Amino Acids (1999) 16: 287–295

Amino
Acids

A new protection/activation strategy for the synthesis of naturally occurring and non-natural α-N-alkylamino acids

Review Article

K. Burger, H. Schedel, and **J. Spengler**

Institut für Organische Chemie der Universität Leipzig,
Leipzig, Federal Republic of Germany

Accepted November 6, 1998

Summary. A new method for the preparation of N-methylamino acids and some of their derivatives starting from hexafluoroacetone protected amino acids is described. The new concept results in saving of steps compared to conventional protection/activation techniques. Protection and deprotection proceed without racemization.

Keywords: Amino acids – Hexafluoroacetone – α-N-Methylamino acids – α-N-Phosphinoylmethylamino acids – Pro-Glu-chimeras – Pro-Tau-chimeras

Introduction

The development of new strategies for the synthesis of non-proteinogenic and non-natural amino acids is of current interest (O'Donnell, 1988; Williams, 1989; Duthaler, 1994). Some represent versatile building blocks for the construction of peptide mimetics, glycopeptide mimetics, depsipeptide mimetics, synthetic enzyms, new drugs and agrochemicals (Toniolo, 1990; Giannis and Kolter, 1993; Liskamp, 1994; Gante, 1994). Furthermore, they are valuable starting materials for combinatorial chemistry.

Recently, we have developed a new protection/activation concept for the derivatization of multifunctional amino acids (Burger et al., 1995; Windeisen et al., 1995; Pires et al., 1996). Hexafluoroacetone reacts with α-amino acids to give 2,2-bis(trifluoromethyl) substituted oxazolidin-5-ones in high yield. This heterocyclization process results in a simultaneous protection of the α-amino and α-carboxylic group. Functional groups present in the side chain, like -COOH and -OH remain unaffected. Consequently, this method can be applied for regioselective functional group manipulation of multifunctional α-amino acids (Burger and Rudolph, 1990; Pires et al., 1996).

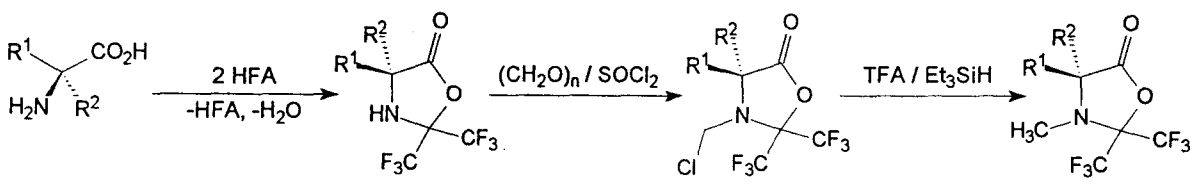
Deprotection of the α-carboxy and the α-amino group can be achieved simultaneously under mild conditions (water/2-propanol, room temperature). Likewise, aminolytic ring opening reactions are coupled with the deprotection of the amino group. Therefore, the new concept results in saving of steps compared to conventional protection/activation techniques. Furthermore, protection and deprotection proceed without racemization.

Finally, the presence of the fluoroalkyl substituents enables monitoring the progress of the protection, the functional group transformation and the deprotection process by ^{19}F NMR spectroscopy. We now disclose, that this new protection/activation strategy is also applicable for the synthesis of various N-substituted α-amino acids.

Synthesis of α-N-methylamino acids

α-N-Methylamino acids are constituents of various peptides and depsipeptides isolated from plant strains, microorganisms and marine species. Some of them exhibit highly interesting therapeutic profiles (Chruma et al., 1997). Incorporation of α-N-methylamino acids into strategical positions of peptides and depsipeptides leads to an enhanced proteolytic stability, to an increase in lipophilicity and to a stabilization of secondary structure domains. Furthermore, certain α-N-methylamino acids itself are biologically active compounds (Paruszewski et al., 1996; Okamoto and Quastel, 1997). Consequently, a number of synthetic routes to optically pure α-N-methylamino acids have been developed (Effenberger et al., 1983; Oppolzer et al., 1993; Dorow and Gingrich, 1995; Ebata et al., 1996; Bowman and Coghlan, 1997; Chruma et al., 1997; Muller et al., 1997; Bhatt et al., 1997).

