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Sulfoximines in Pseudopeptides

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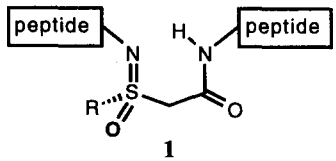
Abstract: Syntheses of sulfoximine-containing pseudopeptides of type **2** are reported. Intramolecular hydrogen bonds have been revealed by NMR spectroscopy.

Various modifications have been introduced to alter the chemical and biological properties of peptides.[2] The significant changes of the conformation, polarity and metabolic stability created by these modifications have been used in drug discovery to influence attributes such as potency, specificity and oral bioavailability. In this article, we report on our approaches for synthesizing novel pseudopeptides **1** having α-sulfonimidoyl carboxy derivatives as key elements in the peptide backbone.[3-5] The absolute configuration at sulfur and the capability of the sulfoximine moiety to form intramolecular hydrogen-bonds[6] are tools which allow to direct the overall orientation of a peptide chain and its conformation. To investigate various synthetic strategies, pseudotripeptides **2** became our first targets.



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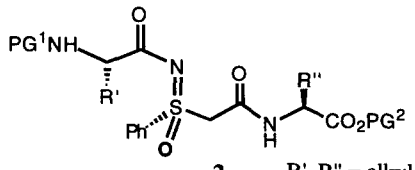
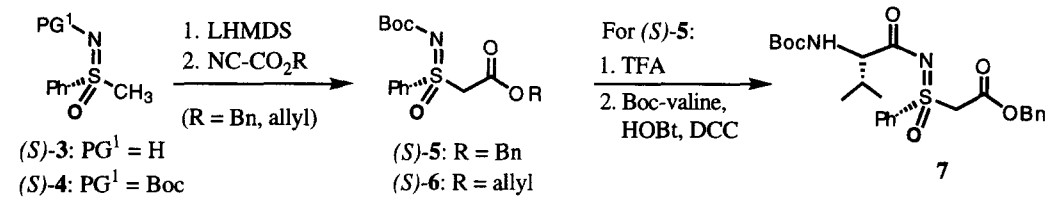


2 R', R" = alkyl

We initially regarded N-Boc-esters *(S)*-**5** and *(S)*-**6** as important intermediates hoping that they would allow the sequential introduction of amino acids at both ends of the imino ester. For their syntheses, *(S)*-N-Boc-S-methyl-S-phenylsulfoximine [*(S)*-**4**] was prepared in 90% yield by treatment of enantiomerically pure *(S)*-**3**[7] with $(Boc)_2O$ in the presence of KO*t*Bu.[8] Lithiation of *(S)*-**4** with lithium hexamethyldisilazane (LHMDS) followed by the addition of cyano benzyl- or cyano allylformate[9] gave *(S)*-**5** and *(S)*-**6** in 98% and 85% yield, respectively.[10] In order to show the general conceivability of the peptide coupling at the sulfoximine nitrogen of the α-sulfonimidoyl esters[11] pseudodipeptide **7** was synthesized. The Boc-group of *(S)*-**5** was cleaved by treatment with trifluoroacetic acid (TFA; 94% yield) and HOBt/DCC-coupling[12] of the resulting NH-sulfoximine with N-Boc-valine afforded **7** (35%). Throughout this sequence no racemization was detected by ^1H NMR spectroscopy.



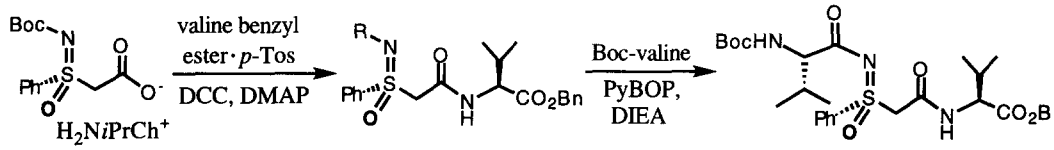
(*S*)-**3**: PG^1 = H
(*S*)-**4**: PG^1 = Boc

(*S*)-**5**: R = Bn
(*S*)-**6**: R = allyl

7

Whereas the Boc-group was a very suitable protective group for the sulfoximine nitrogen, deprotection of (*S*)-**5** and (*S*)-**6** at the carboxy terminus to give the corresponding α-sulfonimidoyl carboxylic acids remained unsuccessful. Benzyl ester (*S*)-**5** could not be cleaved by hydrogenolysis under various conditions and Pd-catalyzed deallylation of (*S*)-**6** led to rapid decarboxylation to give (*S*)-**4**. We therefore had to focus on different strategies avoiding the use of this particular kind of esters.

