Synthesis and Use of Tetrahydrofuran- and Tetrahydropyran-Amino Acids

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Abstract. Progress in the synthesis and the use of amino acids containing a THF or THP ring is reported. Different synthetic routes from carbohydrates or α-amino acids as starting compounds are discussed. Examples for THF- and THP-amino acids as peptidomimetics or building blocks for foldamers and combinatorial libraries are given. The role of THF-amino acids in the synthesis of artificial ion channels, *e.g.* THF-gramicidin hybrids, is highlighted.

Introduction

The structures of the 20 amino acids commonly found in proteins display a variety of functionalities in the side chain. The ether function is not among them. Bearing in mind the cation binding ability of ether groups, one may wonder why ether amino acids have not appeared or not persisted during biomolecular evolution. The relative high chemical inertness of ethers could have been a disadvantage in terms of biodegradability and recycle potential. Examples of naturally occurring non-proteinogenic ether-amino acids are muraminic acid a constituent of bacterial cell walls and neuraminic acid an oligosaccharide subunit.

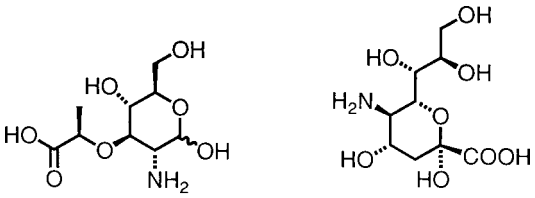

Fig. 1 Naturally occurring ether amino acids

It was the synthesis of crown ethers and cryptands that started supramolecular chemistry. Here, chemical synthesis allowed a predictable three-dimensional arrangement of ether groups for cation binding and transport [1]. There is a great potential in combining the knowledge from ether-cation binding with the rational design of amino acids and peptidomimetics. Because cyclic ethers over the advantage of conformational constrain, amino acids with tetrahydrofuran (THF) and tetrahydropyran (THP) subunits are subject to active investigations.

In this account we highlight important contributions of others and summarize results from our laboratory.

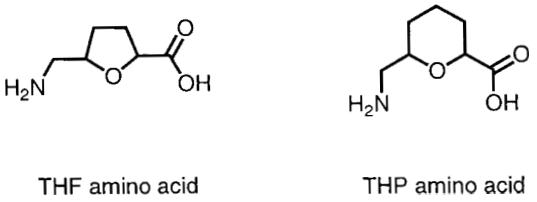

Fig. 2 General structure of THF- and THP-amino acids

Sugar-Amino Acids

Carbohydrates offer a facile synthetic entry into sugar-amino acids. Pioniering work was done by Paulsen [2]. The THP-sugar amino acids **1**–**4** were synthesized and conformationally characterized by Kessler *et al.* (Figure 3) [3–5]. They were incorporated into cyclic peptides to evaluate their potential as peptidomimetic scaffold.

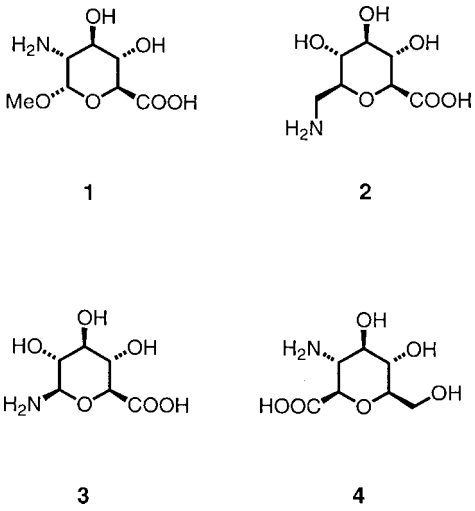

Fig. 3 THP-amino acids synthesized by Kessler *et al.*

It was found, that **1** acts as a linear dipeptide isoster, **2** and **3** are β-turn mimetics and **4** induces a γ-turn. The

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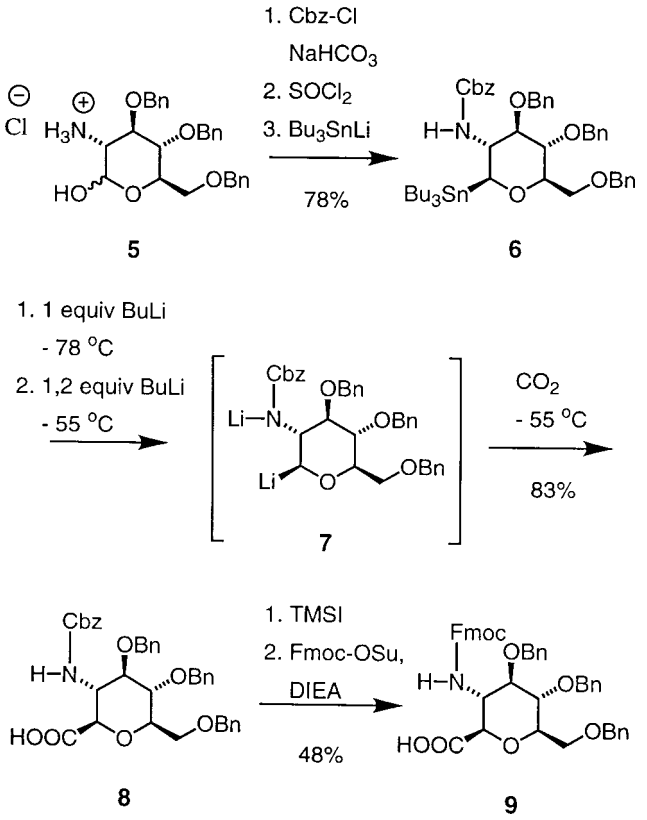
synthesis of **4** is shown in scheme 1 [4]. *D*-Glucoseamine was converted into the benzyl-protected compound **5**. Cbz-Protection of the amino group followed by chlorination provided the α-chloro compound which was allowed to react with tributyltin lithium to provide **6**. A lithiation of the urethane hydrogen and a subsequent tin lithium exchange gave the glycosyl dianion **7** which was trapped with carbon dioxide to form the acid **8**. The latter was transformed into the Fmoc derivative **9**.



Scheme 1 Synthesis of the THP sugar-amino acid **9** by Kessler *et al.*

Sugar-amino acids such as **10**, **11** and **12** were introduced by Lansbury *et al.* as new building blocks for combinatorial synthesis [6]. These compounds are interesting monomers for structurally diverse yet conformationally restrained oligomeric combinatorial libraries with potential pharmaceutical applications. The term glycotide was coined for the sugar-amino acid oligomers.