In a three component reaction hexafluoroacetone protected α-amino acids, paraformaldehyde and thionyl chloride react to give α-N-chloromethylamino acid derivatives. The compounds obtained are readily transformed on treatment with triethylsilane/trifluoroacetic acid into α-N-methylamino acid derivatives. Both steps can be performed as one-pot procedure without solvent in nearly quantitative yield (Spengler and Burger, 1998a). When phosphorus tribromide is used instead of thionyl chloride, the corresponding N-bromomethyl compounds are available (Spengler and Burger, 1998b). The latter can be transformed into the iodo compounds applying the Finkelstein protocol.



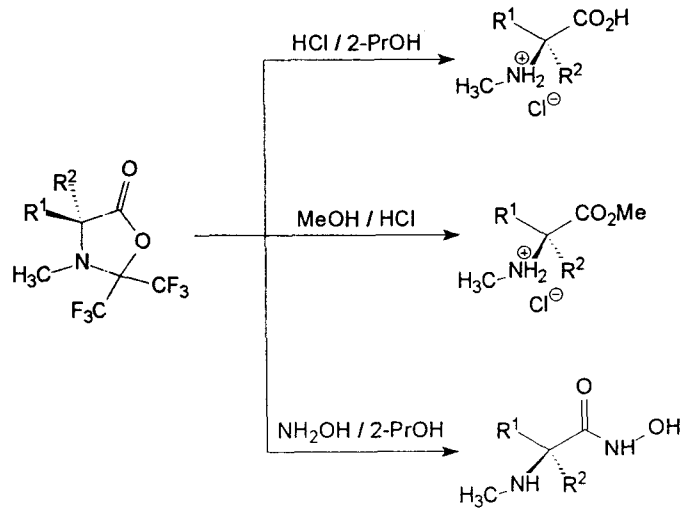
R^1 = H, alkyl, aryl; R^2 = H, aryl

Scheme 1

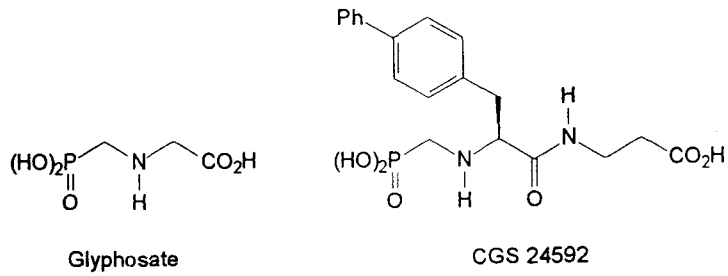
Since the N-methylated amino acid derivatives are carboxylic group activated species, they readily can be deprotected or derivatized to give the unprotected, optically active α-N-methylamino acids, ester hydrochlorides, amides, dipeptides and hydroxamic acids, respectively.

N-Phosphinoylmethylamino acids

N-Phosphorylated peptides are naturally occurring species. Phosphoramidon isolated from *Actinomycetes* is a powerful inhibitor of the Zn metalloprotease thermolysin (Murano et al., 1982; Gómez-Monterrey et al., 1992). However, the biological half-life is short because of the phosphorus-nitrogen bond is sensitive to hydrolysis. A methylene spacer has been introduced between phosphorus and nitrogen to overcome this drawback. This special class of amino acids has potential as building block for the synthesis of new drugs, e.g. CGS 24592 (De Lombaert et al., 1994) and agrochemicals. N-Phosphonomethyl glycine ("glyphosate") inhibits the shikimic acid pathway in plants and

