Synthesis and CD Spectra in MeCN, MeOH, and H_2O of γ-Oligopeptides with Hydroxy Groups on the Backbone

Preliminary Communication

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Dedicated to Professor *Siegfried Hünig* with best wishes on the occasion of his 80th birthday

γ^4-Tripeptides and γ^4-hexapeptides, **1**–**4**, with OH groups in the 2- or 3-position on each residue have been prepared. The corresponding 2-hydroxy amino acids were obtained by Si-nitronate (3 + 2) cycloadditions to the acryloyl derivative of *Oppolzer*'s sultam and *Raney*-Ni reduction of the resulting 1,2-oxazolidines (*Scheme 1*). The 3-hydroxy amino acid derivatives were prepared by chain elongation *via Claisen* condensation of Boc-Ala-OH, Boc-Val-OH, and Boc-Leu-OH, and $NaBH_4$ reduction of the methyl 4-amino 3-oxo carboxylates formed (*Scheme 2*). The *N*-Boc hydroxy amino acids were coupled in solution to give the γ-peptides. CD Spectra of the new types of γ-peptides were recorded and compared with those of simple γ^2-, γ^3-, γ^4-, and $\gamma^{2,3,4}$-peptides (*Figs. 3*, *4*, and *5*). An intense *Cotton* effect at *ca.* 200 nm ($[\Theta] = -2 \cdot 10^5$ deg · cm^2 · dmol^{-1}) indicates that the hexapeptide built of (3*R*,4*S*)-4-amino-3-hydroxy acids (with the side chains of Val, Ala, Leu) folds to a secondary structure so far unknown. The stability of peptides from β- and γ-amino acids, which carry heteroatoms on their backbones is discussed (*Fig. 1*). Positions on the γ-peptidic 2.6_{14} helix are identified at which non-H-atoms are 'allowed' (*Fig. 2*).

Introduction. – In an α-peptidic chain of a protein, we do not find heteroatom substituents X bonded to the C(α)-atom (*Fig. 1*,*a*). This heterosubstitution would lead to a hydrolytically labile N–C bond (*Erlenmeyer*'s rule [1]). The least labile of such bonds is expected to exist in a glycine residue (R = H), because the hydrolysis product would be a most reactive oxo aldehyde. Indeed, small peptides with a number of different X groups on a glycine moiety have been prepared by *Steglich* and co-workers [2], and by others [3], who used them to introduce – mostly unnatural – side chains with diastereoselective C,C-bond formation.[2])

In contrast to α-amino acids and α-peptides, the homologs with one or two CH_2 groups inserted in the backbone, *i.e.*, the β- and γ-amino acids, and β- and γ-peptides, can very well carry a heteroatom on one or two of their C-atoms, respectively (*Fig. 1*,*b* and *c*). Thus, there are altogether six isomers of a β- and twenty of a γ-amino acid with a single side chain and a single heterosubstituent! Why are oligopeptides with functional

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[1]) Part of the projected Ph.D. thesis of *M. B.*, ETH Zürich

[2]) See the discussions of cationic, radical, and anionic reactions at the C(α)-atom of glycine and sarcosine residues of peptides and proteins in [4]. Radical hydrogen abstraction from a glycine CH_2 group on a protein β-turn section occurs on the active site of the enzyme pyruvate formate lyase (PFL) [5].