A representative synthetic example from the work of Lansbury is the synthesis of the THF-amino acid precursor **17** (Scheme 2) [6]. Peracetylated ribose **13** was *C*-glycosylated to the homoallyl ether **14**. Chemoselective addressing of the C(5) position (**14** $\rightarrow$ **15**) and introduction of an azide functionality as a latent amino group gave compound **16**. Oxidative cleavage of the

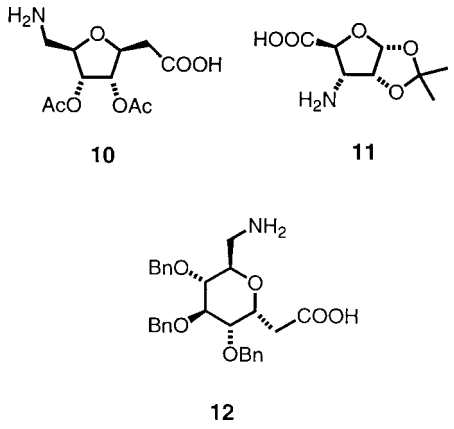
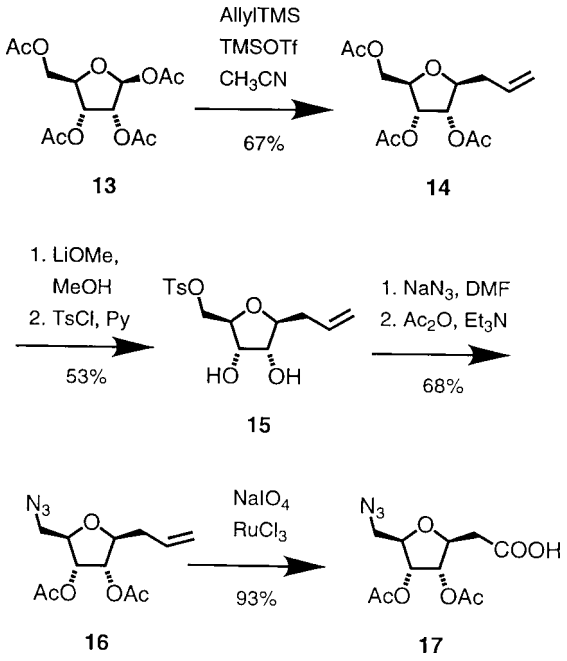


Fig. 4 Sugar-amino acids from the work of Lansbury *et al.*



Scheme 2 Lansbury's synthesis of the THF sugar-amino acid presursor **17**

double bond in **16** afforded the carboxylic acid **17**.

Sugar-amino acids have been developed as building blocks for oligosaccharide mimetics. The group of Ishikawa prepared tetramers such as **18** and **19** [7, 8]. The sulfated derivative of **19** was found to be a potent inhibitor of HIV replication [8].

Wessel *et al.* from Roche synthesized saccharide-peptide hybrids of type **20** as oligosaccharide mimetics (scheme 3) [9]. A key reaction was the etherfication of the *N*-protected sugar aminoalcohol **21** to the THP-amino acid derivative **22**.

The systematic investigation of the conformational properties of oligomers from different stereoisomers of 5-aminomethyl-3,4-dihydroxy-tetrahydrofuran-2-carb-

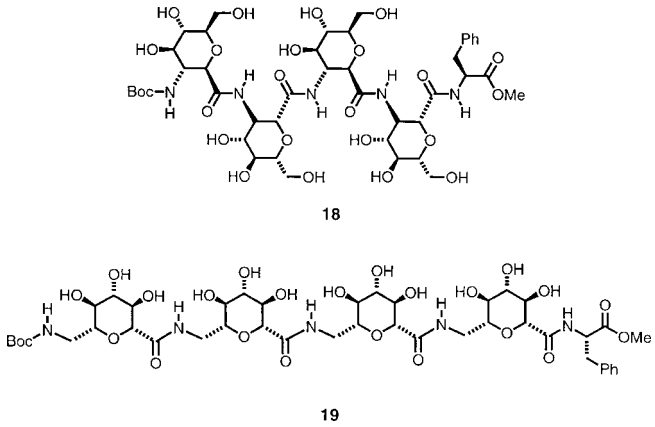
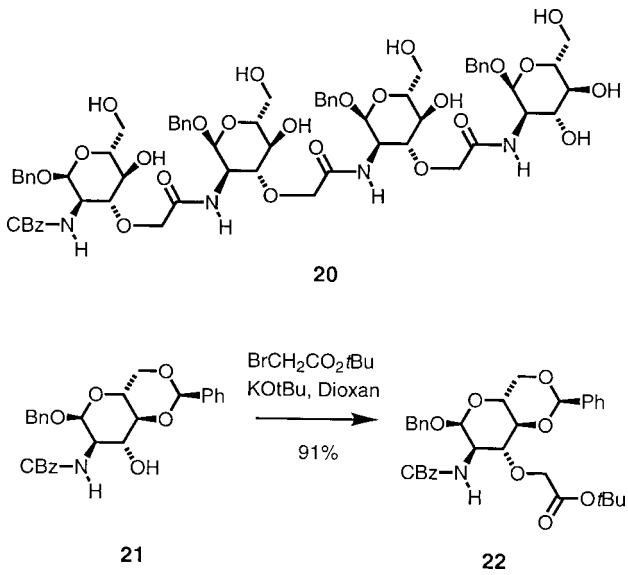


Fig. 5 Ishikawa's oligosaccharide mimetics prepared from Sugar-amino acids



Scheme 3 A key step in the synthesis of the saccharide-peptide hybrid **20**

oxylic acid **23** is the subject of ongoing work by Fleet *et al*. (figure 6) [10–12]. The different monomer units can be prepared enantiomerically pure *e.g.* from *D*-galactolactone or *D*-ribose. The monomers were assembled to tetramers such as **24**–**27** and octamers.

^{1}H NMR studies indicate that the 2,5-*cis* disubstituted tetramers **24** and **25** adopt a conformation reminiscent of a repeating β turn. For the 2,5-*trans* disubstituted tetramer **26** and its corresponding octamer a tendency towards a left handed α-helix was observed. The stereocenters at C-3 and C-4 of the THF ring have a pronounced effect on the conformational behaviour of the oligomers. This was show *e.g.* by the tetramer **27**, which displayed no conformational preference.

Dondoni *et al*. developed a route from lactones of type **28** to THP-α-amino acids **29** (scheme 4) [14, 15].

