	85
15	proline	leucine	**34**	73
16	proline	isoleucine	**35**	71

[a] Reaction conditions: 1 equiv DMAP, 1.03 equiv DCC, CH_2Cl_2. [b] After column chromatography.

NMR studies of the pseudotripeptides: To gain more information about the secondary structure of the pseudotripeptides and to reveal a possible effect of the sulfoximine as the modified backbone, NMR studies were carried out. The characteristic AB-systems for the diastereotopic methylene protons next to sulfur in the ^{1}H NMR spectra of some pseudotripeptides are listed in Table 4.

Table 4. Chemical shifts of the AB-systems of the methylene groups in some pseudotripeptides.

Entry	Compound	AB-systems [δ]
1	**20**	4.18/4.56
2	**24**	4.21/4.63
3	**26**	4.28/4.51
4	**28**	4.24/4.56
5	**29**	4.23/4.62
6	**31**	4.19/4.63
7	**32**	4.24/4.61
8	**25**	4.15/4.62; 4.17/4.83[a]

[a] Double set of signals due to rotamers (ratio = 2:1).

Such a distinct pattern is similar to that observed for fixed six-membered cyclic compounds. In the pseudopeptides discussed here, a cyclic ring structure of such type could result from the involvement of an intramolecular hydrogen bond between the amide hydrogen and the sulfoximine nitrogen (Figure 1a). Related structures have been found in β-hydroxy sulfoximines where the hydroxy proton also connects with the sulfoximine nitrogen (Figure 1b).[53, 54] However, alternative cyclic arrangements, for example, those which involve the sulfoximine oxygen, can not be excluded.

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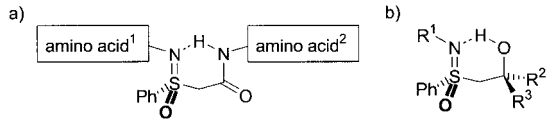

Figure 1. a) Possible six-membered ring structure as a result of intramolecular hydrogen bonding; b) observed cyclic structure in β-hydroxysulfoximines.

More evidence for a cyclic structure comes from the NH-shift data in the ^{1}H NMR spectra (Figure 2). Clearly, the amide proton of **23** with the Boc group gives the most upfield resonance at 5.13 ppm. In comparison, all NH protons of **23**, **36**, and **37** which connect the α-sulfonimidoyl carboxy moiety

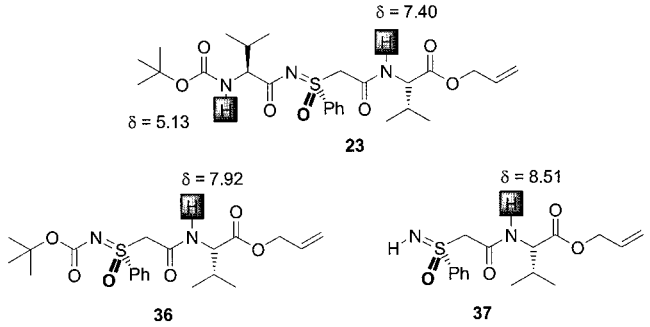

Figure 2. Pseudopeptides with characteristic chemical shifts of the amide protons in ^{1}H NMR spectra.

with the allyl-protected amino acid resonate above $\delta = 7.4$. Compound **37** with a free NH-sulfoximine unit shows the most downfield signal for this amide proton ($\delta = 8.51$). If the sulfoximine nitrogen is Boc-protected, as in **36**, the NH proton is shifted upfield to $\delta = 7.92$. This signal order may indicate a six-membered ring structure as shown in Figure 1. As a result of the presence of an acyl or a Boc group at the sulfoximine nitrogen its hydrogen-acceptor capability is lowered and a weakening of the connecting hydrogen bond occurs. This effect is then indicated by the upfield shift of the respective NH proton.

Next, concentration-dependent ^{1}H NMR studies of **23** were performed to reveal potential intermolecular interactions. In a concentration range between 10 and 0.625 mM (in $CDCl_3$) no significant shifts for the amide proton signals were observed [$\Delta\delta = -0.01$ ppm (H_a) and -0.09 ppm (H_b); see Figure 3 for assignment]. Even at concentrations up to 319 mM the positions of the signals remained almost unchanged. We therefore exclude major intermolecular interactions.

In order to determine the H/D-exchange rate D_2O was added to a sample of **23** in $CDCl_3$ (106 mM) and ^{1}H NMR spectra were recorded after 15, 30, and 40 min.

As depicted in Figure 3 the proton at $\delta = 5.13$ (H_a) exchanges very fast. In contrast, the signal at $\delta = 7.42$ (H_b) moves slightly downfield but remains present which demonstrates that the exchange of this proton is comparably slow. At a 2.5 mM concentration of **23** in $CDCl_3$ analogous results were obtained. This behavior is indicative of a situation in which proton H_b is involved in an intramolecular hydrogen bond, whereas H_a is not. The small downfield shift of the signal for H_b can be accounted for by the polarity change of the solvent upon addition of D_2O.

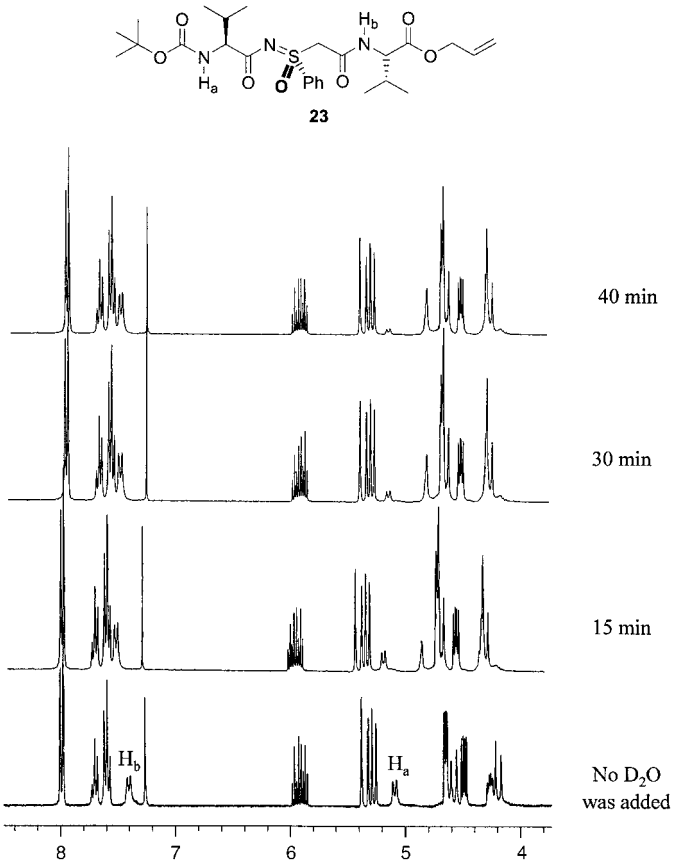

Figure 3. H/D-exchange with D_2O in $CDCl_3$ using pseudotripeptide **23**.

In order to determine the solvent dependence of the H/D-exchange, compound **23** was treated with D_2O in [D_6]DMSO instead of $CDCl_3$. In the absence of D_2O, significant shift differences were obvious which suggested a conformational change of **23** in the more polar solvent. Most apparent is the reduced chemical shift difference in the AB-system of the diastereotopic methylene hydrogens. It is therefore reasonable to assume that in DMSO the weakly connected six-membered ring conformation is opened and leads to a more solvated stretched structure. The acidic protons at the S–CH_2-group exchange the fastest when D_2O is added. Interestingly and in contrast to the NMR studies in $CDCl_3$, it is the proton H_b which undergoes the H/D-exchange more rapidly than H_a. This finding indicates that the possible hydrogen bond between H_b and the sulfoximine donor atom is weakened in the more polar solvent DMSO compared with $CDCl_3$ (Figure 4).

Another useful technique to reveal hydrogen bonds is NMR-titration. For example, Yang et al. recently used [D_6]DMSO titration to demonstrate that in an oligomer of α-aminoxyacetic acid with six residues all amide protons except the one at the *N*-terminus are involved in hydrogen bonds.[55] They found a dramatic downfield shift for the nonbonded amide proton (about 2.5 ppm) only, when [D_6]DMSO was added to a substrate sample dissolved in $CDCl_3$. In analogy to these studies, a 106 mM solution of **23** in $CDCl_3$ was gradually titrated with [D_6]DMSO. The results are summarized in Table 5 and Figure 5.

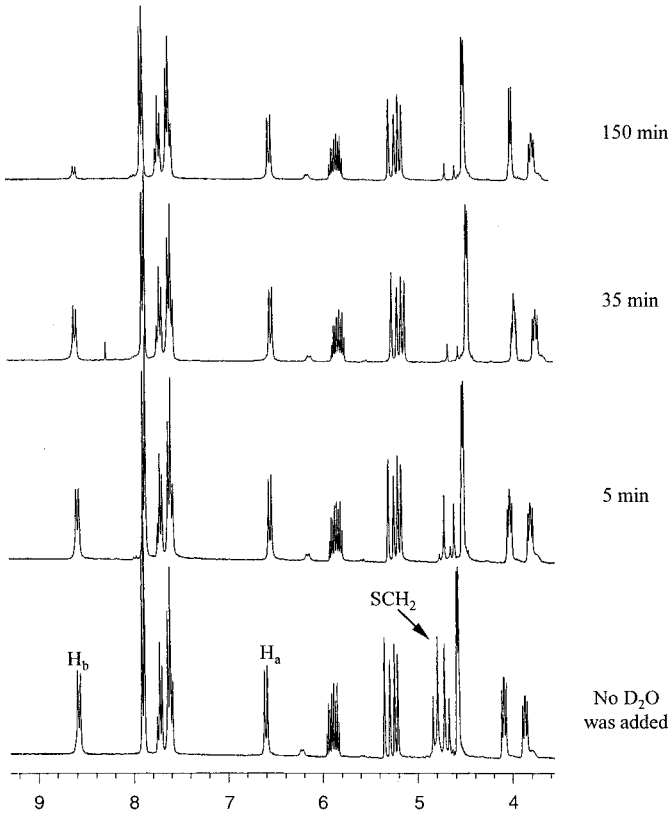

Figure 4. H/D-exchange with D_2O in [D_6]DMSO using pseudotripeptide **23**.

