Pergamon

Tetrahedron 54 (1998) 3471–3478

TETRAHEDRON

ELECTROGENERATED CHIRAL CATIONIC GLYCINE EQUIVALENTS - PART 1: THE 6-METHOXY DERIVATIVE OF CYCLO(*L*-Pro-Gly)

Georgios Kardassis, Peter Brungs and Eberhard Steckhan*

Kekulé-Institut für Organische Chemie und Biochemie der Universität Bonn,
Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany

Received 27 November 1997; accepted 21 January 1998

Abstract: The cyclic *N,O*-acetal cyclo(*L*-Pro-Gly(OMe)OMe (**8**) has proved to be an effective chiral electrophilic glycine equivalent which is applicable in nucleophilic substitution reactions not only under *Broenstedt* acid catalysis but also under *Lewis* acid catalysis with excellent diastereoselectivities. This chiral building block can easily be obtained by electrochemical methoxylative decarboxylation of the cyclic dipeptide **6** generated from *L*-proline and aminomalonic diester. Thus, enantiomerically pure *D*-allyl glycine has been generated.

INTRODUCTION

The generation of enantiomerically pure non-proteinogenic α-amino acids has been an important field of organic synthesis for a long time and has been reviewed by *Williams*.[1] Most often, the introduction of the side-chain as an electrophile into a chiral anionic glycine equivalent has been used as the key step, especially in the famous *Schöllkopf* bislactime ether and *Seebach* Boc-BMI reagents. The alternative introduction of the side-chain as a nucleophile *via* chiral cationic glycine equivalents found only limited application, the key intermediates being chiral α-iminoesters, *N*-acylimines and *N*-acyliminium ions as amidoalkylation reagents.[2] Open-chain electrophilic glycine equivalents have been obtained by introduction of the chiral information into the carboxylic function under formation of a chiral ester or using a chiral substituent at the nitrogen. Typical examples have been given by *Kagan*,[3] *Yamamoto*,[4] *Obrecht*,[5] *Steglich*,[6] *Harding*,[7] and *Enders*.[8] Also, some cyclic chiral cationic glycine equivalents have been applied with more or less limited applicability. In the case of the *Schöllkopf* bislactime ethers[9] and the *Seebach* imidazolidine-4-ones,[10] chiral cationic glycine equivalents could be obtained by halogenation in the α-position. Broader applicability found the chiral α-brominated oxazinone developed by *Williams*.[11] However, in the reductive liberation of the amino acid the chiral auxiliary is destroyed. Starting from phenyl glycinol, a thiophenylated morpholine derivative can also be used as key intermediate.[12] Finally, *Altenbach* has applied another imidazolidin-4-one derivative containing menthone as chiral auxiliary as chiral cationic glycine equivalent.[13]

Chiral building blocks for diastereoselective amidoalkylation reactions as in this special case the electrophilic chiral glycine equivalents, can very often easily be generated by electrochemical methoxylation of chiral amides or carbamates starting from compounds of the chiral pool. Generally three different methods are applicable: A. The direct anodic α-methoxylation of amides and carbamates;[2b,14] B. Anodic methoxylative decarboxylation of α-amino acid derivatives (*Hofer-Moest* reaction);[15] C. Indirect NaCl mediated anodic α-methoxylation of α-amino acid derivatives[16] (see

0040-4020/98/$19.00
PII: S0040-4020(98)00081-7

Fig. 1). In case A, the presence of an α-carboxylic ester group usually increases the oxidation potential so that the direct electrochemical methoxylation is prevented. This can be circumvented by the indirect process C in the presence of NaCl. In case B, the *Hofer-Moest* reaction of an α-aminomalonic halfester leads to the desired product. By reaction of carbon nucleophiles with these chiral amidoalkylation reagents the diastereoselective transformation into non-proteinogenic α-amino acids is possible.