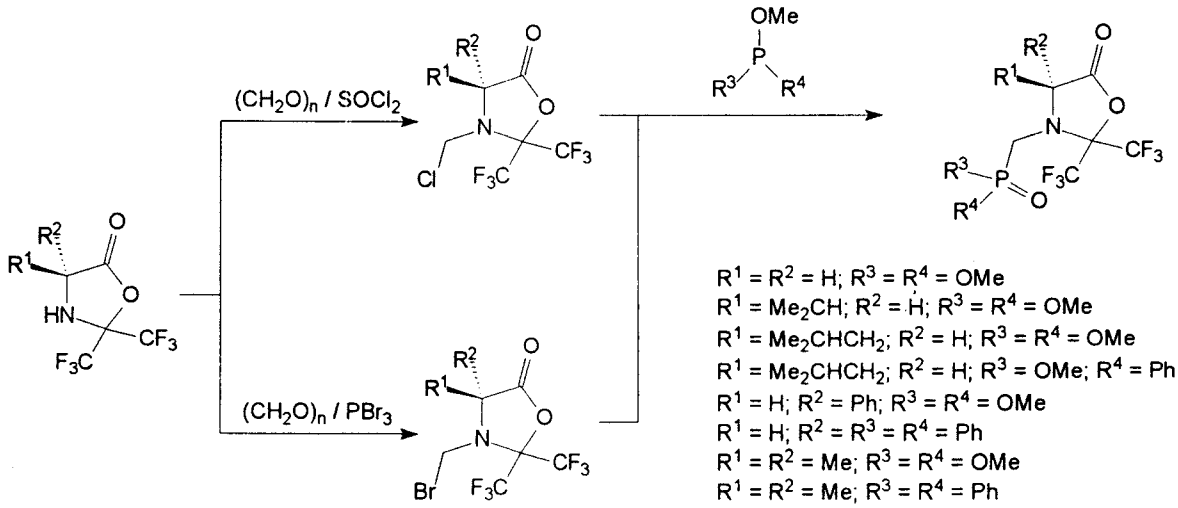


Scheme 2



Glyphosate CGS 24592

Scheme 3



Scheme 4

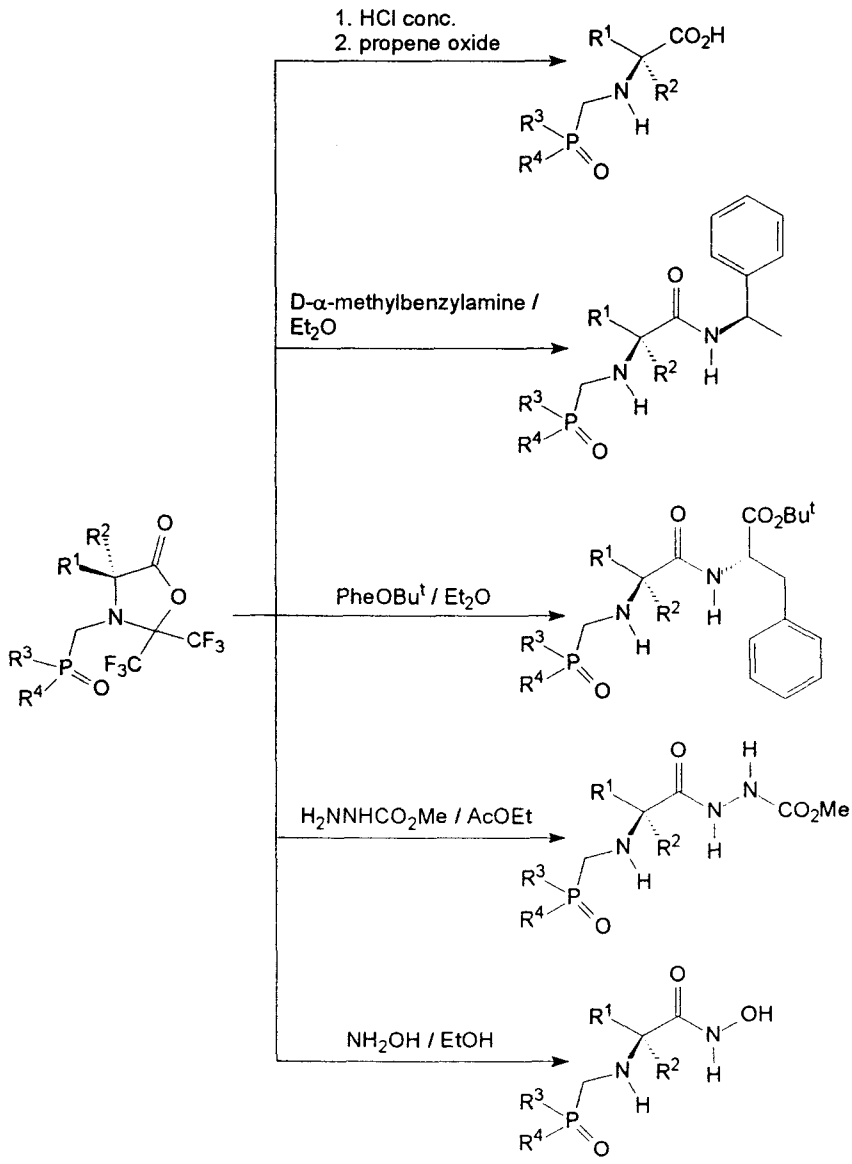
represents the most widely used herbicide today (Sikorski and Gruys, 1997; Pfliegel et al., 1977).