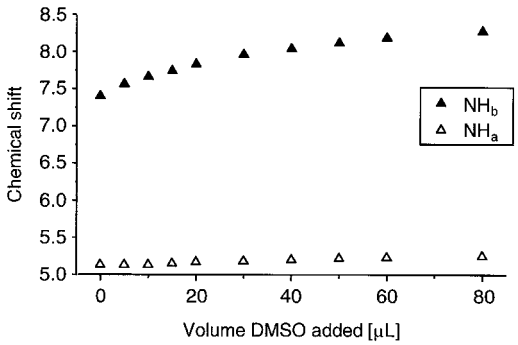

Figure 5. ^{1}H NMR chemical shifts of amide protons of compound **23** in $CDCl_3$ at room temperature upon addition of increasing amounts of [D_6]DMSO.

Table 5. Titration of **23** with [D_6]DMSO in $CDCl_3$.

Entry	DMSO added [mL]	Shift of H_a [ppm]	Shift of H_b [ppm]
1	0	5.13	7.40
2	5	5.13	7.56
3	10	5.13	7.66
4	15	5.15	7.74
5	20	5.17	7.83
6	30	5.18	7.96
7	40	5.20	8.04
8	50	5.22	8.12
9	60	5.23	8.19
10	80	5.25	8.28

Apparently, both protons H_a and H_b undergo a downfield shift of 0.12 and 0.88 ppm, respectively, when [D_6]DMSO is added. Repeating the experiment with a 2.5 mM solution of **23** in $CDCl_3$ gave analogous results [$\Delta\delta = 0.16$ ppm (H_a) and 0.83 ppm (H_b)]. Unfortunately, these chemical shift differences are comparably small and as such they can not serve as an unequivocal indication for the breaking of a hydrogen bond.

In order to determine the hydrogen-bonding state of the amide protons of **23** we also measured the temperature dependence of their ^{1}H NMR chemical shifts. For this purpose the temperature coefficients $\Delta\delta(NH)/\Delta T$ were determined with a solution of **23** in dry CCl_4/C_6D_6 (9:1) between 233 and 306 K. For H_a and H_b they were found to be $-4.4(4)$ ppb K^{-1} and $-5.3(9)$ ppb K^{-1}, respectively. Following the discussion of Gennari, Scolastico, and co-workers[56] these data suggest that both amide protons are in an equilibrium between a hydrogen-bonded and a nonhydrogen-bonded state.

Conclusion

We have established a straightforward method for the synthesis of pseudotripeptides **1** in good overall yields starting from (S_S)-*S*-methyl *S*-phenyl sulfoximine [(S_S)-**3**] and protected natural α-amino acids. This new class of compounds with a chiral α-sulfonimidoyl carboxy moiety in its backbone appears to adopt well-defined conformations. From the results of the NMR investigations we propose equilibria between secondary structures with hydrogen-bonded and nonhydrogen-bonded states.

The application of this synthetic strategy in the preparation of larger pseudopeptides and the exploitation of potentially biologically active molecules with sulfoximines in the backbone will be presented in following publications.

Experimental Section

General: All reactions under anhydrous conditions were performed under argon by means of standard Schlenk techniques. Solvents were dried and distilled prior to use under an inert atmosphere (THF from sodium/benzophenone, CH_2Cl_2 from lithium aluminum hydride). Unless otherwise specified all starting materials were purchased from commercial suppliers and were used without further purification. (S_S)-*S*-Methyl *S*-phenyl sulfoximine [(S_S)-**3**] was prepared according to literature procedures.[34, 37] A hexane solution of *n*-butyllithium (1.6 M, Aldrich) was used as supplied. ^{1}H NMR and ^{13}C NMR spectra were recorded using tetramethylsilane (TMS) as internal standard. The following abbreviations are used to indicate multiplicities: s singlet, br s broad singlet, d doublet, dd doublet of a doublet, ddd doublet of a doublet of a doublet, t triplet, q quartet, quin quintet, sept septet, m multiplet. Mass spectra were obtained with a Finnigan SSQ 7000 and with a Varian MAT 212 S spectrometer. FT-IR spectra were recorded on a Perkin–Elmer PE-1760 FT. Elemental analyses were carried out on a Heraeus CHNO-Rapid instruments. Melting points were measured with a Büchi B-540 and are uncorrected. Optical rotations were obtained with a Perkin–Elmer PE-241. Flash chromatography was performed using Merck silica gel 60, mesh 37–70 µm.

General procedure A) for the synthesis of pseudodipeptides: A solution of the *N-tert*-butyloxycarbonyl-protected amino acid (1 equiv), (S_S)-*S*-methyl *S*-phenyl sulfoximine [(S_S)-**3**] (1 equiv), and HOBt (1 equiv) in CH_2Cl_2 (8 mL mmol^{-1} reagents) was cooled to 0 °C and treated with a solution of DCC (1.03 equiv) in CH_2Cl_2 (1 mL mmol^{-1} reagents). The solution was

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stirred for 1 h at 0 °C and 12 h at room temperature. The precipitate was filtered off and the solvent removed in vacuo. Unless otherwise noted the resulting residue was purified by flash chromatography with ethyl acetate/hexanes 1:1 to yield the pure product.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-alaninyl)-*S*-methyl *S*-phenyl sulfoximine (Boc-Ala-Sulf-H, 8): Compound **8** was prepared according to general procedure A after purification by flash chromatography (ethyl acetate/hexanes 3:1) as a colorless solid (90 %). M.p. 112 °C; $[\alpha]_D^{25} = -4.1$ ($c = 1.0$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.97$ (d, $J = 7.1$ Hz, 2H), 7.69 (t, $J = 7.7$ Hz, 1H), 7.60 (t, $J = 7.7$ Hz, 2H), 5.26 (d, $J = 6.0$ Hz, 1H), 4.21–4.34 (m, 1H), 3.34 (s, 3H), 1.43 (s, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.7$, 155.4, 138.5, 134.0, 129.8, 127.2, 79.3, 52.7, 44.5, 28.5, 19.4; IR (KBr): $\tilde{\nu}$ = 3394, 1702, 1657, 1226, 1195 cm^{-1}; MS (CI): m/z: 327 $[M+H]^+$; elemental analysis calcd (%) for $C_{15}H_{22}N_2O_4S$ (326.4): C 55.19, H 6.79, N 8.58; found C 55.38, H 6.65, N 8.65.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-valinyl)-*S*-methyl *S*-phenyl sulfoximine (Boc-Val-Sulf-H, 9): Compound **9** was prepared according to general procedure A as a colorless solid (97 %). M.p. 105 °C; $[\alpha]_D^{25} = +6.3$ ($c = 1.03$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.99$ (d, $J = 7.3$ Hz, 2H), 7.69 (t, $J = 7.3$ Hz, 1H), 7.61 (t, $J = 7.6$ Hz, 2H), 5.13 (d, $J = 8.9$ Hz, 1H), 4.25 (dd, $J = 4.3$, 8.8 Hz, 1H), 3.33 (s, 3H), 2.35–2.26 (m, 1H), 1.43 (s, 9H), 1.11 (d, $J = 7.0$ Hz, 3H), 0.91 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.9, 156.1, 138.6, 134.0, 129.8, 127.2, 79.2, 61.5, 44.4, 28.5, 19.7, 17.4; IR (KBr): $\tilde{\nu}$ = 3380, 1691, 1648, 1223, 1160 cm^{-1}; MS (EI): m/z: 355 $[M+H]^+$; elemental analysis calcd (%) for $C_{17}H_{26}N_2O_4S$ (354.5): C 57.60, H 7.39, N 7.90; found: C 57.91, H 7.71, N 7.64.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-leucinyl)-*S*-methyl *S*-phenyl sulfoximine (Boc-Leu-Sulf-H, 10): Compound **10** was prepared according to general procedure A as a colorless solid (97 %). M.p. 106 °C; $[\alpha]_D^{25} = +3.0$ ($c = 1.1$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.99$ (d, $J = 7.3$ Hz, 2H), 7.75–7.57 (m, 3H), 5.06 (d, $J = 8.4$ Hz, 1H), 4.36–4.20 (m, 1H), 3.37 (s, 3H), 1.83–1.60 (m, 3H), 1.45 (s, 9H), 0.96 (d, $J = 6.1$ Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.8$, 155.5, 138.4, 133.7, 129.5, 127.1, 79.1, 55.4, 44.1, 42.2, 28.2, 22.9, 22.0; IR (KBr): $\tilde{\nu}$ = 3409, 1696, 1655, 1224, 1165 cm^{-1}; MS (EI): m/z: 182 [(Ph)(Me)(O)S=N=C=O]$^+$; elemental analysis calcd (%) for $C_{18}H_{28}N_2O_4S$ (368.5): C 58.67, H 7.66, N 7.60; found C 58.60, H 7.54, N 7.53.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-isoleucinyl)-*S*-methyl *S*-phenyl sulfoximine (Boc-Ile-Sulf-H, 11): Compound **11** was prepared according to general procedure A as a colorless solid (93 %). M.p. 93 °C; $[\alpha]_D^{25} = +15.6$ ($c = 1.08$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.89$ (d, $J = 7.9$ Hz, 2H), 7.61 (t, $J = 7.2$ Hz, 1H), 7.52 (t, $J = 7.4$ Hz, 2H), 5.06 (d, $J = 8.6$ Hz, 1H), 4.19–4.16 (m, 1H), 3.26 (s, 3H), 1.88–1.78 (m, 1H), 1.35 (s, 9H), 1.22–1.02 (m, 2H), 0.95 (d, $J = 7.0$ Hz, 3H), 0.85 (d, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.6, 155.7, 138.4, 133.7, 129.5, 127.0, 79.0, 60.9, 44.1, 38.3, 28.1, 24.7, 15.7, 11.7; IR (KBr): $\tilde{\nu}$ = 3383, 1691, 1652, 1216, 1159 cm^{-1}; MS (EI): m/z: 369 $[M+H]^+$; elemental analysis calcd (%) for $C_{18}H_{28}N_2O_4S$ (368.5): C 58.67, H 7.66, N 7.60; found C 58.52, H 7.59, N 7.65.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-*tert*-leucinyl)-*S*-methyl *S*-phenyl sulfoximine (Boc-Tle-Sulf-H, 12): Compound **12** was prepared according to general procedure A after purification by flash chromatography (ethyl acetate/hexanes 2:1) as a colorless solid (79 %). M.p. 109.3 °C; $[\alpha]_D^{25} = +2.8$ ($c = 1.05$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.99-7.95$ (m, 2H), 7.68 (t, $J = 7.4$ Hz, 1H), 7.58 (t, $J = 7.7$ Hz, 2H), 5.17 (d, $J = 9.4$ Hz, 1H), 4.11 (d, $J = 9.7$ Hz, 1H), 3.38 (s, 3H), 1.43 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 180.6, 155.9, 138.6, 133.9, 129.7, 127.2, 79.2, 64.5, 44.4, 34.8, 28.5, 27.0; IR (KBr): $\tilde{\nu}$ = 3455, 1717, 1629, 1213, 1171 cm^{-1}; MS (CI): m/z: 182 [M – (Ph)(Me)(O)S=N=C=O]$^+$; elemental analysis calcd (%) for $C_{18}H_{28}N_2O_4S$ (368.5): C 58.67, H 7.66, N 7.60; found C 58.29, H 7.52, N 7.39.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-prolinyl)-*S*-methyl *S*-phenyl sulfoximine (Boc-Pro-Sulf-H, 13): Compound **13** was prepared according to general procedure A as a mixture of two rotamers (2:1) as a colorless solid (91 %) after purification by flash chromatography (ethyl acetate/hexanes 8:1). M.p. 103 °C; $[\alpha]_D^{25} = -36.5$ ($c = 1.0$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.05-7.99$ (d, $J = 7.1$ Hz, 2H), 7.74–7.53 (m, 3H), 4.36/4.26 (m, 1H), 3.60–3.43 (m, 2H), 3.38/3.34 (s, 3H), 2.29–1.69 (m, 4H), 1.41/1.39 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 182.6/182.3, 154.6/154.4, 138.9/138.7, 133.9/133.7, 129.7/129.5, 127.7/127.2, 79.4/79.2, 62.9/62.6, 46.9/46.6, 44.1, 31.4/30.3, 28.6, 24.4/23.5; IR (KBr): $\tilde{\nu}$ = 1686, 1639, 1204, 1168 cm^{-1}; MS (EI): m/z: 352 $[M]^+$; elemental analysis calcd (%) for $C_{17}H_{24}N_2O_4S$ (352.5): C 57.93, H 6.86, N 7.95; found C 58.10, H 6.95, N 7.94.