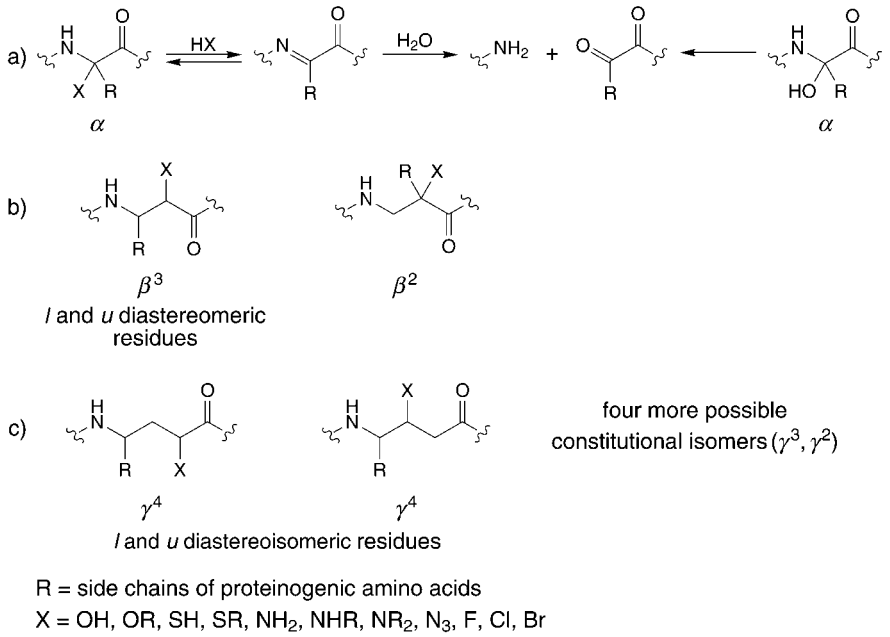

Fig. 1. *Comparison of α-, β-, and γ-amino acid residues with heteroatom X substitution on a peptidic chain. a*) A heteroatom on the backbone of a natural peptide or protein leads to lability of the chain. *b*) A β-peptide built of homologated β^3- or β^2-amino acids can contain a heteroatom X in the α-position without causing lability of the backbone. *c*) Two possible heterosubstituted γ-amino acid building blocks in a peptide consisting of doubly homologated amino acids.

groups directly attached to their backbones of interest? First of all, because this kind of peptide structure is novel and does not occur in nature. While the investigation of β- and γ-peptides with proteinogenic side chains has provided many surprising results and revealed numerous differences between the natural α-peptides and these homologs [6], it has also confirmed a number of common features such as hydrophobic interactions [7], disulfide [8] and salt bridging [9] between side chains, and amphipathic character [10] of helices, as well as similar turn geometries [11]. The effect of a substituent such as OH or NH_2, capable of forming H-bonds, directly on the peptidic backbone is likely to change the secondary structures, as compared to the known helices [7], sheets, and turns [11]. To learn about the influence of OH groups on the folding of β- and γ-peptidic chains, we [12] and others[3]) are synthesizing oligomers of α-hydroxy-β-amino acids (*Fig. 1*, *b*; X = OH) and of α- and β-hydroxy-γ-amino acids (*Fig. 1*, *c*, and *Fig. 2*, **A**

[3]) *Grierson* and co-workers have prepared and determined the NMR structure of a protected oligomer of the (2*R*,3*S*)-3-amino-2-hydroxy-3-phenylpropanoic acid (the taxol side-chain amino acid) [13]. *Brussee* and co-workers have prepared a hexamer containing the (2*R*,3*S*)-3-amino-2-hydroxypropanoic acids with the side chains of Val, Ala, Leu in the 3-position (personal communication to *D.S.* by *M. Overhand* prior to publication in *Org. Lett.* [14] is gratefully acknowledged).

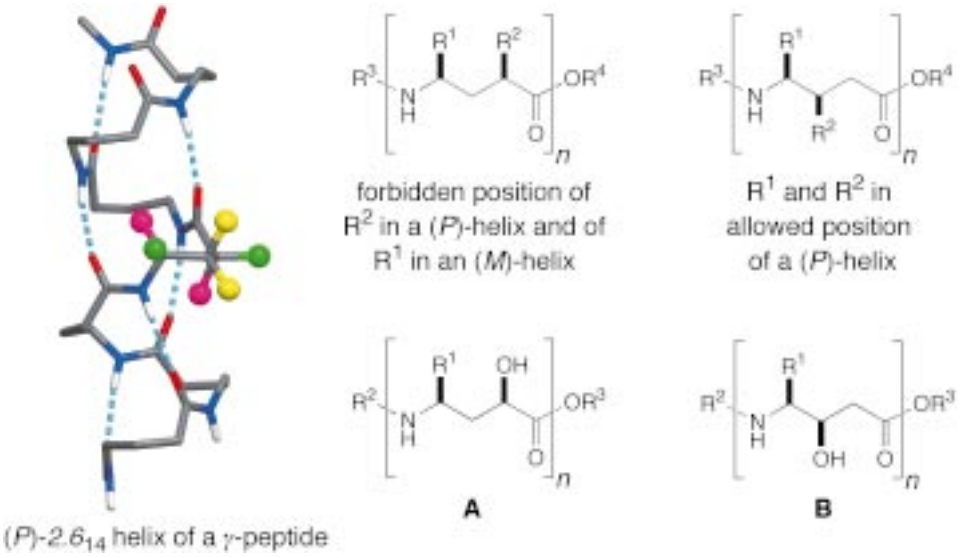

Fig. 2. *Schematic representation of a γ-peptidic (*P*)-2.6$_{14}$ helix as found in solution* [15–17] *and in the solid state* [17] *with known and expected folding of chains containing various γ-amino acid residues.* There are lateral positions at C(2) and C(4) of the γ-amino acid residues (in an approximately perpendicular arrangement with respect to the helix axis, green labeling) and there are *quasi*-axial positions at C(2) and C(4) of γ-amino acid residues (approximately parallel to the helix axis, magenta labeling). Non-H-atoms may be placed in the lateral (green) but not in the *quasi*-axial positions (magenta), due to massive *van der Waals* interactions. At C(3), the geometry is such that both *Re* and the *Si* positions could be occupied by non-H-atoms (yellow labeling). **A** and **B** are the types of hydroxy γ-peptides described herein (*cf. Formulae* **1**–**4**).