Metallation of (*S*)-**4** with lithium cyclohexyl isopropyl amide (LCHIPA)[13] followed by reaction of the resulting anion with dried gaseous CO_2 gave ammonium salt (*S*)-**8** in 75% yield.[14] DCC coupling of (*S*)-**8** with the *p*-tosylate of valine benzyl ester afforded **9** in 93% yield. After cleavage of the Boc-group of **9** with TFA, NH-sulfoximine **10** was obtained quantitatively. Subsequent treatment of **10** with Boc-valine in the presence of PyBOP/DIEA[15] gave **11** (32% yield).[16]

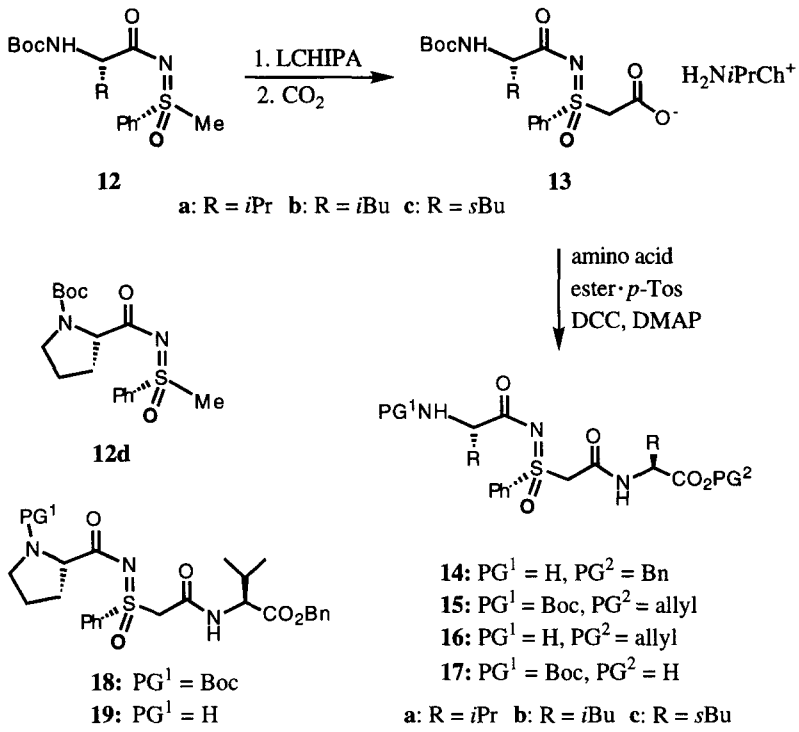


(*S*)-**8** Ch = cyclohexyl

9: R = Boc
10: R = H
TFA

11

Although the first synthetic target was reached by using this reaction sequence, the low yield in the final coupling remained unsatisfying. We therefore decided to change the metallation-coupling order. On the basis of the impressive work by *Seebach* et al. on regio- and stereoselective reactions of lithiated peptides[17] we attempted the carboxylation *after* the coupling of the first amino acid at the sulfoximine nitrogen. Reaction of (*S*)-**3** with Boc-valine in the presence of HOBt/DCC gave **12a** in quantitative yield.[18] Using the same reagents, couplings of (*S*)-**3** with Boc-leucine, Boc-isoleucine and Boc-proline afforded **12b** (97%), **12c** (93%) and **12d** (90%), respectively. Ammonium carboxylates **13a-d** were obtained by carboxylation of **12a-d** with LCHIPA/CO_2 without detectable racemization.[19] Standard DCC-coupling of **13a** and **13d** with the *p*-tosylate of valine benzyl ester gave fully protected pseudotripeptides **11** and **18** in 78% and 60% yield, respectively. Again, attempted hydrogenolysis of these benzyl esters was unsuccessful, and we therefore had to focus on the synthesis of pseudotripeptides with a different carboxy protective group. From the reaction of **13a-c** with the corresponding allyl-protected amino acid esters, compounds **15a** (79%), **15b** (76%) and **15c** (68%) were obtained.[20] Here, the carboxy termini could be liberated by the use of $[Pd(PPh_3)_4]$/$PhSiH_3$[21] to give the deallylated products **17a-c**.[22] The Boc-groups of pseudotripeptides **11** and **15a-c** were cleaved with TFA to afford the corresponding compounds with free amino groups (**14a**: 99%; **16a**: 94%; **16b**: 93%; **16c**: 94%). With this successful selective cleavage of the protective groups at both termini larger sulfoximine-containing pseudopeptides can now be synthesized.