General procedure B) for the carboxylation: A solution of cyclohexyl(isopropyl)amine in THF in a flame-dried Schlenk at 0 °C under argon was treated with a solution of *n*BuLi in hexanes. The mixture was stirred for 30 min at 0 °C and cooled to −78 °C. At this temperature a solution of the sulfoximine in THF was added dropwise by means of a cannula. After stirring for 30 min at −78 °C, dried CO_2 was bubbled through the solution until a white precipitate appeared. The cooling bath was removed and the gas flow reduced. After 20 min the gas flow was stopped, and the reaction mixture was allowed to warm to room temperature. Under vigorous stirring water was added, and the organic phase was separated, and the aqueous phase was extracted once with diethyl ether. The organic phases were discarded and to the aqueous phase solid ammonium chloride was added until a precipitate was formed. The suspension was extracted seven times with dichloromethane, the dichloromethane phase dried over $MgSO_4$, the solvent removed under reduced pressure at room temperature (without heating!) and the remaining oil dried in vacuo. The products were then used without any further purification.

Cyclohexyl(isopropyl)ammonium (S_S)-*N*-(*N*-*tert*-butyloxycarbonyl-L-alaninyl)-*S*-methyl *S*-phenyl sulfonimidoyl acetate (Boc-Ala-Sulf-Ac, 14): According to general procedure B cyclohexyl(isopropyl)amine (1.81 mL, 10.73 mmol) was dissolved in THF (12 mL) at 0 °C. Sequentially *n*BuLi (6.69 mL, 10.73 mmol) and, after cooling to −78 °C, compound **8** (1.00 g, 3.07 mmol) in THF (11 mL) were added dropwise. For the workup (see procedure B) the following reagents were used: water (41 mL), diethyl ether (21 mL), and CH_2Cl_2 (13 mL each). Product **14** was obtained as a colorless solid (77 %): ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (m, 2H), 7.60 (t, $J = 7.4$ Hz, 1H), 7.53 (t, $J = 7.2$ Hz, 2H), 5.12 (d, $J = 7.2$ Hz, 1H), 4.42/4.24 (AB-system, $J = 14.6$ Hz, 2H), 4.22–4.32 (m, 1H), 3.29–3.23 (m, 1H), 2.86–2.82 (m, 1H), 1.99–1.96 (m, 2H), 1.77–1.74 (m, 2H), 1.66–1.63 (m, 1H), 1.50–1.14 (m, 5H), 1.42 (s, 9H), 1.23 (dd, $J = 2.5$, 6.3 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.3$, 164.5, 155.8, 138.3, 133.4, 129.1, 128.1, 79.2, 62.2, 53.8, 52.7, 45.9, 30.1, 30.0, 28.6, 25.4, 24.9, 20.1, 19.9, 19.6, 19.5.

Cyclohexyl(isopropyl)ammonium (S_S)-*N*-(*N*-*tert*-butyloxycarbonyl-L-valinyl)-*S*-methyl *S*-phenyl sulfonimidoyl acetate (Boc-Val-Sulf-Ac, 15): According to general procedure B cyclohexyl(isopropyl)amine (1.33 mL, 7.91 mmol) was dissolved in THF (8 mL) at 0 °C. Sequentially *n*BuLi (4.94 mL, 7.91 mmol) and, after cooling to −78 °C, compound **9** (0.80 g, 2.26 mmol) in THF (8 mL) was added dropwise. For the workup (see procedure B) the following reagents were used: water (25 mL), diethyl ether (7 mL), and CH_2Cl_2 (12 mL each). Product **15** was obtained as a colorless solid (85 %): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.91$ (d, $J = 7.2$ Hz, 2H), 7.59 (t, $J = 7.2$ Hz, 1H), 7.49 (t, $J = 7.4$ Hz, 2H), 5.12 (d, $J = 8.6$ Hz, 1H), 4.42/4.19 (AB-System, $J = 14.4$ Hz, 2H), 4.30–4.11 (m, 1H), 3.69 (t, $J = 6.6$ Hz, 2H), 3.23 (sept, $J = 6.4$ Hz, 1H), 2.91–2.72 (m, 1H), 2.27–2.12 (m, 1H), 1.97–1.02 (m, 10H), 1.38 (s, 9H), 1.13 (d, $J = 5.3$ Hz, 6H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.84 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 181.0, 164.4, 155.5, 138.2, 133.1, 127.9, 127.2, 79.0, 61.9, 53.5, 45.6, 31.4, 29.5, 29.2, 28.4, 25.6, 25.2, 24.7, 19.4, 19.1, 17.4.

(S_S)-Cyclohexyl(isopropyl)ammonium (S_S)-*N*-(*N*-*tert*-butyloxycarbonyl-L-leucinyl)-*S*-methyl *S*-phenyl sulfonimidoyl acetate (Boc-Leu-Sulf-Ac, 16): Following general procedure B cyclohexyl(isopropyl)amine (2.28 mL, 13.55 mmol) was dissolved in THF (9 mL) at 0 °C. Sequentially *n*BuLi (8.46 mL, 13.55 mmol) and, after cooling to −8 °C, compound **10** (1.00 g, 2.71 mmol) in THF (8 mL) was added dropwise. For the workup (see procedure B) the following reagents were used: water (42 mL), diethyl ether (14 mL), and CH_2Cl_2 (24 mL each). Product **16** was obtained as a colorless solid (81 %): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.90$ (d, $J = 7.4$ Hz, 2H), 7.53 (t, $J = 7.2$ Hz, 2H), 7.44 (t, $J = 7.2$ Hz, 2H), 5.10 (d, $J = 8.6$ Hz, 1H), 4.22 (m, 1H), 4.42/4.18 (AB-system, $J = 14.7$ Hz, 2H), 3.67 (t, J = 6.6 Hz, 2H), 3.22 (sept, $J = 6.5$ Hz, 1H), 2.79–2.74 (m, 1H), 2.00–1.02 (m, 13H), 1.33 (s, 9H), 1.20 (d, $J = 6.4$ Hz, 6H), 0.87 (dd, $J = 3.5$, 6.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.2$, 164.3, 155.3, 138.1, 133.0, 128.7, 127.8, 77.7, 61.7, 55.4, 53.6, 45.7, 42.6, 29.7, 29.6, 28.3, 25.5, 25.0, 24.6, 23.0, 22.0, 19.7, 19.6.