and **B**). These four have been chosen by us because we know[4]) or can derive (*Fig. 2*) the structures of the corresponding oligomers with Me groups instead of OH groups, and thus compare the influence of the latter[5]). Unfortunately, to the best of our knowledge, nobody has, so far, succeeded in determining the structure of a β- or γ-peptide with OH groups at each residue (in solution or in the solid state). We are, however, able to present here the CD spectra of the hydroxylated γ-peptides **1**–**4** and compare them with previously measured CD spectra of γ-peptides of known secondary structure.

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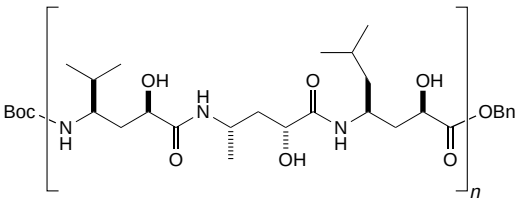
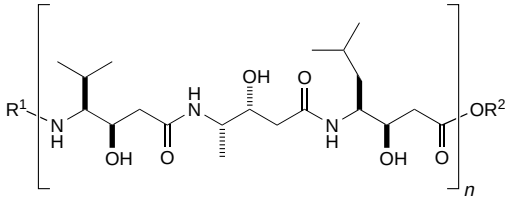
[4]) A $\beta^{2,3}$-peptide with residues –NH–CHR–CHMe–CO– of *like* configuration folds to a 3_{14} helix [7], while pleated-sheet formation is enforced by residues –NH–CHR–CHMe–CO– of *unlike* configuration [11][18]. Thus, the *l*-amino-hydroxy derivative (β^3; X = OH in *Fig. 1,b*) would carry the OH groups in lateral positions of a 3_{14} helix, while the β-peptide with epimeric *u* building blocks would carry OH groups perpendicular to the sheet plane. Solvation of the OH groups could lead to new types of secondary structures, or at least drastically change the properties of the known [7][11][18] structures.

[5]) For conformational analyses of simple *l* and *u* 2,4-disubstituted γ-amino acid derivatives, see publications by *Hoffmann et al.* [19]. The natural product bleomycin A_2 contains a 4-amino-3-hydroxy-2-methylpentanoic acid moiety [20], and *Boger et al.* [21] have studied the influence of the substitution pattern of this γ-amino acid on the DNA-cleaving activity of bleomycin A_2 (*cf.* the work of *Ohno* and co-workers [22]).



1 $n = 1$
2 $n = 2$



3 $n = 1$, R^1 = Boc, R^2 = Bn
4a $n = 2$, R^1 = Boc, R^2 = Bn
4b $n = 2$, $R^1 = R^2 = H$ (as TFA salt)

CD Spectra of Hydroxy γ-Amino Acid Oligomers. – Circular dichroism (CD) spectroscopy is an established tool for the structural characterization of peptides and proteins consisting of α-amino acids [23]. This technique is also useful for examining the secondary structures of unnatural oligomers [24]. In the area of γ-peptides, no specific CD pattern could be related to a secondary structure until now, because only a few γ-peptides have been synthesized and characterized so far. *Fig. 3* shows CD spectra of γ-peptides recorded in our laboratory[1]) prior to the work described herein. NMR Investigation revealed a helical structure for the γ^4- [15] and the $\gamma^{2,3,4}$-peptides [17] ((*P*)- and (*M*)-*2.6*$_{14}$-helix), while the γ^2- and γ^3-peptides appear not to form defined secondary structures [25]. Interestingly, the CD patterns of the two helix-forming peptides look very different. Thus, there is no hope to interpret the CD spectra of the hydroxy γ-peptides presented here, but there will be a qualitative comparison with those of the previously prepared γ-peptides.