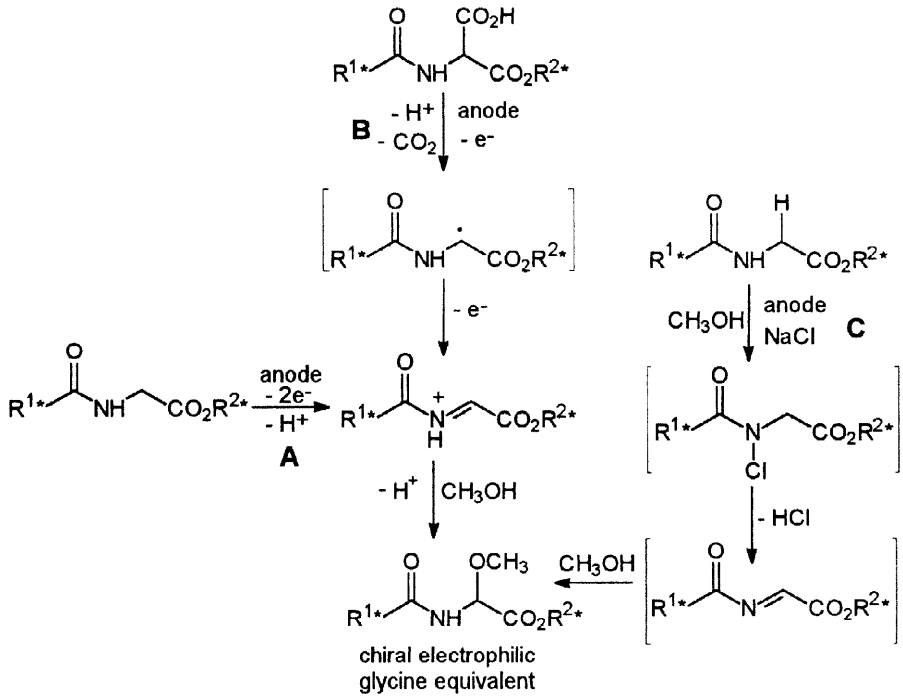
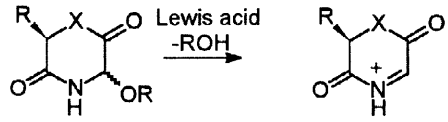


Fig. 1: Possible pathways for the electrochemical generation of *N,O*-acetals as chiral electrophilic glycine equivalents

RESULTS AND DISCUSSION

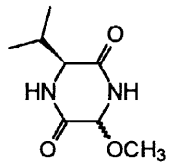
It was our strategy to use electrogenerated cyclic chiral electrophilic glycine equivalents in order to obtain higher diastereoselectivities as compared with the open-chain systems due to a limitation in the conformational flexibility. Therefore, we have generated key building blocks of the following structure:[16b-d,17,18]



These key building blocks were either methoxylated cyclic dipeptides (X = NH, 6-methoxy-2,5-piperazinediones) or methoxylated cyclic dipeptolides (X = O; 3-methoxy-2,5-morpholinediones).[19]

We have already reported on the synthesis and application of the methoxylated cyclic dipeptide **1** obtained from *L*-valine using the chloride mediated anodic methoxylation of an open-chain intermediate as a key step.[16d,17] Nucleophilic substitution of the methoxy group was possible with carbon nucleophiles in the presence of Broenstedt acids with reasonably good diasteroselectivities.

Because of the high polarity of **1** and its low solubility in the appropriate solvents, nucleophilic substitution was not possible in the presence of Lewis acids.



1

Therefore, the methoxylated cyclic dipeptide **8** from *L*-proline and glycine was envisioned as a better chiral cationic glycine equivalent.

8

It was expected that compound **8** would have the following advantages as compared to **1**:

1. The bicyclic ring systems in **8** enhances the diastereoselectivity of the methoxy group exchange (see below).
2. The solubility of **8** in organic media is drastically enhanced thus allowing for methoxy group exchange by nucleophiles under catalysis of Lewis acids as compared with proton acids which are necessary for **1**. Thus in the case of **8** a larger variety of nucleophiles can be employed.