With P(III)-species possessing at least one alkoxide ligand, N-halomethyl oxazolidin-5-ones undergo Michaelis-Arbusov reaction (Spengler and Burger, 1998b). While N-bromomethyl and N-iodomethyl compounds react exothermically within minutes, the N-chloromethyl compounds need several days at room temperature until the reactions are complete.

As carboxyl group activated species they can be readily deprotected or transformed into optically active amides, peptides, azapeptides and hydroxamic acids, respectively (Spengler and Burger, 1998b). The nucleophilic ring opening and the deblocking of the α-amino group are simultaneously occurring reactions. The over-all reaction sequence is suitable for generating libraries of N-phosphinoylmethylamino acid derivates, including peptide- and depsipeptide mimetics.

New conformationally restricted phosphorus and sulfur containing structure mimetics of glutamic acid and taurine Pro-Glu-chimeras, Pro-Tau-chimeras

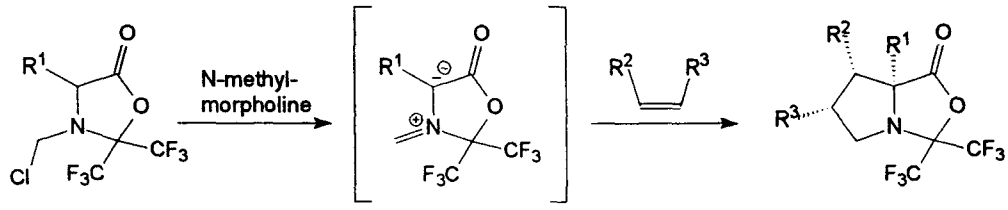
Conformationally restricted amino acids are important tools for the construction of biological active compounds with improved selectivity. In this context, proline analogues possessing the characteristics of other amino acids ("chimeras") are of special interest (Langlois and Andriamialisoa, 1991; Baldwin et al., 1995). Replacement of natural amino acids in biologically active peptides by proline-Xaa-chimeras has led to better understanding of their bioactive conformation (Plucinska et al., 1993). E.g. the neuroexcitatory activity of kainic acid is intrinsically associated to its action as conformationally constrained glutamate (Carpes et al., 1997). Since L-glutamate is a major