The α-hydroxy γ-peptides **1** and **2** show rather moderate CD intensities (*Fig. 4*). The CD curve in MeCN of the γ^4-peptide **2** with an α-OH group in each residue has a maximum molar ellipticity $[\Theta]$ of $3.9 \cdot 10^4$ deg $\cdot$ cm$^2 \cdot$ dmol^{-1} at 215 nm, reminiscent of the CD spectrum of the (*M*)-*2.6*$_{14}$-helix-forming $\gamma^{2,3,4}$-peptide ($[\Theta] = 3 \cdot 10^4$ deg $\cdot$ cm$^2 \cdot$ dmol^{-1} at 212 nm in MeOH; *cf. Fig. 3*), and this in spite of the fact that we would not expect this peptide to form this kind of helix (*vide supra*). Changing the solvent from the aprotic MeCN to the protic MeOH leads to a strong decrease in the intensity, and, in a way, the shoulder at *ca.* 200 nm in the spectrum in MeCN becomes the new maximum. Since MeOH can form H-bonds (as a donor and acceptor!) with the amide *and* OH groups of the peptides **1** and **2**, and thus

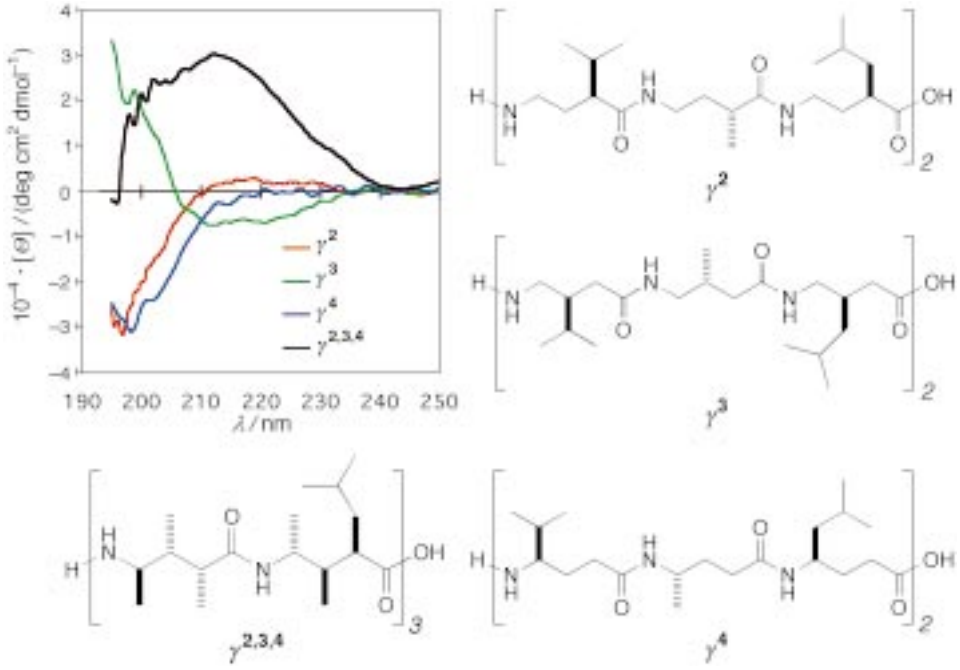


Fig. 3. *CD Spectra of γ-hexapeptides without heteroatoms attached to the backbone.* The γ^2- and γ^3-peptides probably do not fold to a preferred secondary structure [25] while the γ^4-peptides [15] and the $\gamma^{2,3,4}$-peptides [17] form (*P*)- and (*M*)-2.6_{14}-helices, respectively. The measurements were carried out with solutions of the TFA salts of the peptides in MeOH. All spectra – like all other spectra shown herein – have been recorded at a concentration of 0.2 mM and are not normalized to the number of residues.

compete with intramolecular H-bonding, such a change in the CD pattern is not unexpected[6]).

In contrast to the α-hydroxy γ-peptides **1** and **2**, the β-hydroxy γ-peptides show much higher CD intensities. The CD curves of peptides **3** and **4a** in MeCN are characterized by a maximum at 220 nm, a zero-crossing at 212 nm, and an intense trough at 198 nm. The negative *Cotton* effect observed with the γ-hexapeptide **4a** is approximately twice as intense as that of the tripeptide **3**. Thus, in a spectrum normalized to the number of residues, the intensities would be equal. This would not be the case for the positive *Cotton* effect, the intensity of which for the hexamer **4a** at 220 nm is almost three times as high as that for the trimer **3**. In MeOH, the CD spectra are slightly blue-shifted (by *ca.* 3 nm) and somewhat less intense than in MeCN.