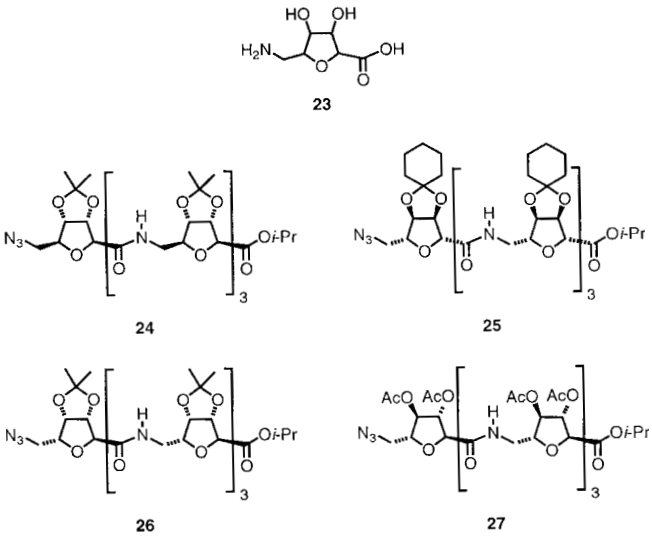
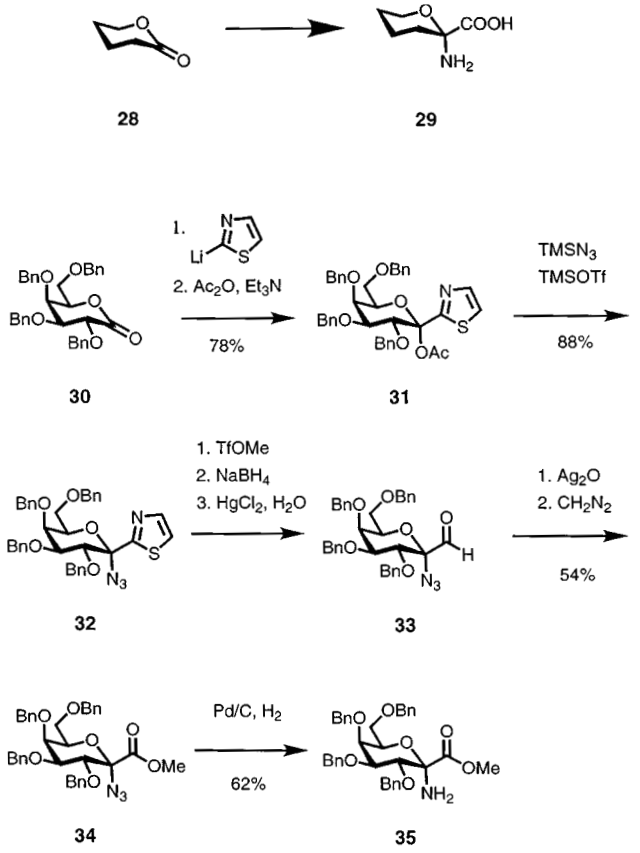


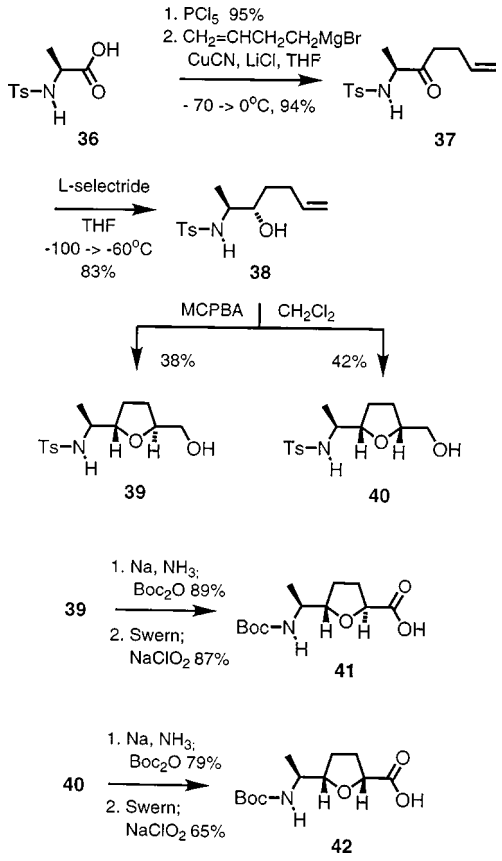
Fig. 6 Fleet's stereoisomeric tetramers from the THF-amino acid **23**

Addition of 2-lithiothiazole to the sugar lactone **30** gave after acetylation compound **31**. After stereocontrolled introduction of an anomeric azide (**31** → **32**) the thiazol was converted into an aldehyde function to provide **33**, which was transformed *via* the azidoester **34** into the sugar α-amino ester **35**.



Scheme 4 Dondoni's synthesis of the THP-amino acid **35**

Our approach to THF amino acids is based on α-amino acids as a chiral pool source (scheme 5) [16]. *N*-Tosylalanine **36** was converted into the corresponding acid chloride which gave in a Cu(I) catalysed Grignard reaction the ketone **37**. A *L*-selectride reduction of **37** provided the alcohol **38** with a stereoselectivity of 85:15. After epoxidation of the double bond and intramolecular 5-*exo* opening of the resulting epoxy function the two THF-alcohols **39** and **40** were obtained in a stereodivergent manner. The *trans* alcohol **39** was converted into the *N*-Boc protected *trans* THF amino acid **41** by a reprotection/oxidation sequence, while the *cis* alcohol **40** gave the *cis* THF amino acid **42**.



Scheme 5 Synthesis of the *N*-protected THF-amino acids **41** and **42**

The *cis* THF-amino acid was converted into the dipeptide **43** (figure 7) [16]. An X-ray structural analysis of **43** showed a β-turn type solid-state conformation with a 10-membered ring hydrogen bond. The same conformation of **43** was found in $CDCl_3$ solution by a combination of NMR studies and MD simulations. In DMSO however, no β-turn type conformation was detected. In order to further explore the potential of the *cis* THF-amino acid, a water soluble heptapeptide **44** was synthesized [17]. Peptides with related amino-acid sequences were used as test systems for hairpin induction [18] and β-sheet formation before [19]. NOE studies in D_2O indicated no hairpin formation of **44**, but the presence of an extended conformation for the peptide chain [17]. These results show that the THF-amino acids are conformational biased but not monoconformational. The substitution pattern and the environment have a pronounced effect on the local conformation.