Cyclohexyl(isopropyl)ammonium (S_S)-*N*-(*N*-*tert*-butyloxycarbonyl-L-isoleucinyl)-*S*-methyl *S*-phenyl sulfonimidoyl acetate (Boc-Ile-Sulf-Ac, 17): According to general procedure B cyclohexyl(isopropyl)amine (1.56 mL,

9.25 mmol) was dissolved in THF (9 mL) at 0 °C. Subsequently *n*BuLi (5.78 mL, 9.25 mmol) and, after cooling to −78 °C, compound **11** (0.68 g, 1.85 mmol) in THF (7 mL) was added dropwise. For the workup (see procedure B) the following reagents were used: water (28 mL), diethyl ether (8 mL), and CH_2Cl_2 (16 mL each). Product **17** was obtained as a colorless solid (82 %): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.98$ (d, $J = 7.3$ Hz, 2H), 7.60 (t, $J = 7.2$ Hz, 1H), 7.51 (t, $J = 7.4$ Hz, 2H), 5.18 (d, $J = 8.7$ Hz, 1H), 4.52/4.24 (AB-system, $J = 14.8$ Hz, 2H), 4.29–4.23 (m, 1H), 3.74 (t, $J = 6.6$ Hz, 2H), 3.31 (sept, $J = 6.5$ Hz, 1H), 2.89–2.83 (m, 1H), 2.27–1.15 (m, 13H), 1.41 (s, 9H), 1.31 (d, $J = 6.5$ Hz, 6H), 0.94 (d, $J = 7.4$ Hz, 3H), 0.89 (d, $J = 7.4$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.0$, 164.4, 155.6, 138.2, 133.0, 128.5, 127.8, 78.8, 61.6, 60.7, 53.8, 45.9, 38.6, 29.7, 29.6, 28.2, 25.5, 24.9, 24.7, 19.6, 15.6, 11.7.

(S_S)-Cyclohexyl(isopropyl)ammonium *N*-(*N*-*tert*-butyloxycarbonyl-L-*tert*-leucinyl)-*S*-methyl *S*-phenyl sulfonimidoyl acetate (Boc-Tle-Sulf-Ac, 18): Following general procedure B cyclohexyl(isopropyl)amine (1.16 mL, 6.89 mmol) was dissolved in THF (8 mL) at 0 °C. Sequentially *n*BuLi (4.30 mL, 6.89 mmol) and, after cooling to −78 °C, compound **12** (0.73 g, 1.97 mmol) in THF (6 mL) was added dropwise. For the workup (see procedure B) the following reagents were used: water (25 mL), diethyl ether (9 mL), and CH_2Cl_2 (15 mL each). Product **18** was obtained as a colorless solid (76 %): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.90$ (br s, 2H), 7.97 (d, $J = 7.4$ Hz, 2H), 7.59 (t, $J = 7.1$ Hz, 1H), 7.52 (t, $J = 7.4$ Hz, 2H), 5.23 (d, $J = 9.4$ Hz, 1H), 4.49/4.26 (AB-system, $J = 14.8$ Hz, 2H), 4.08 (d, $J = 9.4$ Hz, 1H), 3.28–2.33 (m, 1H), 2.91–2.85 (m, 1H), 2.00–1.61 (m, 10H), 1.33 (s, 9H), 1.22 (d, $J = 6.4$ Hz, 6H), 1.02 (d, $J = 8.7$ Hz, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 180.2$, 164.8, 155.8, 137.9, 133.4, 128.2, 127.2, 79.1, 64.4, 61.6, 53.7, 46.0, 35.1, 29.1, 28.8, 28.4, 26.9, 25.0, 24.7, 19.1, 18.9.

(S_S)-Cyclohexyl(isopropyl)ammonium *N*-(*N*-*tert*-butyloxycarbonyl-L-prolinyl)-*S*-methyl *S*-phenyl sulfonimidoyl acetate (Boc-Pro-Sulf-Ac, 19): Following general procedure B cyclohexyl(isopropyl)amine (1.26 mL, 7.45 mmol) was dissolved in THF (8 mL) at 0 °C, *n*BuLi (4.65 mL, 7.45 mmol) and, after cooling to −78 °C, compound **13** (0.75 g, 2.13 mmol) in THF (6 mL) was added dropwise. For the workup (see procedure B) the following reagents were used: water (9 mL), diethyl ether (6 mL), and CH_2Cl_2 (13 mL each). Product **19** was obtained as a colorless solid (82 %) as a mixture of two rotamers (2:1): ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.99/7.93$ (d, $J = 7.4$ Hz, 2H), 7.59–7.37 (m, 3H), 4.46/4.10, 4.53/4.18 (AB-system, $J = 14.5$ Hz, 2H), 4.30–4.26, 4.17–4.14 (m, 1H), 3.75–3.65 (m, 2H), 3.57–3.25 (m, 2H), 3.23 (sept, $J = 6.4$ Hz, 1H), 2.80–2.85 (m, 1H), 2.25–1.07 (m, 14H), 1.39/1.35 (s, 9H), 1.21 (d, $J = 6.3$ Hz, 3H), 1.20 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 182.0/181.6$, 164.7, 154.4, 138.6/138.4, 133.0/132.8, 128.7/128.6, 128.2/128.0, 79.4/79.2, 62.8/62.4, 61.6, 53.7, 46.6/46.4, 45.8, 31.2/30.2, 29.8, 29.6, 28.4, 25.5, 25.1, 24.8, 24.1/23.3, 19.7, 19.6.