The fully deprotected peptide **4b** shows a CD curve in MeOH very similar to that obtained from the *N*-Boc ester **4a** (*Fig. 5*). Since the unprotected peptide **4b** is soluble in H_2O, we recorded its CD spectra in H_2O at different pH values. We found no pH dependence of the CD pattern in the range from pH 3.5 to 9.6. However, the maximum in H_2O is only half as intense as that in MeOH. The intensity of the minimum was not

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[6]) In principle, MeCN is also a H-bond acceptor, and *only* an acceptor, but certainly much weaker than MeOH. For examples of H-bonds between proteins and MeCN see X-ray structures in [26].

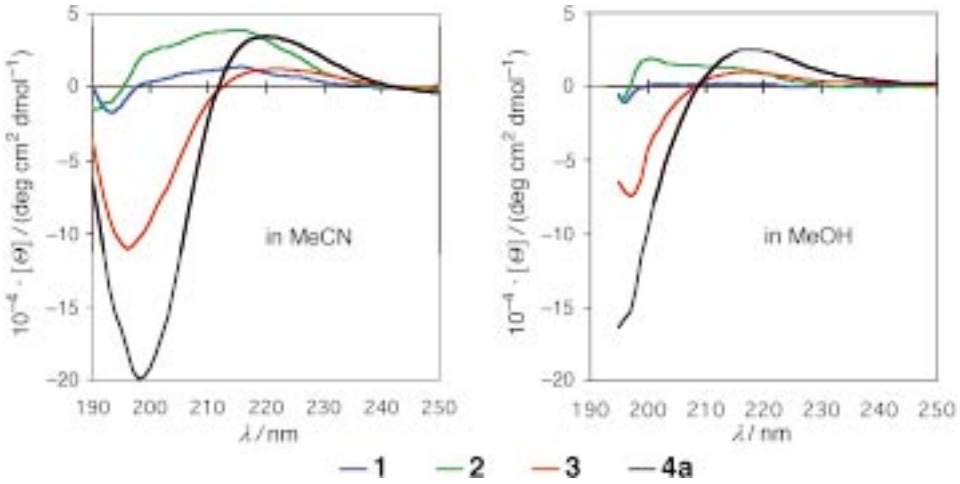


Fig. 4. *CD Spectra of α-hydroxy γ-peptides*, **1** *and* **2**, *and of β-hydroxy γ-peptides*, **3** *and* **4a**, *in an aprotic* (MeCN) *and in a protic solvent* (MeOH)

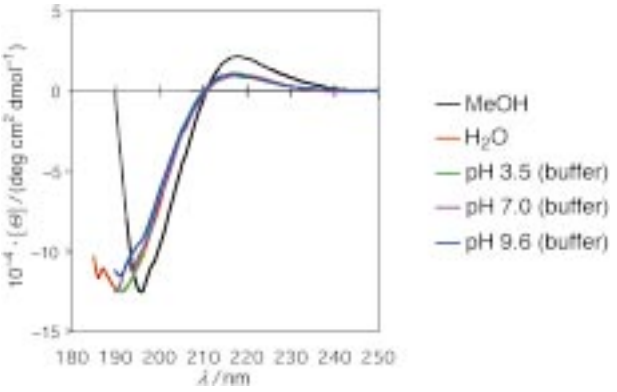


Fig. 5. *CD Spectra of the fully deprotected β-hydroxy γ-peptide* **4b** *in MeOH and in aqueous solutions at different pH values*

affected by change of the solvent, but it was blue-shifted (by *ca.* 5 nm) when going from MeOH to H_2O.

The observed solvent dependence of the CD curves is compatible with the presence of a preferred secondary structure, which is destabilized when the solvent is changed from MeCN to MeOH and finally to H_2O. Unfortunately, we were not able to grow crystals suitable for X-ray single-crystal structure analysis of the hydroxy γ-peptides. We are currently carrying out NMR investigations of the γ-peptides to determine their solution structures.