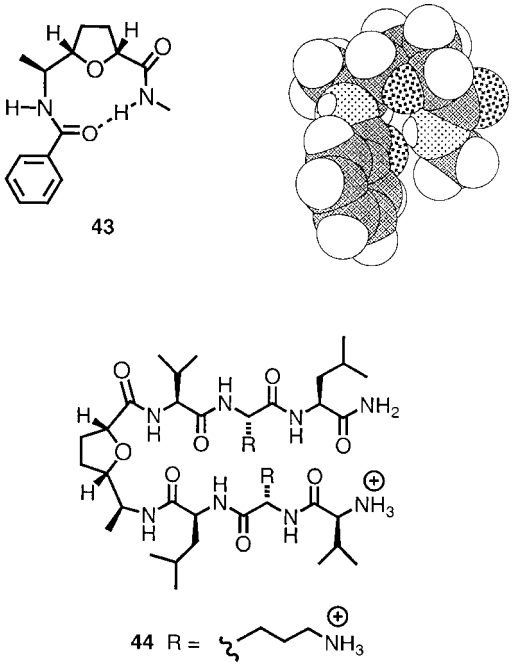


Fig. 7 β-Turn type solid-state structure of the THF dipeptide **43** and structure of the hairpin candidate **44**

THF-amino Acids as Peptidomimetics

THF-amino acids are suitable candidates as peptidomimetics for drug design. In particular their potential as building blocks for integrin antagonists has been evaluated [20]. The integrins are a group of cell-surface receptors, which control cell-cell and cell-matrix adhesion processes [21]. These heterodimeric glycoproteins bind to extracellular matrix adhesive proteins such as fibrinogen and vitronectin. Particular attention has been paid to the $\alpha_v\beta_3$-integrin and the $\alpha_{IIb}\beta_3$-integrin. The $\alpha_v\beta_3$-integrin is involved in many physiological processes such as angiogenesis and tumor growth and $\alpha_v\beta_3$-antagonists are good drug candidates for cancer and osteoporosis [22]. The $\alpha_{IIb}\beta_3$-integrin is important for blood platelet aggregation and $\alpha_{IIb}\beta_3$-antagonists are investigated as antithrombotic agents [23]. The common structural motif for integrin ligands is the RGD triad (figure 8). Studies with cyclic peptides such as **45** and **46** have shown that potent $\alpha_v\beta_3$-antagonists adopt a "glycine centered in a γ-turn" conformation (*e.g.* **45**) while the most active $\alpha_{IIb}\beta_3$-antagonists display a "turn-extended-turn conformation (*e.g.* **46**) [24, 25].

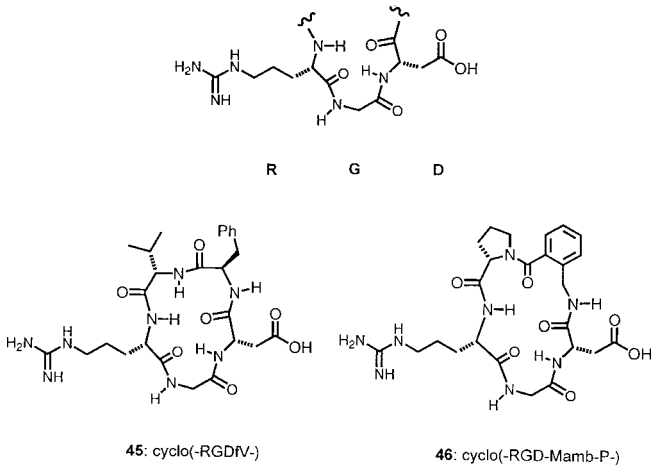


Fig. 8 General structure of the RGD motif and examples of cyclopeptide-based RGD mimetics **45** and **46**

The use of THF-amino acids in RGD mimetics allows the variation of the relative and absolute configuration at the stereogenic centers C-2 and C-5 of the THF ring with the aim of tuning the receptor activity and selectivity. Towards this end the four stereoisomers **47**–**50** were synthesized and evaluated as integrin antagonists (figure 9) [20].

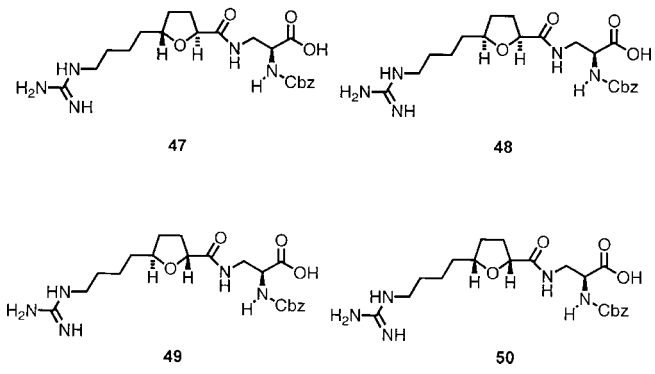
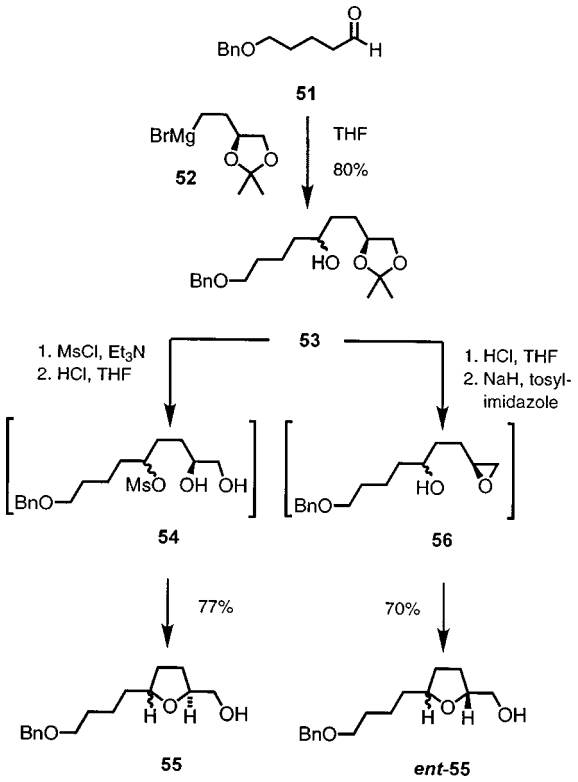