Scheme 5

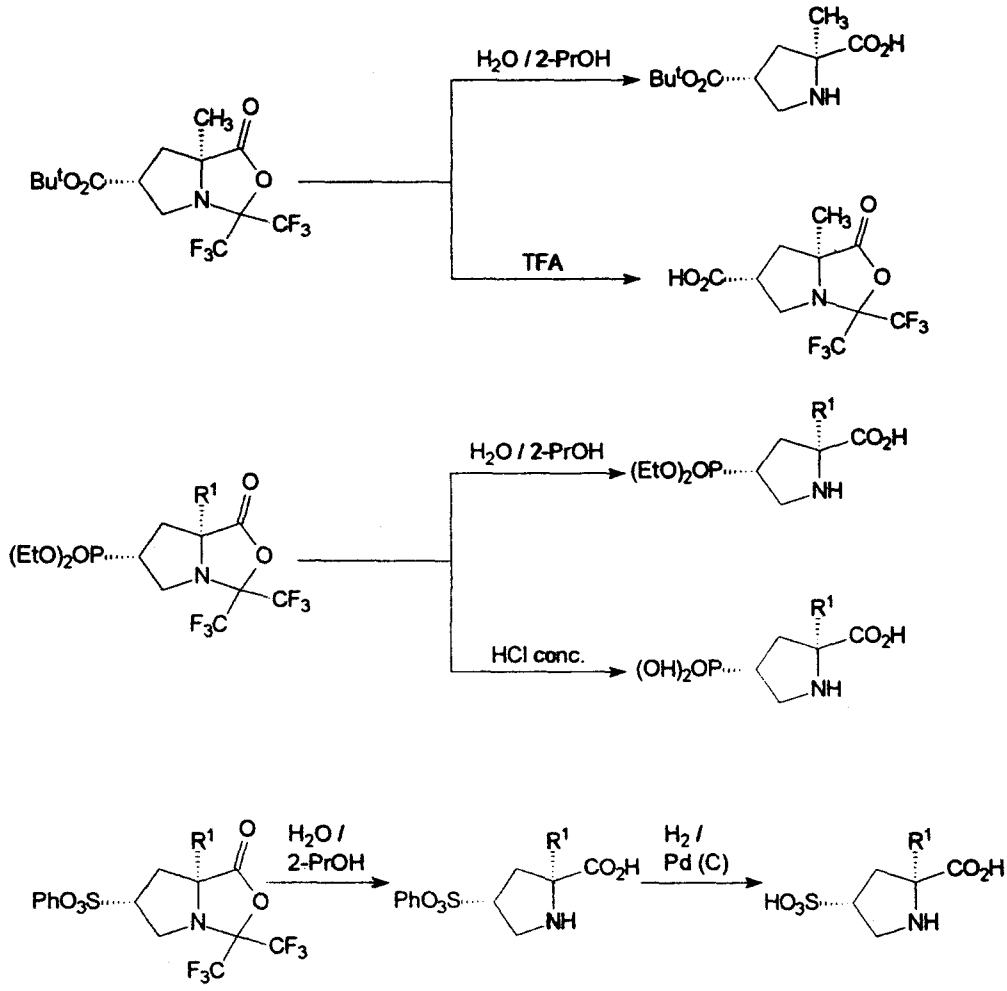
neurotransmitter in the mammalian central nervous system (CNS), its mimetics might be of interest for the development of new types of drugs for treatment of pathological processes like Alzheimer's, Huntington's, Parkinson's disease as well as epilepsy (Garcia-Barradas and Juaristi, 1997).

Among the many routes so far developed for the synthesis of proline-Xaa-chimeras, the concept of the 1,3-dipolar cycloaddition (Huisgen, 1984) turned out to be the most powerful one in respect of generating substituent patterns showing a maximum in variability (Gordon et al., 1996). Azomethine ylides are generated from N-halomethyl substituted 2,2-bis(trifluoromethyl)-



R^1 = H, alkyl, aryl; R^2 = H, CO_2Bu^t; R^3 = H, $PO(OEt)_2$, $SO_2OC_6H_5$, CO_2Bu^t

Scheme 6



Scheme 7

oxazolidin-5-ones on treatment with *tert.* amines like N-methylmorpholine. The 1,3-dipoles obtained via 1,3-elimination can be trapped *in situ* by a large number of dipolarophiles providing highly functionalized proline derivatives.

The [3+2] cycloaddition proceeds via a concave transition state, the two five-membered ring systems being cis fixed. Therefore, the relative stereochemistry can be controlled efficiently. The products obtained are racemates. The progress of the [3+2] cycloaddition process can be monitored by ^{19}F NMR spectroscopy.

With *tert.* butyl acrylate two regioisomers are formed, which can be separated by flash chromatography. The cycloadducts represent Pro-Glu and Pro-Asp chimeras, respectively. In contrast, diethyl vinylphosphonate and phenyl vinylsulfonate on reaction with the 1,3-dipoles provide the corresponding cycloadducts regio- and stereospecifically, which represent conformationally rigid glutamic acid analogues (Schedel et al., 1999). Furthermore, the sulfur-containing proline derivative mimics a conformationally rigid taurine. Multifunctional proline derivatives are structurally interesting scaffolds for drug design and potential secondary structure mimetics.

Acknowledgements

The authors are grateful to Deutsche Forschungsgemeinschaft (Bu 277-19-1), Fonds der Chemischen Industrie, Hermann Schlosser Stiftung and Bayer AG, Leverkusen, for financial support, and to Hoechst AG, Frankfurt, for providing chemicals.