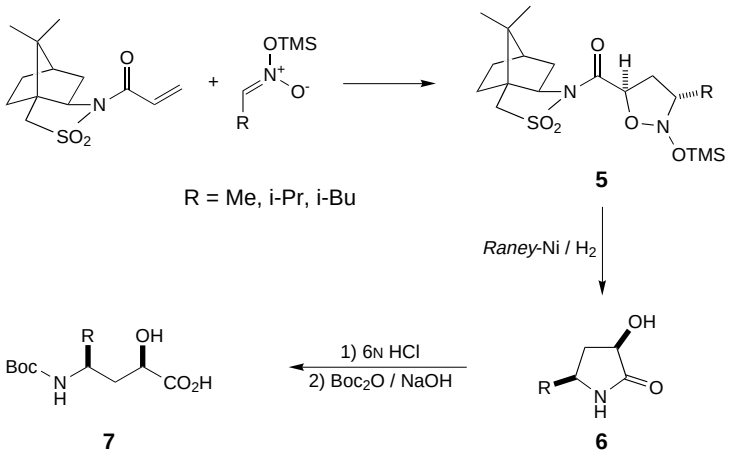
Comments on the Synthesis of Peptides 1–4. – The peptides **1**–**4** were prepared from Boc-protected γ-amino acids with unprotected OH groups. The coupling steps were performed in CH_2Cl_2 solution at $-10°$ with *N*-[3-(dimethylamino)propyl]-*N*′-ethylcarbodiimide (EDC)/1-hydroxybenzotriazole (HOBt) as reagents. The hexapep-

tides **2** and **4a** were obtained from the corresponding tripeptides by fragment coupling. The peptides were purified by preparative RP-HPLC and characterized by IR, ^{1}H- and ^{13}C-NMR, and CD spectroscopy, and by high-resolution mass spectrometry.

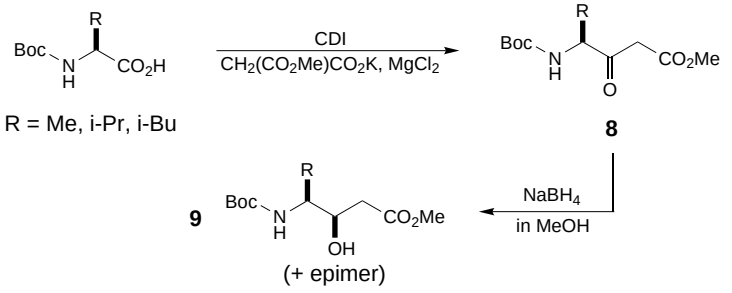
Since the hydroxy γ-amino acid moiety is part of compounds with interesting biological activities, a variety of different routes for their stereoselective synthesis has been described in the literature [27]. For the preparation of the α-hydroxy γ-amino acids, we used as the key step a 1,3-dipolar cycloaddition reaction of acrylcamphorsultam [28] and the appropriate trimethylsilyl nitronates [29][30], introduced by *Kim et al.* [31] (products **5** in *Scheme 1*). Catalytic hydrogenation over *Raney*-Ni [30] of the 1,2-oxazolidines from the cycloaddition yielded the pyrrolidones **6** as crystalline solids. Acidic hydrolysis followed by Boc protection finally furnished the amino acid derivatives **7**.

The β-hydroxy γ-amino acids **9** were prepared from Boc-protected α-amino acids (*Scheme 2*): conversion to the β-oxo esters **8** by a published procedure [33] and

Scheme 1. *Synthesis of α-Hydroxy γ-Amino Acids* **7**. The isoxazolidines **5** were obtained together with small amounts of other stereoisomers. The crude products were employed in catalytic hydrogenations without purification. Pyrrolidinones **6** were obtained with dr $\geq$ 98 : 2 and er $\geq$ 90 : 10 after crystallization.



Scheme 2. *Synthesis of β-Hydroxy γ-Amino Acids* **9**. The major stereoisomers of **9** have the (3*R*,4*S*)-configuration (assigned by comparison with literature values [32] of NMR data and optical activities) and were separated from the mixture and purified by chromatography or crystallization. CDI = 1,1′-Carbonyldiimidazole.



reduction with $NaBH_4$ [34] provided the *N*-Boc esters **9**. In all cases, the (3*R*,4*S*)-diastereoisomer was the major product, which was purified by chromatography or crystallization.

REFERENCES

[1] M. Conrad, *Ber. dtsch. chem. Ges.* **1910**, *43*, 3645; W. Walter, W. Francke 'Bayer Walter, Lehrbuch der organischen Chemie', 23. Auflage, S. Hirzel Verlag, Stuttgart, Leipzig, 1998, p. 120.

[2] R. Kober, K. Papadopoulos, W. Miltz, D. Enders, W. Steglich, H. Reuter, H. Puff, *Tetrahedron* **1985**, *41*, 1693; G. Apitz, W. Steglich, *Tetrahedron Lett*. **1991**, *32*, 3163; G. Apitz, M. Jäger, S. Jaroch, M. Kratzel, L. Schäfferler, W. Steglich, *Tetrahedron* **1993**, *49*, 8223; S. Jaroch, T. Schwarz, W. Steglich, P. Zistler, *Angew. Chem*. **1993**, *105*, 1803; *Angew. Chem., Int. Ed*. **1993**, *32*, 1771; W. Steglich, M. Jäger, S. Jaroch, P. Zistler, *Pure Appl. Chem*. **1994**, *66*, 2167.