Fig. 9 Four stereoisomers **47**–**50** of THF-RGD mimetics

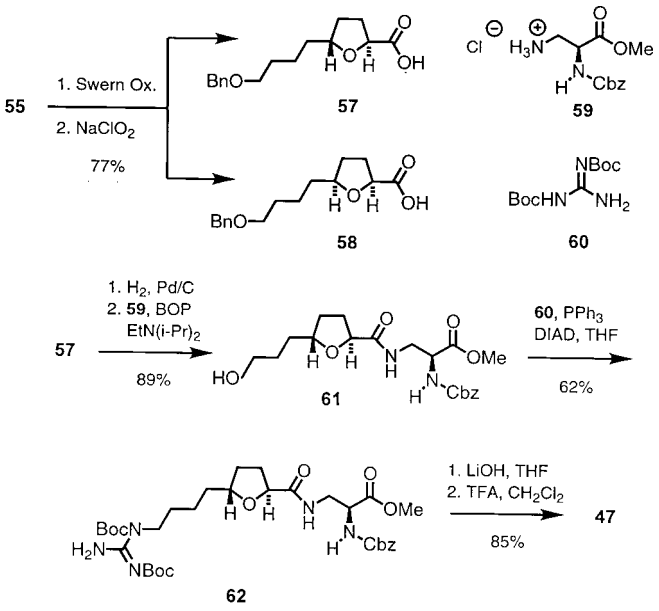
The synthesis of the RGD mimetics **47**–**50** required the elaboration of all four possible stereoisomers at the THF ring. This was accomplished from one stereocenter as a common starting point (scheme 6). The stereocenter was taken from *L*-malic acid and incorporated into the Grignard reagent **52**. Reaction of **52** with the aldehyde **51** gave the secondary alcohol **53** as a 1:1 epimeric mixture. **53** was converted into the enantiomeric THF alcohols **53** and ***ent*-53** by stereochemical complementary ways for closing the THF ring. When the alcohol **53** was transformed into the mesylate a subsequent cleavage of the acetonide gave the dihydroxymesylate **54**, which directly underwent an intramolecular Williamson reaction to yield the THF alcohol **55** (retention at C-2, inversion at C-5). If the acetonide function of **53** was cleaved first and the resulting triol was converted into the epoxy alcohol **56** an intramolecular 5-exo opening of the epoxide by the OH group gave the THF alcohol ***ent*-55** (inversion at C-2, retention at C-5) [20].



Scheme 6 A stereodivergent approach to the THF alcohols **55** and ***ent*-55**

The alcohol **55** was oxidized by a two-step procedure into the corresponding carboxylic acids **57** and **58**, which could be separated by chromatography (scheme 7). After hydrogenolytic cleavage of the benzyl ether in **57** a BOP coupling with the amine building block **59** gave the amide **61**. Next, the guanidino group was introduced in *N*-Boc protected form *via* a Mitsunobu reaction of **61** with the guanidine reagent **60** to form compound **62**. After hydrolysis of the methyl ester, *N*-Boc deprotection and RP-HPLC purification the desired THF-RGD mimetic **47** was obtained. The target compounds **48**–**50** were synthesized along the same route. The THF-RGD mimetics **63**–**69** with different linkers between the THF ring and the guanidine function were prepared to investigate the role of the distance between the THF ring and the guanidine function as well as the role of additional substitutents and stereocenters (figure 10) [20].

The biological activity of the THF-RGD mimetics was tested in a receptor binding assay. The four compounds **47**–**50** showed a stronger binding with the



Scheme 7 Synthesis of the THF-RGD mimetic **47**. BOP = 1-benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, DIAD = diisopropyl azodicarboxylate, TFA = trifluoroacidic acid

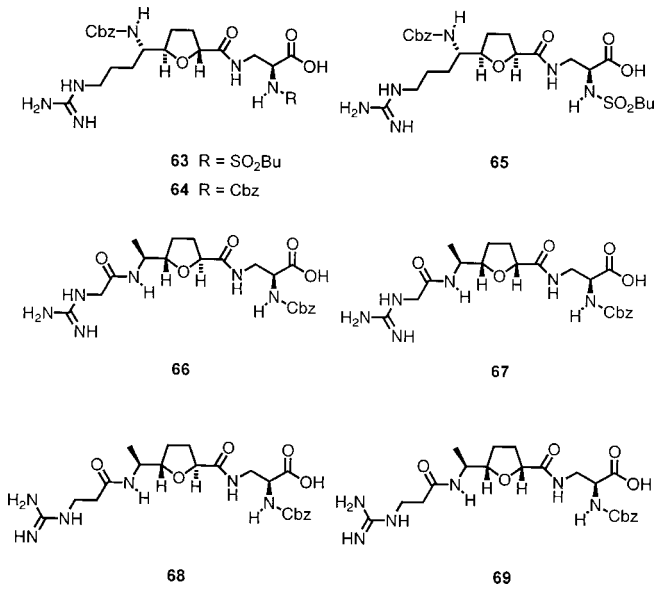


Fig. 10 THF-RGD mimetics with different substitutents and linker length between die guanidin and the THF ring

$\alpha_{IIb}\beta_3$ than with the $\alpha_v\beta_3$-integrin. In particular compound **47** displayed a high activity and selectivity for $\alpha_{IIb}\beta_3$ (IC_{50} = 20 nM, IC_{50} ($\alpha_v\beta_3$) = 3.5μM). The three compounds **63**–**65** were found to be active in the nanomolar range for both the $\alpha_{IIb}\beta_3$ and the $\alpha_v\beta_3$ receptor. The stereocenters had a remarkable effect on the activity: the *trans* compounds are generally more active than the *cis* compounds. This was most pronounced in the series **66**–**69**.

The group of Chakraborty and Kunwar studied the use of sugar derived THF-amino acids as peptidomimetics [26]. They incorporated the THF-amino acid in the Gly-Gly positions of Leu-enkephalin **70** (figure 11). Leu-enkephalin is an endogeneous opoide. Compound **71**, with the *cis*-THF configuration showed biological activities (ED_{50} = 1.48 μM) similar to that of Leu-enkephalin methyl ester (ED_{50} = 1.35 μM). In contrast, compound **72** with the *trans*-THF configuration exhibited no significant activity. A folded conformation of the *cis* isomer **71** was claimed to be responsible for the bioactivity. Kessler et al. synthesized the *cis* THP-enkephalin analog **73** with the opposite absolute configuration at C-2 and C-6 of the THP ring. For this compound no significant bioactivity was reported [4].