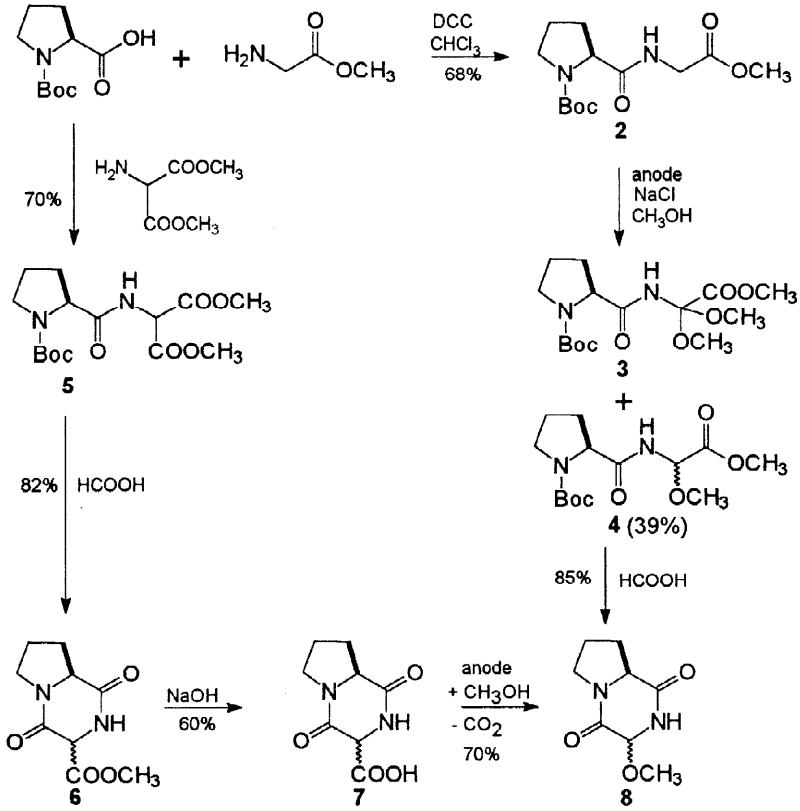


Fig. 2: Electrochemical formation of the chiral electrophilic glycine equivalent **8**

For the synthesis of **8**, two different pathways were employed (Fig. 2). The first strategy which we already published, started with the formation of the dipeptide **2** of Boc-*L*-proline and glycine methyl ester followed by the indirect regioselective electrochemical methoxylation in the glycine part (method C). However, in contrast to the dipeptide from L-valine and glycine we did not selectively obtaine only the monomethoxylated product **4** but also the dimethoxylated compound **3**. Cyclization to give the diketo piperazine **8** went smoothly.[16d] To prevent the undesired dimethoxylation, we used aminomalonic diester instead of glycine ester. The thus obtained dipeptide **5** was smoothly cyclized to give **6**. Saponification of the ester group followed by anodic methoxylative decarboxylation (method B) yielded **8** as the only product in a clean reaction. If after the saponification step the anodic oxidation is directly performed without work-up, almost quantitative yields of **8** can be obtained.

The diastereoselectivity of the two chiral building blocks has been compared for the introduction of 1,1-diphenyl ethylene under proton acid catalysis which in the case of **1** only gave 57% *de* (Fig. 3). This olefin was selected because it resulted in the poorest diastereoselectivity with **1**. The diastereomeric excess of 97% for **8** demonstrates the superiority of **8**.[16d]

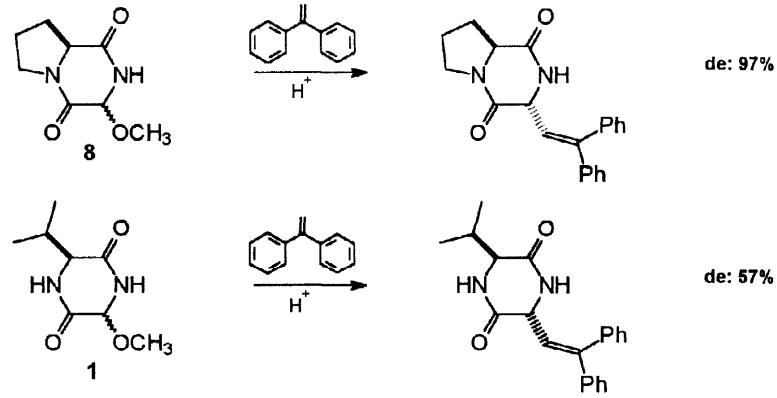


Fig. 3: Comparison of the diastereoselectivity of the methoxy group exchange by 1,1-diphenyl ethylene in the chiral cationic glycine equivalents **1** and **8**.