[3] Z. Bernstein, D. Ben-Ishai, *Tetrahedron* **1977**, *33*, 881; Z. Lidert, S. Gronowitz, *Synthesis* **1980**, 322; R. M. Williams, D. Zhai, P. J. Sinclair, *J. Org. Chem*. **1986**, *51*, 5021; J. H. Udding, H. Hiemstra, M. N. A. van Zanden, W. Speckamp, *Tetrahedron Lett*. **1991**, *32*, 3123; P. M. Esch, H. Hiemstra, R. F. de Boer, W. N. Speckamp, *Tetrahedron* **1992**, *48*, 4659; J. H. Udding, C. J. M. Tuijp, H. Hiemstra, W. N. Speckamp, *Tetrahedron* **1994**, *50*, 1907.

[4] D. Seebach, A. K. Beck, A. Studer, in 'Modern Synthetic Methods 1995', Eds. B. Ernst, C. Leumann, Verlag Helvetica Chimica Acta, Basel, VCH, Weinheim, 1995, pp. 1 – 178.

[5] M. Frey, M. Rothe, A. F. V. Wagner, J. Knappe, *J. Biol. Chem*. **1994**, *269*, 12432.

[6] D. Seebach, J. L. Matthews, *Chem. Commun*. **1997**, 2015; S. H. Gellman, *Acc. Chem. Res.* **1998**, *31*, 173; K. Gademann, T. Hintermann, J. V. Schreiber, *Curr. Med. Chem*. **1999**, *6*, 905.

[7] D. Seebach, S. Abele, K. Gademann, G. Guichard, T. Hintermann, B. Jaun, J. L. Matthews, J. V. Schreiber, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1998**, *81*, 932.

[8] A. Jacobi, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1150; M. Rueping, B. Jaun, D. Seebach, *Chem. Commun*. **2000**, 2267.

[9] P. I. Arvidsson, M. Rueping, D. Seebach, *Chem. Commun*. **2001**, in print.

[10] M. Werder, H. Hauser, S. Abele, D. Seebach, *Helv. Chim. Acta* **1999**, *82*, 1774; D. Seebach, J. V. Schreiber, P. I. Arvidsson, J. Frackenpohl, *Helv. Chim. Acta* **2001**, *84*, 271.

[11] D. Seebach, S. Abele, K. Gademann, B. Jaun, *Angew. Chem*. **1999**, *111*, 1700; *Angew. Chem., Int. Ed*. **1999**, *38*, 1595; K. Gademann, T. Kimmerlin, D. Hoyer, D. Seebach, *J. Med. Chem*. submitted.

[12] Part of the projected Ph. D. theses of A. Häne and M. Rueping, ETH-Zürich, unpublished results, 2001.

[13] I. A. Motorina, C. Huel, E. Quiniou, J. Mispelter, E. Adjadj, D. S. Grierson, *J. Am. Chem. Soc*. **2001**, *123*, 8.

[14] R. A. Tromp, M. van der Hoeven, A. Amore, J. Brussee, M. Overhand, G. A. van der Marel, A. van der Gen, *Org. Lett*. **2001**, submitted.

[15] T. Hintermann, K. Gademann, B. Jaun, D. Seebach, *Helv. Chim. Acta* **1998**, *81*, 983.

[16] S. Hanessian, X. Luo, R. Schaum, S. Michnick, *J. Am. Chem. Soc*. **1998**, *120*, 8569; S. Hanessian, X. Luo, R. Schaum, *Tetrahedron Lett*. **1999**, *40*, 4925.

[17] D. Seebach, M. Brenner, M. Rueping, B. Schweizer, B. Jaun, *Chem. Commun*. **2001**, 207.

[18] D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913; S. Abele, Dissertation ETH-Zürich, No. 13203, 1999.

[19] R. W. Hoffmann, M. A. Lazaro, F. Caturla, E. Framery, *Tetrahedron Lett*. **1999**, *40*, 5983; R. W. Hoffmann, F. Caturla, M. A. Lazaro, E. Framery, M. C. Bernabeu, I. Valancogne, C. A. G. N. Montalbetti, *New J. Chem*. **2000**, *24*, 187.