References

Baldwin JE, Adlington RM, Gollins DW, Godfrey CRA (1995) The stereospecific synthesis of (2S, 3R) 3-carboxyproline and (2S, 3R) 3-aminoproline. Tetrahedron 51: 5169–5180

Garcia-Barradas O, Juaristi E (1997) Enantioselective synthesis of both enantiomers of 2-amino-6-phosphonohexanoic acid [(R)- and (S)-AP6], a potent and specific agonist of AMPA receptor subtype. Tetrahedron Asymm 8: 1511–1514

Bhatt U, Mohamed N, Just G (1997) Derivatized oxopiperazine rings from amino acids. Tetrahedron Lett 38: 3679–3682

Bowman WR, Coghlan DR (1997) A facile method for the N-alkylation of α-amino esters. Tetrahedron 53: 15787–15798

Burger K, Rudolph M (1990) Regiospezifische Reaktionen mit ω-Carboxy-α-Aminosäuren – Eine einfache Synthese für Aspartam. Chem-Ztg 114: 249–251

Burger K, Gold M, Neuhauser H, Rudolph M, Höß E (1992) Synthese von 3-(Thiazol-4-yl)-alanin- und 3-(Selenazol-4-yl)alanin-Derivaten aus Asparaginsäure. Synthesis: 1145–1150

Burger K, Rudolph M, Fehn S, Worku A, Golubev A (1995) Application of hexafluoroacetone as protecting and activating reagent in amino acid and peptide chemistry. Amino Acids 8: 195–199

Carpes MJS, Miranda PCML, Correia CRD (1997) Stereoselective synthesis of conformationally restricted analogues of aspartic and glutamic acids from endocyclic enecarbamates. Tetrahedron Lett 38: 1869–1872

Chruma JJ, Sames D, Polt R (1997) General method for the synthesis of N-methyl amino acids and N-alkyl amino esters from O'Donnell's Schiff bases. Tetrahedron Lett 38: 5085–5088

De Lombaert S, Erion MD, Tan J, Blanchard L, El-Chehabi L, Ghai RD, Sakane Y, Berry C, Trapani AJ (1994) N-Phosphonomethyl dipeptides and their phosphonate produgs, a new generation of neuronal endopeptidase (NEP, EC 3.4.24.11) inhibitors. J Med Chem 37: 498–511