General procedure C for the synthesis of pseudotripeptides: The allyl-protected amino acid (1 equiv) and DMAP (0.1 equiv) were added to sulfonimidoyl acetate (1 equiv) in CH_2Cl_2. After cooling to 0 °C, DCC (1.03 equiv) in CH_2Cl_2 was added and the reaction mixture was stirred for 1 h at 0 °C, and for 12 h at room temperature. The precipitate was filtered off, and the solvent was removed in vacuo. The remaining oil was then dissolved in ethyl acetate, and the newly formed precipitate was filtered off again. The solvent was removed in vacuo, and the crude product was purified by flash chromatography.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-alaninyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-valinyl)carboxyamide (Boc-Ala-Sulf-CO-Val-OAll, 20): DCC (0.21 g, 1.01 mmol) dissolved in CH_2Cl_2 (3 mL) was added to a cooled solution (0 °C) of sulfonimidoyl acetate **14** (0.50 g, 0.98 mmol), H-Val-OAll·*p*Tos (0.32 g, 0.98 mmol), and DMAP (12.21 mg, 0.10 mmol) in CH_2Cl_2 (6 mL). Purification by flash chromatography (ethyl acetate/hexanes 3:2) gave **20** as a colorless oil (56 %). $[\alpha]_D^{25} = -26.6$ ($c = 1.05$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.04–8.00$ (m, 2H), 7.73–7.67 (m, 1H), 7.59 (t, $J = 7.4$ Hz, 2H), 7.51 (d, $J = 8.4$ Hz, 1H), 5.98–5.84 (m, 1H), 5.39–5.32 (m, 1H), 5.28–5.23 (m, 2H), 4.71–4.61 (m, 2H), 4.56/4.30 (AB-system, $J = 14.4$ Hz, 2H), 4.52–4.46 (m, 1H), 4.38–4.33 (m, 1H), 2.27–2.13 (m, 1H), 1.48–1.42 (m, 12H), 0.98 (d, $J = 6.8$ Hz, 3H), 0.96 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.1$, 170.7, 159.9, 155.4, 136.3, 134.6, 131.6, 129.7, 128.3, 119.2, 79.4, 66.0, 60.9, 58.0, 52.9, 31.3, 28.5, 19.0, 17.9; IR (KBr): $\tilde{\nu} = 3365$, 1742, 1689, 1218, 1165 cm^{-1}; MS (EI): *m*/*z*: 510 $[M+H]^+$; elemental analysis calcd (%) for $C_{24}H_{35}N_3O_7S$ (509.6): C 56.56, H 6.92, N 8.25; found C 56.36, H 7.04, N 8.23.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-alaninyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-leucinyl)carboxyamide (Boc-Ala-Sulf-CO-Leu-OAll, 21): According to general procedure C H-Leu-OAll·*p*Tos (0.34 g, 0.98 mmol), and DMAP (12.21 mg, 0.10 mmol) were added to sulfonimidoyl acetate **14** (0.50 g, 0.98 mmol) in CH_2Cl_2 (6 mL), and after cooling to 0 °C, DCC (0.21 g, 1.01 mmol) in CH_2Cl_2 (3 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 3:2) gave **21** as a colorless oil (66 %). $[\alpha]_D^{25} = -30.7$ ($c = 1.06$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.01$ (d, $J = 7.7$ Hz, 2H), 7.70 (t, $J = 7.2$ Hz, 1H), 7.62–7.52 (m, 3H), 5.96–5.84 (m, 1H), 5.35–5.31 (m, 1H), 5.27–5.23 (m, 2H), 4.63 (d, $J = 5.8$ Hz, 2H), 4.59–4.53 (m, 1H), 4.57/4.32 (AB-system, $J = 14.0$ Hz, 2H), 4.36–4.31 (m, 1H), 1.45–1.41 (m, 12H), 0.95 (d, $J = 5.8$ Hz, 3H), 0.93 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.1$, 171.7, 159.8, 155.4, 136.0, 134.6, 131.6, 129.6, 128.3, 118.8, 79.4, 66.0, 60.7, 52.9, 51.5, 41.1, 28.4, 24.8, 22.7, 21.8, 18.9; IR (KBr): $\tilde{\nu} = 3354$, 1745, 1688, 1238, 1163 cm^{-1}; MS (EI): *m*/*z*: 524 $[M+H]^+$; elemental analysis calcd (%) for $C_{25}H_{37}N_3O_7S$ (523.7): C 57.34, H 7.12, N 8.02; found C 56.95, H 7.21, N 7.89.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-alaninyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-isoleucinyl)carboxyamide (Boc-Ala-Sulf-CO-Ile-OAll, 22): According to general procedure C H-Ile-OAll·*p*Tos (0.28 g, 0.82 mmol) and DMAP (9.78 mg, 0.08 mmol) were added to sulfonimidoyl acetate **14** (0.42 g, 0.82 mmol) in CH_2Cl_2 (5 mL), and after cooling to 0 °C, DCC (0.18 g, 0.85 mmol) in CH_2Cl_2 (2 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 3:2) gave **22** as a colorless oil (55 %). $[\alpha]_D^{25} = -19.0$ ($c = 1.05$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.00$ (d, $J = 7.7$ Hz, 2H), 7.74–7.70 (m, 1H), 7.63–7.56 (m, 2H), 7.53 (d, $J = 7.7$ Hz, 1H), 5.97–5.86 (m, 1H), 5.35 (ddd, $J = 1.4$, 3.0, 15.7 Hz, 1H), 5.29–5.24 (m, 2H), 4.69–4.61 (m, 2H), 4.58–4.52 (m, 1H), 4.54/4.29 (AB-system, $J = 14.6$ Hz, 2H), 4.36–4.31 (m, 1H), 1.99–1.89 (m, 1H), 1.48–1.42 (m, 12H), 1.30–1.18 (m, 2H), 0.96–0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.1$, 170.6, 159.8, 155.4, 136.2, 134.6, 131.5, 129.7, 128.2, 119.1, 79.4, 66.0, 60.9, 57.3, 52.9, 37.9, 28.4, 25.2, 19.1, 15.6, 15.4, 11.6; IR (KBr): $\tilde{\nu} = 3361$, 1742, 1687, 1221, 1166 cm^{-1}; MS (EI): *m*/*z*: 524 $[M+H]^+$; elemental analysis calcd (%) for $C_{25}H_{37}N_3O_7S$ (523.7): C 57.34, H 7.12, N 8.02; found C 56.97, H 7.28, N 7.90.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-valinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-valinyl)carboxyamide (Boc-Val-Sulf-CO-Val-OAll, 23): Following general procedure C, H-Val-OAll·*p*Tos (0.45 g, 1.36 mmol) and DMAP (16.62 mg, 0.14 mmol) were added to sulfonimidoyl acetate **15** (0.74 g, 1.36 mmol) in CH_2Cl_2 (12 mL), and after cooling to 0 °C, DCC (0.29 g, 1.40 mmol) dissolved in CH_2Cl_2 (4 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **23** as a colorless oil (82 %). $[\alpha]_D^{25} = -14.1$ ($c = 1.03$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.92$ (d, $J = 7.8$ Hz, 2H), 7.92 (d, $J = 7.8$ Hz, 2H), 7.62 (t, $J = 7.1$ Hz, 1H), 7.51 (t, $J = 7.6$ Hz, 2H), 7.40 (d, $J = 8.1$ Hz, 1H), 5.92–5.74 (m, 1H), 5.27 (dd, $J = 1.0$, 17.2 Hz, 1H), 5.18 (dd, $J = 1.0$, 10.4 Hz, 1H), 5.04 (d, $J = 8.7$ Hz, 1H), 4.62–4.57 (m, 2H), 4.40 (dd, $J = 4.7$, 8.4 Hz, 1H), 4.18–4.13 (m, 1H), 4.56/4.18 (AB-system, $J = 14.6$ Hz, 2H), 2.25–2.12 (m, 2H), 1.36 (s, 9H), 0.97 (d, $J = 6.8$ Hz, 3H), 0.92 (d, $J = 2.6$ Hz, 3H), 0.89 (d, $J = 2.6$ Hz, 3H), 0.86 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.2$, 170.6, 159.9, 155.9, 136.4, 134.5, 131.6, 128.2, 127.2, 119.1, 79.3, 65.9, 61.8, 60.8, 58.0, 31.6, 31.2, 28.4, 19.6, 18.9, 17.8; IR (KBr): $\tilde{\nu} = 3366$, 1740, 1715, 1688, 1207, 1159 cm^{-1}; MS (EI): *m*/*z*: 538 $[M+H]^+$; elemental analysis calcd (%) for $C_{26}H_{39}N_3O_7S$ (537.7): C 58.08, H 7.31, N 7.82; found C 57.86, H 7.42, N 7.54.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-valinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-leucinyl)carboxyamide (Boc-Val-Sulf-CO-Leu-OAll, 24): Following general procedure C H-Leu-OAll·*p*Tos (0.58 g, 1.67 mmol) and DMAP (20.16 mg, 0.17 mmol) were added to sulfonimidoyl acetate **15** (0.90 g, 1.67 mmol) in CH_2Cl_2 (10 mL), and after cooling to 0 °C, DCC (0.36 g, 1.72 mmol) dissolved in CH_2Cl_2 (4 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **24** as colorless oil (70 %). $[\alpha]_D^{25} = -26.5$ ($c = 1.04$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.03–7.98$ (m, 2H), 7.75–7.70 (m 1H), 7.58 (t, $J = 7.4$ Hz, 2H), 7.51 (d, $J = 8.1$ Hz, 1H), 5.98–5.83 (m, 1H), 5.33 (ddd, $J = 1.4$, 3.0, 17.5 Hz, 1H), 5.25 (ddd, $J = 1.4$, 2.3, 10.4 Hz, 1H), 5.14 (d, $J = 9.1$ Hz, 1H), 4.63/4.21 (AB-system, $J = 14.4$ Hz, 2H), 4.67–4.61 (m, 2H), 4.57–4.52 (m, 1H), 4.29–4.23 (m, 1H), 2.35–2.25 (m, 1H), 1.69–1.64 (m, 3H), 1.44 (s, 9H), 1.03 (d, $J = 6.7$ Hz, 9H), 0.93 (t, $J = 2.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 181.3$, 171.7, 159.9, 156.0, 136.2, 134.6, 131.6, 129.7, 128.3, 118.9, 79.4, 66.0, 61.9, 60.7, 51.6, 41.2, 31.5, 28.5, 24.9, 22.8, 21.6, 19.7, 17.5; IR (KBr): $\tilde{\nu} = 3371$, 1746, 1701, 1677, 1221, 1159 cm^{-1}; MS (CI): *m*/*z*: 552 $[M+H]^+$; elemental analysis calcd