[20] H. Umezawa, *Pure Appl. Chem*. **1971**, *28*, 665; T. Takita, Y. Muraoka, T. Yoshioka, A. Fujii, K. Maeda, H. Umezawa, *J. Antibiot.* **1972**, *25*, 755; Y. Muraoka, A. Fujii, T. Yoshioka, T. Takita, H. Umezawa, *J. Antibiot*. **1977**, *30*, 178; T. Takita, Y. Muraoka, T. Nakatani, A. Fujii, Y. Umezawa, H. Naganawa, H. Umezawa, *J. Antibiot*. **1978**, *31*, 801; T. Fukuoka, Y. Muraoka, A. Fujii, H. Naganawa, T. Takita, H. Umezawa, *J. Antibiot.* **1980**, *33*, 114.

[21] D. L. Boger, S. L. Colletti, S. Teramoto, T. M. Ramsey, J. Zhou, *Bioorg. Med. Chem*. **1995**, *3*, 1281; D. L. Boger, T. M. Ramsey, H. Cai, S. T. Hoehn, J. A. Stubbe, *J. Am. Chem. Soc*. **1998**, *120*, 9149; D. L. Boger, H. Cai, *Angew. Chem*. **1999**, *111*, 177; *Angew. Chem., Int. Ed*. **1999**, *38*, 488.

[22] T. Owa, A. Haupt, M. Otsuka, S. Kubayashi, N. Tomioka, A. Itai, M. Ohno, T. Shiraki, M. Uesugi, Y. Sugiura, K. Maeda, *Tetrahedron* **1992**, *48*, 1193.

[23] 'Circular Dichroism: Principles and Applications', Eds. K. Nakanishi, N. Berova, R. W. Woody, VCH, New York, 1994.
[24] K. D. McReynolds, J. Gervey-Hague, *Tetrahedron: Asymmetry* **2000**, *11*, 337.
[25] Part of the projected Ph. D. theses of M. Brenner and M. Rueping, ETH-Zürich, unpublished results, 2000.
[26] P. A. Fitzpatrick, A. C. U. Steinmetz, D. Ringe, A. M. Klibanov, *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 8653; K. N. Allen, C. R. Bellamacina, X. Ding, C. J. Jeffery, C. Mattos, G. A. Petsko, D. Ringe, *J. Phys. Chem.* **1996**, *100*, 2605; Z. Wang, G. Zhu, Q. Huang, M. Qian, M. Shao, Y. Jan, Y. Tang, *Biochim. Biophys. Acta* **1998**, *1384*, 335; J. L. Schmitke, L. J. Stern, A. M. Klibanov, *Biochem. Biophys. Res. Commun.* **1998**, *248*, 273; J. L. Schmitke, L. J. Stern, A. M. Klibanov, *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 12918.
[27] T. Yokomatsu, Y. Yuasa, S. Shibuya, *Heterocycles* **1992**, *33*, 1051; M. B. Smith, 'Methods of Non α-Amino Acid Synthesis', Marcel Dekker Inc., New York, Basel, Hong Kong, 1995, pp. 189–242.
[28] W. Oppholzer, C. Chapuis, G. Bernardinelli, *Helv. Chim. Acta* **1984**, *67*, 1397.
[29] E. W. Colvin, D. Seebach, *J. Chem. Soc., Chem. Commun.* **1978**, 687; E. W. Colvin, A. K. Beck, B. Bastani, D. Seebach, Y. Kai, J. D. Dunitz, *Helv. Chim. Acta* **1980**, *64*, 697.
[30] K. Torssell, O. Zeuthen, *Acta Chem. Scand., B* **1978**, *32*, 118; S. C. Sharma, K. Torssell, *Acta Chem. Scand., B* **1979**, *33*, 379.
[31] B. H. Kim, J. Y. Lee, K. Kim, D. Whang, *Tetrahedron: Asymmetry* **1991**, *2*, 27; B. H. Kim, J. Y. Lee, *Tetrahedron: Asymmetry* **1991**, *2*, 1359.
[32] S. Hashiguchi, A. Kawada, H. Natsugari, *Synthesis* **1992**, 403; M. M. Midland, M. M. Afonso, *J. Am. Chem. Soc.* **1989**, *111*, 4368; B. Rague, J.-A. Fehrentz, R. Guegan, Y. Chapleur, B. Castro, *Bull. Soc. Chim. Fr., Ser. 2* **1983**, 230.
[33] K. Miyazaki, M. Kobayashi, T. Natsume, M. Gondo, T. Mikami, K. Sakakibara, S. Tsukagoshi, *Chem. Pharm. Bull.* **1995**, *43*, 1706.
[34] T. Shioiri, K. Hayashi, Y. Hamada, *Tetrahedron* **1993**, *49*, 1913.

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