As mentioned above, **8** is less polar as compared with **1** and therefore **8** is soluble in dichloromethane. Therefore, it can undergo methoxy group exchange also under *Lewis* acid catalysis. This was examplified for the reaction with allyl trimethylsilane under catalysis by $TiCl_4$ in this solvent. Even this small nucleophile results in a diastereomeric excess of better than 99% (no other diastereoisomer could be detected) (Fig. 4). Hydrolytic cleavage of **3** by HCl in methanol at 60°C followed by separation of the amino acids via chromatography yielded the enantiomerically pure auxiliary *L*-proline (62 %) and the non-proteinogenic *D*-allyl glycine (**10**) in 80% yield. The total enantiomeric purity of **10** was determined by derivatization with trifluoroacetyl-*L*-prolyl chloride and subsequent GC/MS analysis of the diasteroisomers according to a literature procedure.[20] The recovered *L*-proline had the same specific rotation as the starting material (Degussa). Thus, the cyclic *N,O*-acetal cyclo(*L*-Pro-Gly(OMe)OMe (**8**) has proved to be an effective chiral electrophilic glycine equivalent which is applicable in nucleophilic substitution reactions not only under *Broenstedt* acid catalysis but also under *Lewis* acid catalysis with excellent diastereoselectivities.

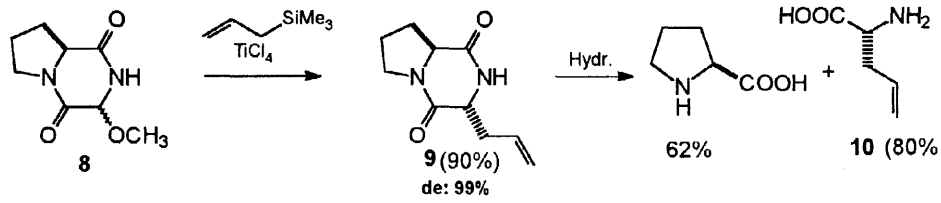


Fig. 4: Methoxy group exchange in **8** by allyl trimethylsilane under *Lewis* acid catalysis.

Instead of *L*-proline also *L*-indoline carboxylic acid can be used as chiral auxiliary with similar results.

EXPERIMENTAL

General. Nuclear magnetic resonance (^{1}H NMR) spectra were determined in the reported solvent using a Bruker WH 90 (90 MHz), Bruker AC 200 (200 MHz), Bruker AC 250 (250 MHz), and a Bruker AC 400 (400 MHz) spectrometer. The same instruments were also used for the measurements of ^{13}C spectra. Chemical shifts (δ) are reported in ppm relative to TMS as reference. IR spectra : Pye Unicam SP 1100, or FT-IR 1600 Perkin Elmer. Mass spectra: A.E.I., Manchester, MS-9, MS-30, and MS-50. Melting points (uncorrected): Kofler micro heating plate (Reichert). R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated aluminum sheets (Merck silica gel F_{254}). The plates were inspected by UV light prior to development with ninhydrine solution, or by treatment with ceric ammonium molybdate reagent and subsequent heating. For liquid chromatography, flash silica gel 30 - 60 μm (Baker), silica gel 65 - 200 μm (Woelm) and neutral aluminium oxide 63 - 200 μm (Merck) were used. All solvents were distilled before using.

Preparative electrolysis: A FuG (Rosenheim) stabilized current source, modified as galvanostat/potentiostat, NTN 700 - 200 M, was used as galvanostat in combination with a digital coulombmeter based on voltage to frequency conversion.

Cells: Undivided beaker-type cell with cooling mantle (50mL, cell 1), equipped with a cylindrical Pt-foil (25cm^2 or 44 cm^2) anode, a coaxial Pt-wire cathode, and a magnetic stirrer, or undivided beaker-type glass cell without/with cooling mantle (350mL, cell 2), equipped with graphite plates (57cm^2) as electrodes and a magnetic stirrer.