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(%) for $C_{27}H_{41}N_3O_7S$ (551.7): C 58.78, H 7.49, N 7.62; found C 58.95, H 7.63, N 7.59.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-valinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-isoleucinyl)carboxyamide (Boc-Val-Sulf-CO-Ile-OAll, 25): Following general procedure C H-Leu-OAll · *p*Tos (0.58 g, 1.67 mmol) and DMAP (20.16 mg, 0.17 mmol) were added to sulfonimidoyl acetate **15** (0.90 g, 1.67 mmol) in CH_2Cl_2 (10 mL), and after cooling to 0 °C, DCC (0.36 g, 1.72 mmol) dissolved in CH_2Cl_2 (4 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **25** as a colorless oil (63 %). $[\alpha]_D^{25} = -14.5$ ($c = 1.05$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.02 – 7.97 (m, 2H), 7.70 (t, $J = 7.4$ Hz, 1H), 7.59 (t, $J = 7.9$ Hz, 2H), 7.48 (d, $J = 7.9$ Hz, 1H), 5.98 – 5.86 (m, 1H), 5.35 (ddd, $J = 1.1$, 2.5, 17.0 Hz, 1H), 4.69 – 4.62 (m, 2H), 4.57 – 4.50 (m, 1H), 5.27 (ddd, $J = 1.1$, 2.5, 11.8 Hz, 1H), 5.12 (d, $J = 8.8$ Hz, 1H), 4.59/4.21 (AB-system, $J = 14.3$ Hz, 2H), 4.28 – 4.23 (m, 1H), 2.37 – 2.30 (m, 1H), 1.96 – 1.91 (m, 1H), 1.49 – 1.43 (m, 1H), 1.44 (s, 9H), 1.28 – 1.21 (m, 1H), 1.02 (d, $J = 6.9$ Hz, 3H), 0.98 – 0.92 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 181.3, 170.6, 159.8, 156.0, 136.3, 134.6, 131.6, 129.7, 128.2, 119.1, 79.3, 65.9, 61.8, 60.8, 57.3, 37.8, 31.6, 28.4, 25.2, 19.6, 17.3, 15.6, 11.6; IR (KBr): $\tilde{\nu} =$ 3358, 1741, 1716, 1688, 1240, 1159 cm^{-1}; MS (CI): *m*/*z*: 552 $[M+H]^+$; elemental analysis calcd (%) for $C_{27}H_{41}N_3O_7S$ (551.7): C 58.78, H 7.49, N 7.62; found C 58.58, H 7.44, N 7.59.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-leucinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-leucinyl)carboxyamide (Boc-Leu-Sulf-CO-Leu-OAll, 26): Following general procedure C H-Leu-OAll · *p*Tos (0.54 g, 1.57 mmol) and DMAP (19.55 mg, 0.16 mmol) were added to a solution of sulfonimidoyl acetate **16** (0.87 g, 1.57 mmol) in CH_2Cl_2 (10 mL), and after cooling to 0 °C, DCC (0.33 g, 1.62 mmol) in CH_2Cl_2 (5 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **26** as a colorless oil (76 %): $[\alpha]_D^{25} = -20.1$ ($c = 1.06$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.00 (d, $J = 7.5$ Hz, 2H), 7.70 – 7.63 (m, 2H), 7.55 (t, $J = 7.4$ Hz, 2H), 5.94 – 5.83 (m, 1H), 5.32 (dd, $J = 1.4$, 15.8 Hz, 1H), 5.24 (dd, $J = 1.2$, 11.5 Hz, 1H), 5.12 (d, $J = 8.4$ Hz, 1H), 4.59 – 4.52 (m, 3H), 4.51/4.28 (AB-system, $J =$ 14.3 Hz, 2H), 4.35 – 4.30 (m, 1H), 1.97 – 1.61 (m, 6H), 1.42 (s, 9H), 1.03 – 0.86 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 182.1, 171.5, 159.7, 155.5, 136.0, 134.3, 131.4, 129.4, 128.1, 118.6, 79.1, 65.7, 60.4, 55.6, 51.3, 49.2, 41.7, 39.9, 34.8, 28.2, 24.5, 23.0, 22.6, 21.8; IR (KBr): $\tilde{\nu} =$ 3429, 1741, 1687, 1204, 1164 cm^{-1}; MS (EI): *m*/*z*: 566 $[M+H]^+$; elemental analysis calcd (%) for $C_{28}H_{43}N_3O_7S$ (565.7): C 59.45, H 7.66, N 7.43; found C 59.17, H 7.74, N 7.65.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-leucinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-valinyl)carboxyamide (Boc-Leu-Sulf-CO-Val-OAll, 27): Following general procedure C H-Val-OAll · *p*Tos (0.80 g, 2.44 mmol) and DMAP (29.32 mg, 0.24 mmol) were added to a solution of sulfonimidoyl acetate **16** (1.35 g, 2.44 mmol) in CH_2Cl_2 (15 mL), and after cooling to 0 °C, DCC (0.52 g, 2.51 mmol) in CH_2Cl_2 (8 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **27** as a colorless oil (54 %). $[\alpha]_D^{25} = -29.7$ ($c = 1.03$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.00 (d, $J = 8.0$ Hz, 2H), 7.69 (t, $J = 7.4$ Hz, 1H), 7.59 – 7.55 (m, 3H), 5.97 – 5.86 (m, 1H), 5.35 (ddd, $J = 1.7$, 3.0, 17.3 Hz, 1H), 5.29 – 5.23 (m, 1H), 5.03 (d, $J = 8.5$ Hz, 1H), 4.68 – 4.62 (m, 2H), 4.58/4.24 (AB-system, $J = 14.3$ Hz, 2H), 4.49 – 4.45 (m, 1H), 4.37 – 4.32 (m, 1H), 2.26 – 2.20 (m, 1H), 1.79 – 1.74 (m, 2H), 1.58 – 1.52 (m, 1H), 1.43 (s, 9H), 0.99 – 0.93 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 182.6, 170.8, 160.1, 149.9, 136.4, 134.7, 131.7, 129.8, 128.4, 119.2, 79.6, 66.2, 61.0, 58.2, 56.0, 42.2, 31.4, 28.6, 25.1, 23.4, 22.1, 19.2, 18.1; IR (KBr): $\tilde{\nu} =$ 3373, 1746, 1677, 1219, 1172 cm^{-1}; MS (CI): *m*/*z*: 552 $[M+H]^+$; elemental analysis calcd (%) for $C_{27}H_{41}N_3O_7S$ (551.7): C 58.78, H 7.49, N 7.62; found C 58.63, H 7.52, N 7.57.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-leucinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-isoleucinyl)carboxyamide (Boc-Leu-Sulf-CO-Ile-OAll, 28): Following general procedure C H-Ile-OAll · *p*Tos (0.84 g, 2.44 mmol) and DMAP (29.32 mg, 0.24 mmol) were added to a solution of sulfonimidoyl acetate **16** (1.35 g, 2.44 mmol) in CH_2Cl_2 (15 mL), and after cooling to 0 °C, DCC (0.52 g, 2.51 mmol) in CH_2Cl_2 (8 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **28** as a colorless oil (52 %). $[\alpha]_D^{25} = -19.9$ ($c = 1.05$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.00 (d, $J = 8.0$ Hz, 2H), 7.69 (t, $J = 7.1$ Hz, 1H), 7.58 (t, $J = 7.7$ Hz, 3H), 5.97 – 5.85 (m, 1H), 5.28 – 5.24 (m, 1H), 5.21 (d, $J = 8.2$ Hz, 1H), 4.68 – 4.63 (m, 2H), 4.58 – 4.52 (m, 1H), 4.56/4.24 (AB-system, $J = 14.3$ Hz, 2H), 4.38 – 4.32 (m, 1H), 1.97 – 1.92 (m, 1H), 1.84 – 1.66 (m, 2H), 1.56 – 1.46 (m, 2H), 1.43 (s, 9H), 1.28 – 1.24 (m, 1H), 0.97 – 0.92 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 182.6, 170.8, 160.0, 155.9, 136.4, 134.7, 131.7, 129.8, 128.4, 119.2, 79.5, 66.1, 60.9, 57.4, 55.9, 42.1, 37.9, 28.6, 25.4, 25.2, 23.4, 22.1, 15.7, 11.8; IR (KBr): $\tilde{\nu} =$ 3358, 1741, 1691, 1239, 1165 cm^{-1}; MS (CI): *m*/*z*: 566 $[M+H]^+$; elemental analysis calcd (%) for $C_{28}H_{43}N_3O_7S$ (565.7): C 59.45, H 7.66, N 7.43; found C 59.25, H 7.64, N 7.39.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-isoleucinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-isoleucinyl)carboxyamide (Boc-Ile-Sulf-CO-Ile-OAll, 29): According to general procedure C H-Ile-OAll · *p*Tos (0.45 g, 1.32 mmol) and DMAP (15.88 mg, 0.13 mmol) were added to a solution of sulfonimidoyl acetate **17** (0.73 g, 1.32 mmol) dissolved in CH_2Cl_2 (9 mL), and after cooling to 0 °C, DCC (0.28 g, 1.36 mmol) in CH_2Cl_2 (3 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **27** as colorless oil (68 %). $[\alpha]_D^{25} = -4.6$ ($c = 1.04$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 7.99 (d, $J = 7.5$ Hz, 2H), 7.69 (t, $J = 7.2$ Hz, 1H), 7.58 (t, $J = 7.5$ Hz, 2H), 7.50 (d, $J = 8.2$ Hz, 1H), 5.96 – 5.86 (m, 1H), 5.34 (dd, $J = 1.4$, 17.3 Hz, 1H), 5.27 (dd, $J = 0.9$, 10.4 Hz, 1H), 5.14 (d, $J = 8.8$ Hz, 1H), 4.68 – 4.61 (m, 2H), 4.62/4.23 (AB-system, $J = 14.1$ Hz, 2H), 4.52 (dd, $J = 3.5$, 8.3 Hz, 1H), 4.32 – 4.26 (m, 1H), 2.04 – 1.84 (m, 2H), 1.44 (s, 9H), 1.25 – 1.10 (m, 4H), 1.06 – 0.86 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 181.1, 170.4, 159.8, 155.8, 136.2, 134.4, 131.5, 129.5, 128.0, 118.9, 79.1, 65.8, 61.3, 60.6, 57.1, 38.1, 37.6, 28.3, 25.2, 24.7, 15.7, 15.4, 11.7, 11.4; IR (KBr): $\tilde{\nu} =$ 3366, 1745, 1714, 1689, 1236, 1164 cm^{-1}; MS (EI): *m*/*z*: 566 $[M+H]^+$; elemental analysis calcd (%) for $C_{28}H_{43}N_3O_7S$ (565.7): C 59.45, H 7.66, N 7.43; found C 59.35, H 7.52, N 7.32.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-isoleucinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-valinyl)carboxyamide (Boc-Ile-Sulf-CO-Val-OAll, 30): Following general procedure C H-Val-OAll · *p*Tos (0.50 g, 1.52 mmol) and DMAP (18.32 mg, 0.15 mmol) were added to sulfonimidoyl acetate **17** (0.84 g, 1.52 mmol) in CH_2Cl_2 (9 mL), and after cooling to 0 °C, DCC (0.32 g, 1.57 mmol) dissolved in CH_2Cl_2 (5 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **30** as colorless oil (48 %). $[\alpha]_D^{25} = -21.2$ ($c = 1.06$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta =$ 8.02 – 7.97 (m, 2H), 7.69 – 7.64 (m, 1H), 7.59 (t, $J = 7.6$ Hz, 2H), 7.47 (d, $J = 8.4$ Hz, 1H), 5.99 – 5.84 (m, 1H), 5.34 (ddd, $J = 1.3$, 2.6, 17.1 Hz, 1H), 5.26 (ddd, $J =$ 1.3, 2.4, 10.4 Hz, 1H), 5.13 (d, $J = 8.7$ Hz, 1H), 4.67 – 4.63 (m, 2H), 4.62/4.23 (AB-system, $J = 13.4$ Hz, 2H), 4.47 (q, $J = 4.7$ Hz, 1H), 4.29 – 4.23 (m, 1H), 2.30 – 2.15 (m, 1H), 2.05 – 1.89 (m, 1H), 1.44 (s, 9H), 1.29 – 1.13 (m, 2H), 1.03 – 0.95 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 181.4, 170.6, 160.0, 155.9, 136.3, 134.6, 131.6, 129.7, 128.2, 119.2, 79.4, 66.0, 61.5, 60.8, 58.0, 38.3, 34.0, 28.5, 24.8, 19.0, 17.9, 15.9, 11.9; IR (KBr): $\tilde{\nu} =$ 3361, 1742, 1689, 1239, 1159 cm^{-1}; MS (CI): *m*/*z*: 552 $[M+H]^+$; elemental analysis calcd (%) for $C_{27}H_{41}N_3O_7S$ (551.7): C 58.78, H 7.49, N 7.62; found C 58.46, H 7.39, N 7.60.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-isoleucinyl *S*-phenyl sulfonimidoyl-*N*-(*O*-allyl-L-leucinyl)carboxyamide (Boc-Ile-Sulf-CO-Leu-OAll, 31): Following general procedure C H-Leu-OAll · *p*Tos (0.52 g, 1.52 mmol) and DMAP (18.32 mg, 0.15 mmol) were added to sulfonimidoyl acetate **17** (0.84 g, 1.52 mmol) in CH_2Cl_2 (9 mL), and after cooling to 0 °C, DCC (0.32 g, 1.57 mmol) dissolved in CH_2Cl_2 (5 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **31** as colorless oil (55 %). $[\alpha]_D^{25} = -22.5$ ($c = 1.04$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.02 – 7.98 (m, 2H), 7.74 – 7.68 (m, 1H), 7.58 (t, $J = 7.7$ Hz, 2H), 7.51 (d, $J =$ 7.9 Hz, 1H), 5.97 – 5.85 (m, 1H), 5.34 (ddd, $J = 1.4$, 2.8, 17.0 Hz, 1H), 5.26 (ddd, $J = 1.4$, 2.5, 10.4 Hz, 1H), 5.14 (d, $J = 8.8$ Hz, 1H), 4.67 – 4.61 (m, 2H), 4.63/4.19 (AB-system, $J = 14.3$ Hz, 2H), 4.59 – 4.53 (m, 1H), 4.32 – 4.25 (m, 1H), 2.04 – 2.00 (m, 2H), 1.71 – 1.66 (m, 2H), 1.56 – 1.51 (m, 1H), 1.44 (s, 9H), 1.26 – 1.21 (m, 1H), 1.01 (d, $J = 6.9$ Hz, 3H), 0.97 – 0.93 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 181.6, 171.2, 160.0, 156.1, 136.2, 134.8, 131.8, 129.8, 128.4, 119.0, 79.4, 66.2, 61.6, 60.8, 51.7, 41.3, 38.3, 28.6, 25.1, 25.0, 22.9, 22.0, 16.1, 12.0; IR (KBr): $\tilde{\nu} =$ 3356, 1745, 1688, 1239, 1160 cm^{-1}; MS (CI): *m*/*z*: 567 $[M+H]^+$; elemental analysis calcd (%) for $C_{27}H_{41}N_3O_7S$ (565.7): C 59.45, H 7.66, N 7.43; found C 59.41, H 7.76, N 7.38.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-*tert*-leucinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-valinyl)carboxyamide (Boc-Tle-Sulf-CO-Val-OAll, 32): Following general procedure C H-Val-OAll · *p*Tos (0.36 g, 1.08 mmol) and DMAP (13.44 mg, 0.11 mmol) were added to sulfonimidoyl acetate **18** (0.60 g, 1.08 mmol) in CH_2Cl_2 (6 mL), and after cooling to 0 °C, DCC (0.23 g, 1.11 mmol) dissolved in CH_2Cl_2 (4 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 1:1) gave **32** as a colorless oil (66 %). $[\alpha]_D^{25} = -24.6$ ($c = 1.02$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.06 – 7.99 (m, 2H), 7.69 (t, $J = 7.4$ Hz, 1H), 7.58 (t, $J = 7.4$ Hz, 2H), 7.47 (d, $J = 8.3$ Hz, 1H), 5.98 – 5.86 (m, 1H), 5.35 (ddd, $J = 1.4$, 3.0, 15.9 Hz, 2H), 5.27 (ddd, $J = 1.4$, 2.5, 10.4 Hz, 1H), 5.18 (d, $J = 9.4$ Hz, 1H), 4.69 – 4.63 (m, 2H), 4.61/4.24 (AB-system, $J = 14.3$ Hz, 2H), 4.50 – 4.45 (m, 1H), 4.13 (d, $J = 9.4$ Hz, 1H), 2.27 – 2.21 (m, 1H), 1.44 (s, 9H), 1.05 (s, 9H), 0.99 (d, $J =$