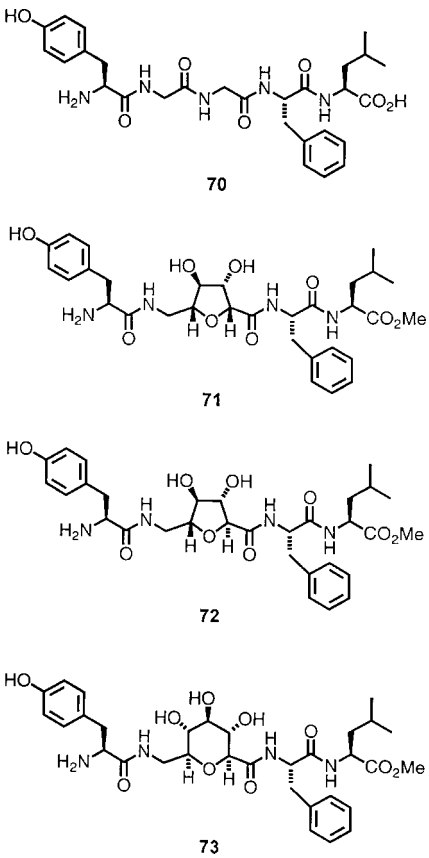
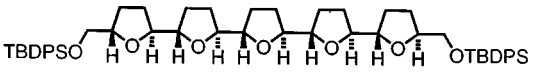


Fig. 11 Structure of Leu-enkephalin **70** and of Leu-enkephalin analogs containing THF- and THP-amino acids in the Gly-Gly position

THF-amino Acids as Building Blocks for Ion Channels

The channel mediated transport of cations through lipid bilayers is a biomolecular function of physiological importance and pharmacological relevance [27]. Synthetic ion channels can contribute to the understanding of biological ion channels [28, 29]. Tetrahydrofuran is

well known for its complexation of cations. Complexation is a prerequisite for transport. Therefore, THFs and THF-amino acids are potential building blocks for cation channels. Oligo-THFs [30,31] such as **74** and oligo-THF peptides **75**–**77** [32] were synthesized to test this hypothesis [33].



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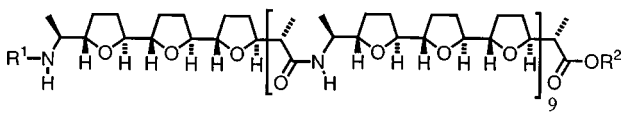
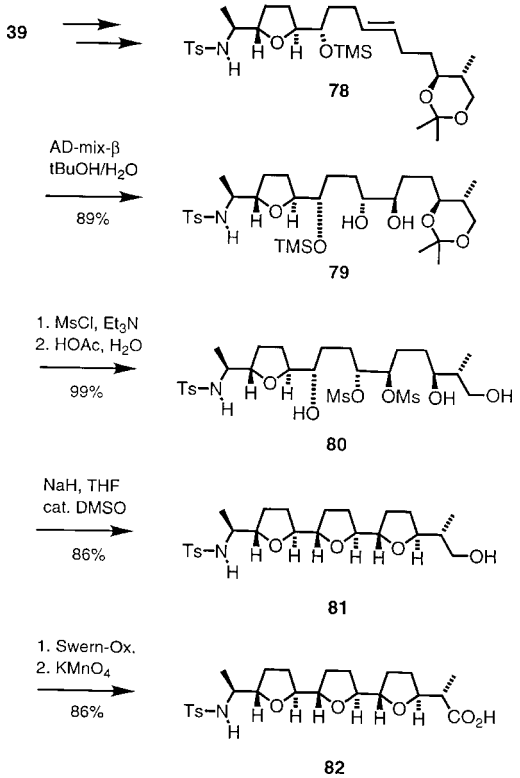


75 R^1 = BOC, R^2 = Bn
76 R^1 = H • CF_3COOH, R^2 = Bn
77 R^1 = H • CF_3COOH, R^2 = H

Fig. 12 Oligo-THFs **74** and Oligo-THF peptides **75**–**77** as potential building blocks for artificial ion channels

An important contribution to the synthesis of oligo-THFs and oligo-THF-amino acids was the development of multiple Williamson reactions [34, 35]. This method was for instance applied in the synthesis of the *N*-protected ter-THF-amino acid **82** (scheme 8) [32].

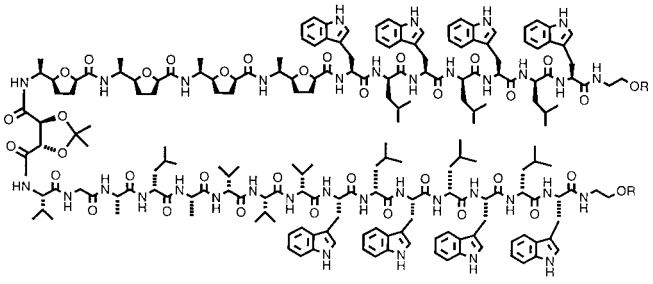


Scheme 8 Application of the multiple Williamson reaction in the synthesis of the *N*-protected ter-THF amino acid **82**

The *trans*-THF alcohol **39** was converted into the olefin **78** first. A Sharpless asymmetric dihydroxylation of **78** gave the diol **79**.After mesylation of the two hydroxy groups in **79** a subsequent cleavage of the acetonide and the TMS ether produced the trihydroxy dimesylate **80**. Now, both THF rings were closed in one step by a multiple Williamson reaction (**80** → **81**). Oxidation of the primary alcohol function gave the desired ter-THF-amino acid derivative **82**.

Inspection of molecular models of the oligo-THF peptides indicated that a decapeptide such as **75** should be large enough to span the 3 nm lipophilic interior of a lipid bilayer in a helical arrangement. The propensity of the oligo-THF peptides to modify membranes and to increase conductance was examined [32]. It was found that compound **76** was inserted into the membrane with an applied potential of +50 mV. This led to rapid changes in conductance on the order of milliseconds, which could not be resolved to the single channel level. When the potential was changed to −50 mV, smaller current peaks were detected. This asymmetric insertion/voltage behaviour was not found for the diprotected decapeptide **75**. However, at the same voltage, current peaks could be detected with **75** at lower peptide concentration. The completely deprotected compound **77** showed no effect on the membrane conductance. The high solubility of **77** in water probably prevented insertion into the membrane.