Conformational details in solution were revealed by ^{1}H-NMR spectroscopy. In the protected pseudotripeptides the valine NH-protons resonated significantly downfield (e.g. in **18**: δ = 7.78 ppm). The position of this signal was almost concentration independent. Experiments with **18** showed that the H/D-exchange with D_2O was slow. We therefore believe that *intra*molecular hydrogen bonds were formed. Which structural element or heteroatom is involved in this kind of intramolecular fixation remains to be determined and is currently a matter of investigation.[6, 23]

In conclusion, we have developed synthetic strategies for the preparation of pseudopeptides with sulfoximine backbones. We are now synthesizing analogues of biologically active molecules containing this structural array and we focus on the solution and solid phase preparation of pseudopeptoic oligomers of this kind.

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18. No racemization was observed under these conditions. This coupling can also be done with PyBOP/DIEA (86% yield). Use of DCC/DMAP gave about 17% of racemization (97% yield).
19. Yields: **13a**: 76%, **13b**: 77%, **13c**: 70% und **13d**: 78%. The ammonium salts are thermolabile and tend to decarboxylate.
20. ^{1}H NMR data (300 MHz, $CDCl_3$/TMS) and optical rotations: **15a**: δ = 0.86 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H), 1.36 (s, 9H), 2.12 - 2.25 (m, 2H), 4.18 / 4.56 (AB-System, *J* = 14.6 Hz, 2H), 4.18 (m, 1H), 4.40 (dd, *J* = 8.4, 4.8 Hz, 1H), 4.58 (m, 2H), 5.04 (d, *J* = 8.9 Hz, 1H), 5.18 (dd, *J* = 10.4, 1.0 Hz, 1H), 5.27 (dd, *J* = 17.2, 1.0 Hz, 1H), 5.74 - 5.92 (m, 1H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 2H), 7.62 (t, *J* = 7.1 Hz, 1H), 7.92 (d, *J* = 7.8 Hz, 2H); $[\alpha]_D$ = -14.1° (*c* = 1.03, acetone). **15b**: δ = 0.86 - 1.03 (m, 12H), 1.42 (s, 9H), 1.61 - 1.97 (m, 6H), 4.28 / 4.51 (AB-System, *J* = 14.3 Hz, 2H), 4.31 (m, 1H), 4.56 (m, 3H), 5.12 (d, *J* = 8.4 Hz, 1H), 5.24 (dd, *J* = 11.5, 1.2 Hz, 1H), 5.32 (dd, *J* = 15.8, 1.4 Hz, 1H), 5.83 - 5.94 (m, 1H), 7.55 (t, *J* = 7.4 Hz, 2H), 7.63 - 7.70 (m, 2H), 8.00 (d, *J* = 7.5 Hz, 2H). $[\alpha]_D$ = -20.1° (*c* = 1.06, acetone). **15c**: δ = 0.86 - 1.06 (m, 12H), 1.10 - 1.25 (m, 4H), 1.44 (s, 9H), 1.84 - 2.04 (m, 2H), 4.23 / 4.62 (AB-System, *J* = 14.1 Hz, 2H), 4.28 (m, 1H), 4.52 (dd, *J* = 8.3, 3.5 Hz, 1H), 4.65 (m, 2H), 5.14 (d, *J* = 8.8 Hz, 1H), 5.27 (dd, *J* = 10.4, 0.9 Hz, 1H), 5.34 (dd, *J* = 17.3, 1.4 Hz, 1H), 5.86 - 5.96 (m, 1H), 7.50 (d, *J* = 8.2 Hz, 1H, 7.58 (t, *J* = 7.5 Hz, 2H), 7.69 (t, *J* = 7.2 1H), 7.99 (d, *J* = 7.5 Hz, 2H). $[\alpha]_D$ = -4.6° (*c* = 1.04, acetone).
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