6.9 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.0, 170.6, 160.0, 155.8, 136.3, 134.5, 131.6, 129.7, 128.2, 119.1, 79.4, 66.0, 64.8, 60.8, 58.0, 34.8, 31.1, 28.5, 27.0, 18.9, 17.9$; IR (KBr): $\tilde{\nu} = 3361, 1742, 1716, 1689, 1220, 1168\ cm^{-1}$; MS (EI): m/z: 552 $[M+H]^+$; elemental analysis calcd (%) for $C_{27}H_{41}N_3O_7S$ (551.7): C 58.78, H 7.49, N 7.62; found C 58.43, H 7.49, N 7.50.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-*tert*-leucinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-leucinyl)carboxyamide (Boc-Tle-Sulf-CO-Leu-OAll, 33): Following general procedure C H-Leu-OAll·*p*Tos (0.37 g, 1.08 mmol) and DMAP (13.44 mg, 0.11 mmol) were added to sulfonimidoyl acetate **18** (0.60 g, 1.08 mmol) in CH_2Cl_2 (6 mL), and after cooling to 0 °C, DCC (0.23 g, 1.11 mmol) dissolved in CH_2Cl_2 (4 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 2:1) gave **33** as a colorless oil (85 %). $[\alpha]_D^{25} = -28.2$ ($c = 1.05$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 8.02 – 7.98 (m, 2H), 7.69 (t, $J = 7.4$ Hz, 1H), 7.63 – 7.55 (m, 3H), 5.97 – 5.86 (m, 1H), 5.59 – 4.53 (m, 1H), 5.34 (ddd, $J = 1.4, 2.7, 17.0$ Hz, 2H), 5.25 (ddd, $J = 1.2, 2.3, 10.4$ Hz, 1H), 5.15 (d, $J = 9.3$ Hz, 1H), 4.69 – 4.63 (m, 2H), 4.55/4.17 (AB-system, $J = 14.3$ Hz, 2H), 4.19 – 4.14 (m, 1H), 1.93 (br s, 1H), 1.72 – 1.67 (m, 2H), 1.44 (s, 9H), 1.05 (s, 9H), 0.96 (d, $J = 6.0$ Hz, 3H), 0.93 (d, $J = 6.1$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 181.2, 171.8, 159.9, 156.1, 136.3, 134.7, 131.8, 129.8, 128.4, 119.1, 79.6, 66.2, 65.0, 60.9, 51.7, 34.7, 28.6, 27.1, 25.0, 22.9, 22.0$; IR (KBr): $\tilde{\nu} = 3354, 1745, 1688, 1222, 1169\ cm^{-1}$; MS (EI): m/z: 379 $[M - t\text{BuCHNHCOO}t\text{Bu}]^+$; elemental analysis calcd (%) for $C_{28}H_{43}N_3O_7S$ (565.7): C 59.45, H 7.66, N 7.43; found C 59.07, H 7.82, N 7.41.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-prolinyl *S*-phenyl sulfonimidoyl-*N*-(*O*-allyl-L-leucinyl)carboxyamide (Boc-Pro-Sulf-CO-Leu-OAll, 34): Following general procedure C H-Leu-OAll·*p*Tos (0.32 g, 0.93 mmol) and DMAP (10.99 mg, 0.09 mmol) were added to sulfonimidoyl acetate **19** (0.50 g, 0.93 mmol) in CH_2Cl_2 (6 mL), and after cooling to 0 °C, DCC (0.20 g, 0.96 mmol) dissolved in CH_2Cl_2 (2 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 3:1) gave **34** as a colorless oil (73 %, as mixture of two rotamers in a ratio of 2:1). $[\alpha]_D^{25} = -52.5$ ($c = 1.01$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.07$ (d, $J = 7.8$ Hz, 1H), 8.05 (d, $J = 7.4$ Hz, 1H), 7.68 (quin, $J = 7.2, 8.2, 8.8$ Hz, 1H), 7.57 (quin, $J = 7.2, 8.2, 8.8$ Hz, 2H), 7.83/7.40 (d, $J = 7.9$ Hz, 1H), 5.97 – 5.85 (m, 1H), 5.38 – 5.23 (m, 2H), 4.83/4.13, 4.63/4.23 (AB-system, $J = 14.3$ Hz, 2H), 4.66 – 4.63 (m, 2H), 4.56/3.40 (m, 1H), 4.39/4.31 (m, 1H), 3.61 – 3.44 (m, 2H), 2.35 – 1.79 (m, 4H), 1.74 – 1.59 (m, 3H), 1.47/1.44 (s, 9H), 0.95 – 0.91 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.8, 171.9, 160.3/160.0, 154.8/154.6, 136.5, 134.8/134.6, 131.8/131.7, 129.8/129.7, 128.7/128.4, 119.1/118.9, 79.9/79.6, 66.2/66.1, 63.3/62.9, 60.8/60.5, 51.7, 46.9/46.6, 41.5/41.3, 31.5/30.4, 28.7, 25.0, 24.8/23.6, 22.9, 22.0, 22.9$; IR (KBr): $\tilde{\nu} = 3318, 1746, 1692, 1200, 1159\ cm^{-1}$; MS (CI): m/z: 549 $[M]^+$; elemental analysis calcd (%) for $C_{27}H_{39}N_3O_7S$ (549.7): C 58.99, H 7.15, N 7.64; found C 58.63, H 7.38, N 7.49.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl-L-prolinyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-isoleucinyl)carboxyamide (Boc-Pro-Sulf-CO-Ile-OAll, 35): Following general procedure C H-Ile-OAll·*p*Tos (0.39 g, 1.13 mmol) and DMAP (13.44 mg, 0.11 mmol) were added to sulfonimidoyl acetate **19** (0.61 g, 1.13 mmol) in CH_2Cl_2 (7 mL), and after cooling to 0 °C, DCC (0.24 g, 1.17 mmol) dissolved in CH_2Cl_2 (2.5 mL) was added. Purification by flash chromatography (ethyl acetate/hexanes 5:1) gave **35** as a colorless oil (71 %, as a mixture of two rotamers (2:1). $[\alpha]_D^{25} = -49.5$ ($c = 1.03$, acetone); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.09 - 7.99$ (m, 2H), 7.83/7.50 (d, $J =$ 8.2 Hz, 1H), 7.73 – 7.64 (m, 1H), 7.62 – 7.52 (m, 2H), 5.98 – 5.86 (m, 1H), 5.39 – 5.33 (m, 1H), 5.29 – 5.24 (m, 1H), 4.83/4.17, 4.62/4.15 (AB-system, $J = 14.3$ Hz, 14.6, 2H), 4.69 – 4.63 (m, 2H), 4.57 – 4.51 (m, 1H), 4.41 – 4.37, 4.31 – 4.28 (m, 1H), 3.60 – 3.56 (m, 2H), 3.37 – 3.33, 2.13 – 1.79 (m, 6H), 1.46/1.43 (s, 9H), 1.30 – 1.20 (m, 1H), 0.93 (t, $J = 7.4$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 182.8, 170.8/170.7, 160.3/160.2, 154.7/154.4, 136.7, 134.8/134.5, 131.8/131.7, 129.8/129.7, 128.7/128.4, 119.3/119.1, 79.8/79.6, 66.1/66.0, 63.2/62.9, 60.9/60.5, 57.5, 47.1/46.7, 38.0, 31.5/30.4, 28.7, 25.4, 24.6/23.6, 15.7, 11.8$; IR (KBr): $\tilde{\nu} = 3326, 1743, 1694, 1200, 1162\ cm^{-1}$; MS (CI): m/z: 550 $[M+H]^+$; elemental analysis calcd (%) for $C_{27}H_{39}N_3O_7S$ (549.7): C 58.99, H 7.15, N 7.64; found C 58.86, H 7.20, N 7.62.