In extension of the THF-peptide work the synthesis of THF-gramicidin hybrid channels was achieved [36]. Here a biomimetic approach was followed for the channel entrance and exit. Gramicidin A is an ion-channel active pentadecapeptide with the sequence HCO-*L*-Val_1-Gly_2-*L*-Ala_3-*D*-Leu_4-*L*-Ala_5-*D*-Val_6-*L*-Val_7-*D*-Val_8-*L*-Trp_9-*D*-Leu_{10}-*L*-Trp_{11}-*D*-Leu_{12}-*L*-Trp_{13}-*D*-Leu_{14}-*L*-Trp_{15}-$CONHCH_2CH_2OH$ [37]. In lipid bilayers gramicidin A forms a hydrogen bridged head-to-head dimer consisting of two right-handed, single stranded $\beta^{6.3}$ helices [38]. The indole side chains of the four *L*-tryptophane residues orient themselves towards the membrane surface



83 R = *t*-$BuPh_2Si$
84 R = H

Fig. 13 Structure of the channel forming THF-gramicidin hybrids **83** and **84**

thus bringing the channel entrance and exit in contact with the hydrophilic exterior of the membrane [39]. This orienting effect of the channel was adopted for the synthetic THF-gramicidin hybrids **83** and **84** (figure 13).

Compound **84** consists of a heptapeptide part (*L*-Trp-*D*-Leu)$_3$-*L*-Trp, a tetra-THF-peptide part, a tartaric acid derived linker [40] and the gramicidin A pentadecapeptide. The tartaric acid linker was chosen to construct an unimolecular ion channel, which is advantageous for the structural characterization and the functional control. The THF-hybrid channel **84** was incorporated into membranes and acts as a functional ion channel. More than one conductance level where observed within the single channel measurements (figure 14). This suggests the existence of more than one channel active conformation in the membrane.

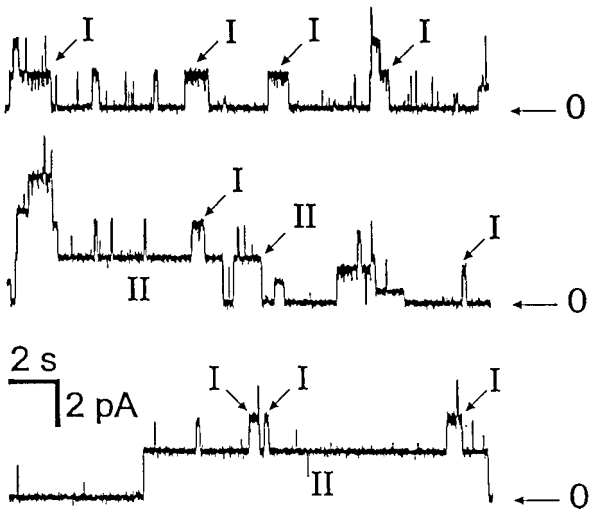


Fig. 14 Typical single channel currents for **84** (0.01 µM) through soy-bean-lecithine membranes in 1M KCl at a membrane potential of + 100 mV. The numbers indicate the closed channel (0), the conductance level with the highest frequency (I) and that with the highest open probability (II)

An Insight/Discover generated structural model of **84** shows a low energy conformation where the four THF-amino acids continue the gramicidin β-helix. However, as mentioned before the THF-amino acids are conformationally biased but not uniconformational. This is *e.g.* shown by the appearance of more than one single channel level. Compound **84** conducts monovalent alkali cations. No transport of divalent cations such as Mg^{2+} or Ca^{2+} was detected. For the alkali cations an Eisenman-I selectivity [41] ($NH_4^+ > Cs^+ > K^+ > Na^+$) was observed. Such an ion-transport selectivity results from a strong influence of the energy necessary for partial dehydration of the ion and a weak binding energy at the channel binding sites. The THF-hybrid channel **85** also exhibited single channel current events. The channel opening times for **85** were shorter than for **84**, an interesting effect of the removal of the lipophilic TBDPS groups.

Summary

THF and THP amino acids with different substitution patterns are accessible most conveniently from carbohydrates or α-amino acids. They are useful peptidomimetics and possess interesting conformational properties as building blocks for combinatorial synthesis or artificial secondary structures (foldamers [42]). In a unique way, they combine the cation binding abilities of ethers with the synthetic potential of amino acids. Their use as substructures in artificial ion channels is one example for possible applications.

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References

[1] J.-M. Lehn, Supramolecular Chemistry, Concepts and Perspectives, VCH, Weinheim, New York 1995
[2] K. Heyns, H. Paulsen, Chem. Ber. **1955**, *88*, 188
[3] E. Graf v. Roedern, H. Kessler Angew. Chem. **1994**,*106*, 684; Angew. Chem. Int. Ed. Engl. **1994**, *33*, 687
[4] E. Graf v. Roedern, E. Lohof, G. Hessler, M. Hoffmann, H. Kessler, J. Am. Chem. Soc. **1996**, *118*, 10156
[5] H. Kessler, B. Diefenbach, D. Finsinger, A. Geyer, M. Gurrath, S. L. Goodman, G. Hölzemann, R. Haubner, A. Jonczyk, G. Müller, E. Graf v.Roedern, Lett. Pept. Sci. **1995**, *2*, 155
[6] J. P. McDevitt, P. T. Lansbury, J. Am. Chem. Soc. **1996**, *118*, 3818
[7] Y. Suhara, J. E. K. Hildreth, Y. Ishikawa, Tetrahedron Lett. **1996**, *37*, 1575
[8] Y. Suhara, M. Ishikawa, J. E. K. Hildreth, Y. Ishikawa, Tetrahedron Lett. **1996**, *37*, 2549
[9] H. P. Wessel, C. Mitchell, C. M. Lobato, G. Schmid, Angew. Chem. **1995**, *107*, 2920; Angew. Chem. Int. Ed. Engl. **1995**, *35*, 2920
[10] M. D. Smith, T. D. W. Claridge, G. E. Tranter, M. S. P. Sansom, G. W. J. Fleet, J. Chem. Soc., Chem. Commun. **1998**, 2041
[11] D. D. Long, N. L. Hungerford, M. D. Smith, D. E. A. Brittain, D. G. Marquess, T. D. W. Claridge, G. W. J. Fleet, Tetrahedron Lett. **1999**, *40*, 2195
[12] T. D. W. Claridge, D. D. Long, N. L. Hungerford, R. T. Aplin, M. D. Smith, D. G. Marquess, G. W. J. Fleet, Tetrahedron Lett. **1999**, *40*, 2199
[13] M. D. Smith, T. D. W. Claridge, G. E. Tranter, M. S. P. Sansom, G. W. J. Fleet, J. Chem. Soc., Chem. Commun. **1998**, 2041
[14] A. Dondoni, M.-C. Scherrmann, A. Marra, J.-L. Delepine, J. Org. Chem. **1994**, *59*, 7517