Dorow RL, Gingrich DE (1995) A novel preparation of scalemic N-methyl-α-amino acids. J Org Chem 60: 4986–4987
Duthaler RO (1994) Recent developments in the stereoselective synthesis of α-amino acids. Tetrahedron 50: 1539–1650
Ebata M, Takahashi Y, Otsuka (1966) The preparation and some properties of N-monomethylated L-amino acids. Bull Soc Chem Jpn 39: 2535–2538
Effenberger F, Burkard U, Willfahrt J (1983) Trifluoromethane sulfonates of α-hydroxy carboxylates – Educts for the racemization-free synthesis of N-substituted α-amino acids. Angew Chem Int Ed Engl 22: 65–66
Fukuyama T, Jow C-K, Cheung M (1995) 2- and 4-Nitrobenzenesulfonamides: exceptionally versatile means for preparation of secondary amines and protection of amines. Tetrahedron Lett 36: 6373–6374
Gante J (1994) Peptidomimetics. Tailored enzyme inhibitors. Angew Chem Int Ed Engl 33: 1699–1720
Giannis A, Kolter T (1993) Peptidomimetics for receptor ligands. Discovery, development, and medical perspectives. Angew Chem Int Ed Engl 32: 1244–1267
Gordon EM, Gallop MA, Patel DV (1996) Strategy and tactics in combinatorial organic synthesis. Applications to drug discovery. Acc Chem Res 29: 144–154
Gómez-Monterrey I, Muniz RG, Pérez-Martin C, López de Ceballos M, Del Rio J, Garcia López MT (1992) Synthesis and inhibitory activities against aminopeptidase B and enkephalin-degrading enzymes of ketomethylene dipeptide analogs of orphamenines. Arch Pharm (Weinheim) 325: 3–8
Huisgen R (1984) 1,3-Dipolar cycloadditions – introduction, survey, mechanism. In: Padwa A (ed) 1,3-Dipolar cycloaddition chemistry, vol 1. Wiley & Sons, New York Chichester Brisbane Toronto Singapore, pp 1–176
Langlois N, Andriamialisoa RZ (1991) Diastereoselective synthesis of (2S, 3R) 2-carboxy-3-pyrrolidine acetic acid, a simple kainic acid analogue. Tetrahedron Lett 32: 3057–3058
Liskamp RMJ (1994) Conformationally restricted amino acids and dipeptides, (non)peptido-mimetics and secondary structure mimetics. Rec Trav Chim Pays Bas 113: 1–19
Muller D, Zeltser I, Bitan G, Gilon C (1997) Building units for N-backbone cyclic peptides. Synthesis of protected N^{α}-(ω-aminoalkyl)amino acids and N^{α}-(ω-carboxyalkyl)amino acids. J Org Chem 62: 411–416
Murano S, Kasai N, Kimura J, Oda K, Fukuhara K (1982) A new metallo-proteinase inhibitor (FMPI) produced by streptomyces rishiriensis NK-122. Agric Biol Chem 46: 855–857
O'Donnell MJ (1988) α-Amino acid synthesis; Tetrahedron Symposia-in-print Nr 33, Tetrahedron 44: 5253–5614
Okamoto K, Quastel JH (1977) Effects of N-methylamino acids and convulsants on spontaneous action potentials in guinea pig cerebellar slices. Br J Pharmacol 59: 551–560
Oppolzer W, Cintas-Moreno P, Tamura O (1993) Enantioselective synthesis of α-N-alkyl-amino acids via sultam-directed "enolate" hydroxyamination. Helv Chim Acta 76: 187–196
Paruszewski R, Rostafinska-Suchar G, Strupinska M, Jaworski P, Stables JP (1996) Synthesis and anticonvulsant activity of some amino acid derivatives. Part 1: Alanine derivatives. Pharmazie 51: 145–148
Pfliegel T, Seres J, Gajáry A, Daóczy née Csuka, Nagy LT (1977) US Patent 4065491
Pires R, Fehn S, Golubev A, Winkler D, Burger K (1996) Stereoconservative and stereoselective syntheses of rare and non-natural α-amino acids from (S)-aspartic acid and (S)-malic acid. Amino Acids 11: 301–312
Plucinska K, Kataoka T, Yodo M, Cody WL, He JX, Humblet C, Lu GH, Lunney E, Major TC, Panek RL, Schelkun P, Skeean R, Marshall GR (1993) Multiple binding

modes for the receptor-bound conformations of cyclic AII agonists. J Med Chem 36: 1902–1913
Schedel H, Sieler J, Hennig L, Burger K (1999) New conformationally restricted phosphorus- and sulfur-containing structure mimetics of glutamic acid – Pro-Glu chimeras. Synthesis: 152–160
Sikorski JA, Gruys KJ (1997) Understanding glyphosate's molecular mode of action with EPSP synthase: Evidence favoring an allosteric inhibitor model. Acc Chem Res 30: 2–8
Spengler J, Burger K (1998a) An efficient synthesis of N-methylamino acids and some of their derivatives. Synthesis: 67–70
Spengler J, Burger K (1998b) An efficient synthesis of N-phosphinoylmethylamino acids and some of their derivatives. J Chem Soc Perkin Trans 1: 2091–2095
Toniolo C (1990) Conformationally restricted peptides through short-range cyclizations. Int Peptide Protein Res 35: 287–300
Williams RM (1989) Synthesis of optically active α-amino acids. In: Baldwin J, Magnus P (eds) Organic chemistry series, vol. 7. Pergamon Press, Oxford
Windeisen E, Pires R, Heistracher E, Burger K (1995) New types of biorelevant α-functional carboxylic acids and their application for peptide modification. Amino Acids 8: 397–400

Authors' address: Prof. Dr. Klaus Burger, Institut für Organische Chemie der Universität Leipzig, Talstraße 35, D-04103 Leipzig, Federal Republic of Germany, E-mail: burger@organik.orgchem.uni-leipzig.de

Received September 15, 1998