Dimethyl *N*-tert-butyloxycarbonyl-*L*-prolyl-aminomalonate (**5**). *N*-Boc-*L*-proline (7.4g, 34 mmol) and dimethyl aminomalonate hydrochloride (6.24g, 34 mmol) are suspended in $CHCl_3$ and stirred. At -10°C the triethylamine (6 mL, 36 mmol) and then the DCC (6.48g, 36 mmol) dissolved in a small quantity of $CHCl_3$ are added. Stirring is continued in an ice bath and the mixture is allowed to reach room temperature overnight. The precipitated urea is separated, the filtrate is concentrated and the remaining oil is dissolved in ethyl acetate. The organic phase is separated from the precipitated urea, extracted with a 5% $NaHCO_3$ / 5 % $KHSO_4$ aqueous solution, dried over $MgSO_4$ and concentrated *in vacuo*. After purification by flash chromatography (SiO_2, eluent: cyclohexane/ethyl acetate 2:1 v/v) 8.2g (70%) of **5** are obtained as an oil. $[\alpha]_D^{21}$ = - 48° (c = 1 in CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 90 MHz): δ = 1.50 (s, 9H, CH_3), 1.75-2.25 (m , 4H, 2 CH_2), 3.35-3.55 (m, 2H, CH_2), 3.80 (s, 6H, 2OCH_3), 4.20-4.45 (m, 1H, CH), 5.15 (d, *J* =7Hz, 1H, CH), 7.40 (broad,1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 24.16 (CH_2), 28.05 (3 CH_3), 30.57 (CH_2), 46.84 (CH_2), 53.17 (2 OCH_3), 55.78 (CH), 60.49 (CH), 80.43 (C), 155.45 (CO), 166.35 (CO), 172.40 (CO) ppm; due to the presence of rotamers, some signals are doubled. MS: *m/z* =344 (M^+, 2%), 271 (4), 243 (4), 211 (3), 183 (6), 170 (15), 114 (80), 70 (100), 57 (55). IR (KBr): ν_{max} = 3400 cm^{-1} (w, N-H), 2900 (m, C-H), 1750 (s, C=O), 1680 (s, C=O), 1440 (m, N-H), 1150 (s, C-O), 1030 (w), 970 (w), 910 (w), 880 (w), 840 (w).

(*3S,6RS*)-6-Carbomethoxy-1,3-trimethylene-2,5-piperazinedione [Cyclo(*L*-Pro-Gly(COOMe)-] (**6**). In order to cleave the Boc protecting group of the dipeptide the open-chain dipeptide **5** (3g, 9 mmol) is dissolved in 98% formic acid (80 mL) and stirred for two hours at room temperature. The solvent is distilled off in *vacuo* at 30°C. The residue is dissolved in an isobutanol/toluene mixture (3:1) and the solution heated to boiling, the liquid level

being kept constant by adding isobutanol. During this process the remaining formic acid is removed azeotropically and the open-chain dipeptide cyclizes spontaneously. After evaporating the solvent, the crude product is purified over SiO_2 using ethyl acetate/cyclohexane (5.5:1 v/v) and 1.5 g (82%) of **6** are obtained as oil. ^{1}H NMR ($CDCl_3$, 90 MHz): δ = 1.75 - 2.40 (m, 4H, CH_2-CH_2), 3.45 - 3.70 (m, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.95 - 4.25 (m, 1H, CH), 5.05 (d, *J* = 7Hz, 1H, CH), 6.85 (broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 23.84 (CH_2), 28.33 (CH_2), 46.70 (CH_2), 53.22 (OCH_3), 57.20 (CH), 60.43 (CH), 162.06 (CO), 167.38 (CO), 170.66 (CO) ppm; due to the presence of rotamers, some signals are doubled. MS: *m/z* =212 (M^+, 75%), 180 (20), 153 (100), 141 (20), 125 (60), 111 (10), 97 (10), 83 (20), 70 (70). IR (KBr): ν_{max} = 3250 cm^{-1} (w, NH), 2920 (m, CH), 1735 (s, CO), 1680 (s, CO), 1440 (m, NH), 1200 (s, CO), 1010 (w), 960 (w), 910 (w). HRMS calcd for $C_9H_{12}N_2O4$ (M^+): 212,0797; found: 212,0793.