(S_S)-*N*-*tert*-Butyloxycarbonyl *S*-methyl *S*-phenyl sulfoximine (Boc-Sulf-H, 38):[57] In a flame-dried Schlenk (S_S)-**3** (0.50 g, 3.22 mmol) was dissolved in THF (10 mL). The solution was cooled to 0 °C and potassium *tert*-butanolate (0.45 g, 3.99 mmol) in THF (8 mL) was added. The reaction mixture was stirred for 30 min at 0 °C and under vigorous stirring di-*tert*-butyl dicarbonate (1.40 g, 6.44 mmol) in THF (15 mL) was added. After stirring for 1 h at 0 °C and 16 h at room temperature the reaction mixture was added to a cold saturated ammonium chloride solution (16 mL), the organic phase was separated, and the aqueous phase was extracted three times with CH_2Cl_2 (10 mL). The combined organic phases were dried over $MgSO_4$, the solvent removed under reduced pressure and the remaining oil purified by flash chromatography (ethyl acetate/hexanes 2:1) to give **38** as a colorless oil (89 %). $[\alpha]_D^{25} = +69.9$ ($c = 1.00$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.96 - 7.92$ (m, 2H), 7.65 – 7.32 (m, 3H), 3.21 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.2, 138.8, 133.5, 129.5, 127.4, 80.5, 44.8, 27.9$; IR (KBr): $\tilde{\nu} = 1659, 1288, 1222, 1161\ cm^{-1}$; MS (EI): m/z: 256 $[M+H]^+$; elemental analysis calcd (%) for $C_{12}H_{17}NO_3S$ (255.3): C 56.45, H 6.71, N 5.49; found C 56.57, H 6.67, N 5.47.

(S_S)-Cyclohexyl(isopropyl)ammonium *N*-(*N*-*tert*-butyloxycarbonyl)-*S*-methyl *S*-phenyl sulfonimidoyl acetate (Boc-Sulf-Ac, 39): According to general procedure B cyclohexyl(isopropyl)amine (1.91 mL, 11.31 mmol) was dissolved in THF (16 mL) at 0 °C. Sequentially *n*BuLi (6.08 mL, 11.31 mmol) and, after cooling to – 78 °C, **38** (0.85 g, 3.77 mmol) in THF (10 mL) were added dropwise. For the workup (see procedure B) the following reagents were used: water (41 mL), diethyl ether (15 mL), and CH_2Cl_2 (26 mL). Product **39** was obtained as a colorless solid (85 %). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.00$ (br s, 2H), 8.02 – 7.94 (m, 2H), 7.62 – 7.57 (m, 1H), 7.55 – 7.49 (m, 2H), 4.31 – 4.17 (AB-system, $J = 14.7$ Hz, 2H), 3.32 – 3.25 (m, 1H), 3.00 – 2.91 (m, 1H), 2.10 – 2.02 (m, 2H), 1.86 – 1.77 (m, 2H), 1.69 – 1.62 (m, 1H), 1.50 – 1.10 (m, 5H), 1.33 (s, 9H), 1.29 (dd, $J = 3.0, 6.3$ Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.6, 157.8, 138.8, 133.0, 128.9, 128.2, 80.1, 62.5, 53.7, 46.0, 29.1, 28.9, 28.0, 25.0, 24.8, 19.2, 19.0$.

(S_S)-*N*-(*N*-*tert*-Butyloxycarbonyl *S*-phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-valinyl)carboxyamide (Boc-Sulf-CO-Val-OAll, 36): Following general procedure C H-Val-OAll·*p*Tos (0.43 g, 1.37 mmol) and DMAP (17.10 mg, 0.14 mmol) were added to sulfonimidoyl acetate **39** (0.67 g, 1.37 mmol) in CH_2Cl_2 (11 mL), and after cooling to 0 °C, DCC (0.29 g, 1.41 mmol) in CH_2Cl_2 (5 mL) was added. Purification by column chromatography (ethyl acetate/hexanes 1:1) gave **36** (73 %) as a viscous colorless oil. $[\alpha]_D^{25} = -0.9$ ($c = 1.05$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.05 - 7.97$ (m, 1H), 7.72 – 7.56 (m, 3H), 6.00 – 5.84 (m, 1H), 5.40 – 5.34 (m, 1H), 5.26 (dd, $J = 1.3, 10.4$ Hz, 1H), 4.64 (d, $J = 5.7$ Hz, 2H), 4.51/4.40 (AB-system, $J = 14.4$ Hz, 2H), 4.47 (dd, $J = 3.7, 8.3$ Hz, 1H), 2.31 – 2.24 (m, 1H), 1.41 (s, 9H), 1.00 – 0.97 (dd, $J = 1.4, 6.7$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.6, 160.4, 157.6, 136.4, 134.4, 131.6, 128.4, 119.1, 81.4, 66.0, 60.8, 58.0, 31.2, 28.3, 19.2, 17.8$; IR (KBr): $\tilde{\nu} = 3312, 1736, 1649, 1254, 1149\ cm^{-1}$; MS (CI): m/z: 439 $[M+H]^+$; elemental analysis calcd (%) for $C_{21}H_{30}N_2O_6S$ (438.5): C 57.51, H 6.90, N 6.39; found C 57.47, H 6.98, N 6.57.

(S_S)-(*S*-Phenyl sulfonimidoyl)-*N*-(*O*-allyl-L-valinyl)carboxyamide (H-Sulf-CO-Val-OAll, 37): Compound **36** (0.30 g, 0.68 mmol) was dissolved in CH_2Cl_2 (3 mL), cooled to 0 °C and TFA (1 mL) was added dropwise. After stirring for 30 min at 0 °C the ice bath was removed, the reaction mixture was allowed to warm to room temperature and again TFA (0.5 mL) was added dropwise. The reaction mixture was stirred for 4 h, water and then K_2CO_3 were added until no gas evolution was observed. The phases were separated, the aqueous phase extracted three times with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$. After removing the solvent under reduced pressure, **37** was obtained as a pale yellow oil (83 %). $[\alpha]_D^{25} = +1.0$ ($c = 1.04$, acetone); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.51$ (d, $J = 8.6$ Hz, 1H), 7.99 – 7.91 (m, 2H), 7.65 – 7.57 (m, 1H), 7.53 – 7.45 (m, 2H), 5.92 – 5.78 (m, 1H), 5.39 – 5.33 (m, 1H), 5.29 – 5.26 (m, 1H), 4.62 – 4.55 (m, 2H), 4.44 (dd, $J = 5.0, 8.7$ Hz, 1H), 4.05/3.98 (AB-System, $J = 14.4$ Hz, 2H), 3.02 (br s, 1H), 2.22 – 2.08 (m, 1H), 0.99 (d, $J = 7.0$ Hz, 3H), 0.98 (d, $J = 7.7$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 171.0, 161.3, 141.0, 133.8, 131.7, 129.4, 128.4, 119.1, 66.0, 62.5, 57.9, 31.3, 19.2, 17.9$; IR (KBr): $\tilde{\nu} = 3296, 1739, 1681, 1243, 1152\ cm^{-1}$; MS (CI): m/z: 339 $[M+H]^+$; elemental analysis calcd (%) for $C_{16}H_{22}N_2O_4S$ (338.4): C 56.78, H 6.55, N 8.28; found C 56.52, H 6.72, N 8.43.

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