[15] A. Dondoni, M.-C. Scherrmann, J. Org. Chem. **1994**, *59*, 6404
[16] A. Schrey, F. Osterkamp, A. Straudi, C. Rickert, H. Wagner, U. Koert, B. Herrschaft, K. Harms, Eur. J. Org. Chem. **1999**, 2977
[17] F. Osterkamp, Ph. D. Thesis, Humboldt University Berlin 1999
[18] C. L. Nesloney, J. W. Kelly, J. Am. Chem. Soc. **1996**, *118*, 5836
[19] H. E. Stanger, S. H. Gellman, J. Am. Chem. Soc. **1998**, *129*, 4236
[20] F. Osterkamp, B. Ziemer, U. Koert, M. Wiesner, S. L. Goodman, Chem. Eur. J. **2000**, *6*, 666
[21] E. A. Clark, J. S. Brugge, Science **1995**, *268*, 233
[22] a) R. Haubner, D. Finsinger, H. Kessler, Angew. Chem. **1997**, *109*, 1440; Angew. Chem. Int. Ed. Engl. **1997**, *36*, 1374; J. M. Samanen, Z. Jonak, D. Rieman, T. L. Yue, Curr. Pharm. Design **1997**, *3*, 545
[23] I. Ojima, S. Chakravarty, Q. Dong, Bioorg. Med. Chem. **1995**, *3*, 337
[24] R. Haubner, R. Gratias, B. Diefenbach, S. L. Goodman, A. Jonczyk, H. Kessler, J. Am. Chem. Soc. **1996**, *118*, 7461
[25] A. C. Bach II, J. R. Espina, S. A. Jackson, P. F. W. Stouten, J. L. Duke, S. A. Mousa, W. F. DeGrado, J. Am. Chem. Soc. **1996**, *118*, 293
[26] T. K. Chakraborty, S. Jayaprakash, P. V. Diwan, R. Nagaraj, S. R. B. Jampani, A. C. Kunwar, J. Am. Chem. Soc. **1998**, *120*, 12962
[27] a) A. Kreusch, P. J. Pfaffinger, C. F. Stevens, S. Choe, Nature **1998** *392*, 945; b) D. Doyle, J. M. Cabral, R. A. Pfuetzner, A. Kuo, J. M. Gulbis, S. L. Cohen, B. T. Chait, R. MacKinnon, Science **1998**, *280*, 69; c) B. Hille "Ionic Channels of Excitable Membranes" Sinauer, Sunderland, **1992**
[28] Reviews: a) Y. Kobuke in Advances in Supramolecular Chemistry, Vol. 4 (Eds.: G. W. Gokel), JAI Press Inc., Greenwich, London 1997, p. 163; b) N. Voyer, Top. Curr. Chem. **1996**, *184*, 1; c) G. W. Gokel, O. Murillo, Acc. Chem. Res. **1996**, *29*, 425, d) U. Koert, Chemie in unserer Zeit **1997**, *31*, 20
[29] Recent contributions: a) T. D. Clark, L. K. Buchler, M. R. Ghadiri, J. Am. Chem. Soc. **1998**, 120, 651; b) T. M. Fyles, D. Loock, X. Zhou, J. Am. Chem. Soc. **1998**, 120, 2997; c) O. Murillo, I. Suzuki, E. Abel, C. L. Murray, E. S. Meadows, T. Jin, G. W. Gokel, J. Am. Chem. Soc. **1997**, 119, 5540; d) C. L. Murray, E. S. Meadows, O. Murillo, G. W. Gokel J. Am. Chem. Soc. **1997**, 119, 7887; e) L. A. Weiss, N. Sakai, B. Ghebremariam, C. Ni, S. Matile, J. Am. Chem. Soc. **1997**, *119*, 12142; f) J.-C. Meillon, N. Voyer, Angew. Chem. **1997**, *109*, 1004; Angew. Chem. Int. Ed. Engl. **1997**, *36*, 967; g) T. M. Fyles, D. Loock, W. F. van Straaten-Nijenhuis, X. Zhou, J. Org. Chem. **1996**, *61*, 8866; h) D. Seebach, A. Brunner, H.-M. Bürger, R. N. Reusch, L. L. Bramble, Helv. Chim. Acta **1996**, *79*, 507; f) S. Matile, K. Nakanishi, Angew. Chem. **1996**, *108*, 812; Angew. Chem. Int. Ed. Engl. **1996**, *35*, 757
[30] U. Koert, M. Stein, K. Harms, Angew. Chem. **1994**, *106*, 1238; Angew. Chem. Int. Ed. Engl. **1994**, *33*, 1180
[31] U. Koert, M. Stein, H. Wagner, Liebigs. Ann. **1995**, 1415
[32] H. Wagner, K. Harms, U. Koert, S. Meder, G. Boheim, Angew. Chem. **1996**, *108*, 2836; Angew. Chem. Int. Ed. Engl. **1996**, *35*, 2643
[33] U. Koert, Synthesis **1995**, 115
[34] H. Wagner, U. Koert, Angew. Chem. **1994**, *106*, 1939; Angew. Chem. Int. Ed. Engl. **1994**, *33*, 1873
[35] U. Koert, H. Wagner, M. Stein, Chem. Eur. J. **1997**, *3*, 1170
[36] A. Schrey, A. Vescovi, A. Knoll, C. Rickert, U. Koert, Angew. Chem. Int. Ed. **2000**, *39*, 900
[37] R. E. Koeppe, O. S. Andersen, Ann. Rev. Biophys. Biomol. Struct. **1996**, *25*, 231
[38] N. A. Manan, J. F. Hinton, Biochemistry **1994**, *33*, 6773; V. F. Bystrov, A. S. Arseniev, I. L. Barsukov, A. L. Lomize, Bull. Magn. Res. **1987**, *8*, 84; B. Roux, R. Brüschweiler, R. B. Ernst, Eur. J. Biochem. **1990**, *194*, 57
[39] O. S. Andersen, D. V. Greathouse, L. L. Providence, M. Becker, R. E. Koeppe, *J*. Am. Chem. Soc. **1998**, 120, 5142
[40] a) C. J. Stankovic, S. H. Heinemann, J. M. Delfino, F. J. Sigworth, S. L. Schreiber, Science **1989**, *244*, 813; b) C. J. Stankovic, S. H. Heinemann, S. L. Schreiber, J. Am. Chem. Soc. **1990**, 112, 3702
[41] G. Eisenman, Biophys. J.(Suppl. 2) **1962**, *2*, 259
[42] S. H. Gellman, Acc. Chem. Res. **1998**, *31*, 173

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