(3*S*,6*RS*)-6-Carboxy-1,3-trimethylene-2,5-piperazinedione [Cyclo(*L*-Pro-Gly(COOH)-] (**7**). KOH (0.5g, 10 mmol) dissolved in a small quantity of water is added dropwise to an ice-cooled solution of **6** (1.2g, 5 mmol) in methanol (40 mL). After stirring the mixture for four hours at room temperature the solvent is distilled off in *vacuo* at 30°C and the residue is dissolved in 20 mL of H_2O. The solution is acidified to a pH of 4.3 with dilute HCl and extracted with ethyl acetate for twelve hours in a continuous light phase extractor. The extract is dried with $MgSO_4$ and the solvent evaporated with a rotary evaporator. 0.7g (60%) of **7** is isolated as an oil after purification by column chromatography (eluent: $CHCl_3$/ethyl acetate 2:1 v/v). ^{1}H NMR ($CDCl_3$, 90 MHz): δ =1.60 - 2.15 (m, 4H, CH_2-CH_2), 3.60 (ddd, *J* = 16 Hz, 7Hz, 2H, CH_2), 4.00-4.20 (m, 1H, CH), 4.35-4.50 (m, 1H, CH), 6.40 (s, broad, 1H, NH), 6.25 (s, 1H, COOH) ppm. IR (KBr): ν_{max} = 3100 cm^{-1} (m, broad, NH), 2990 (m, CH), 2350 (w, OH), 1700 (s, CO), 1450 (m, NH), 1200 (s, CO), 1100 (w), 1040 (w), 900 (m, OH).

(3*S*,6*RS*)-6-Methoxy-1,3-trimethylene-2,5-piperazinedione [Cyclo(*L*-Pro-Gly(OMe)-] (**8**) from **7**. The electrolysis of **7** is carried out in cell 2 under galvanostatic conditions (5 mA/cm^2) using graphite plates as the electrodes. The starting material **7** (0,5g, 2.5 mmol) is dissolved in 100 mL of MeOH containing NaOAc (0.2M). Electrolysis is carried out until a charge of 3 F/mol is consumed. Then the solvent is evaporated to dryness *in vacuo*, and the residue is mixed with water, extracted with ethyl acetate and the organic phase dried over $MgSO_4$. 0.33g (70%) of **8** is isolated as an oil. (*cis:trans 4.3:1*). ^{1}H NMR ($CDCl_3$, 90 MHz): δ =1.65 - 2.45 (m, 4H, CH_2-CH_2), 3.40 - 3.90 (m, 2H, CH_2), 3.50 (s, 3H, OCH_3), 4.10 (dd, *J* = 8Hz, 1H, CH), 4.65 (d, *J* = 5Hz, 1H, CH, *trans*-diastereomer), 5.05 (s, 1H, CH, *cis*-diastereomer), 6.75 (s, broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): δ = 22.13 (CH_2), 28.55 (CH_2), 45.03 (CH_2), 55.35 (OCH_3), 59.22 (CH), 81.78 (CH), 162.36 (CO), 168.23 (CO) ppm; MS : *m/z* = 184 (M^+, 25%), 154 (35), 125 (10), 98 (7), 82 (5), 70 (100), 60 (50), 42 (20). IR (KBr): ν_{max} = 3380 cm^{-1} (w, N-H), 3000 (m, C-H), 1670 (s, C=O), 1440 (m, N-H), 1200 (m, C-O), 1080 (w), 1040 (w), 900 (m).

N-*tert*-Butoxycarbonyl-*L*-prolyl-glycine methyl ester (**2**). *N*-Boc-*L*-proline (7.4g, 36 mmol) and glycine methyl ester hydrochloride (4.5g, 36 mmol) are suspended in 70 mL of $CHCl_3$ and cooled to -10°C. After adding triethylamine (5.4 mL, 40 mmol) the *N,N'*-dicyclohexylcarbodiimide (7.9 g, 40 mmol) dissolved in 20 mL of $CHCl_3$ is added dropwise to the reaction mixture. Stirring is continued in an ice bath and the mixture is allowed to reach room temperature overnight. The precipitated urea is filtered off and the filtrate concentrated, dissolved in ethyl acetate and kept at 0°C overnight. After repeated filtration the organic solution is washed with a 5% $NaHCO_3$ / 5% $KHSO_4$ aqueous solution and dried with Na_2SO_4. After distilling off the solvent, the obtained oil is dissolved in diethyl ether, precipitated by using petroleum ether and recrystallized from ethyl acetate/petroleum ether. 7.0g (68%) of **2** are obtained. M.p 67 - 68 °C, $[\alpha]_D^{21}$ = - 68.5° (c = 1 in MeOH). ^{1}H NMR ($CDCl_3$, 90 MHz): δ = 1.5 (s, 9H, $3CH_3$), 1.7 - 2.4 (m, 4H, $2CH_2$), 3.4 (t, *J* = 6 Hz, 2H, NCH_2), 3.7 (s, 3H, CO_2CH_3), 4.1 (d, *J* = 6 Hz, 2H, CH_2), 4.2 - 4.4 (m, 1H, NCH), 7.2 (broad, 1H, NH) ppm. MS: *m/z* = 286 (M^+, 2%), 230 (4), 170 (18), 114 (76), 70 (100), 57 (67).

N-*tert*-Butoxycarbonyl-*L*-prolyl-*D,L*-α-methoxyglycine methyl ester (**3**). The electrolysis of **2** is carried out in cell 1 under galvanostatic conditions (8 mA/cm^2) using Pt as the electrodes. The starting material **2** (1g, 3.5 mmol) and 245mg of NaCl are dissolved in 35 mL of MeOH (0.1M $LiCLO_4$). Electrolysis is carried out until a charge of 3.8 F/mol is consumed. Then the solvent is evaporated to dryness in *vacuo*, and the residue is mixed with water, extracted with ethyl acetate, the organic phase dried over $MgSO_4$, filtered, and the solvent evaporated. **3** is separated from **4** by flash chromatography on silica gel with diethyl ether/cycloexane (3:1 v/v) as eluents. 423 mg (39 %) of **3** are obtained as an oil. ^{1}H NMR ($CDCl_3$, 90 MHz : δ = 1.75 - 2.3 (m, 6H, 2 CH_3), 3.3 (s, 3H, OCH_3), 3.4 (t, 2H, CH_2), 3.73 (s, 3H, OCH_3) 4.24 (dd, broad, 1H, CH), 5.46 (d, *J* = 9Hz, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz) : δ = 24.11 (CH_2), 28.12 (3 CH_3), 30.03 (CH_2), 46.93 (CH_2), 52.66 (OCH_3), 56.15 (OCH_3),

60.98 (CH), 78.08 (CH), 80.53 (C), 168.05 (CO), 168.05 (CO), 173.16 (CO) ppm. MS: *m/z* = 316 (M^+, 1.2%), 201(7), 170 (32), 115 (8), 114 (94), 103 (10), 86 (10), 84 (18), 70 (100), 60 (15), 57 (61). Found: C, 53.31; H, 7.66; N, 8.61. $C_{14}H_{24}N_2O_6$ requires: C, 53.15; H, 7.64; N, 8.85.

(*3S,6RS*)-6-Methoxy-1,3-trimethylene-2,5-piperazinedione [Cyclo(*L*-Pro-Gly(OMe)-] (**8**) from **3**. In order to cleave off the *N*-terminal Boc protective group the dipeptide **3** (1.65g, 5.2 mmol) is stirred in 100 mL of 98% formic acid for 2.5 hours. Then the formic acid is distilled off in *vacuo* at a bath temperature of 30°C and the residue dissolved in 30 mL of toluene and 50 mL of isobutanol. The reaction mixture is heated to boiling, during which the remaining formic acid is distilled off azeotropically and the open-chain dipeptide ester cyclizes to form the diketopiperazine. When the azeotropic distillation is complete (approx. 2 hours, monitored by TLC) the solvent mixture is evaporated. The crude product, in the form of a mixture of diastereomers, can be separated into its diastereomers by flash chromatography (SiO_2, eluent: ethyl acetate/ethanol = 20:1 v/v). 835 mg (87 %) of **8** are obtained. The spectroscopic data correspond to those reported above.

(*3S,6RS*)-6-(2-Propenyl)-1,3-trimethylene-2,5-piperazinedione [Cyclo(*N*-Pro-Gly(allyl)-] (**9**). $TiCl_4$ (3.2 mL, 3.2 mmol) dissolved in 5 mL of absolute methylene chloride is initially introduced into a three-necked flask which has been flame dried and purged with argon. The three-necked flask is cooled to -65°C. Then the 6- methoxy-2,5-piperazinedione **8** (198mg, 1.1mmol), dissolved in methylene chloride, and the allyl trimethylsilane (0.49 mL, 3.2 mmol) are added dropwise in succession. While stirring for 4.5 hours, the reaction mixture is slowly warmed to approx. 0°C. In order to drive out the reaction to completion, the mixture is stirred for an additional 22 h at room temperature. The product is extracted with $CHCl_3$ for ten times. Purification by chromatography on silica gel using diethyl ether/ethanol (8:1v/v) as eluents yields 190 mg (90 %) of **9**. M.p. 91 - 94 °C. $[\alpha]_D^{21}$ = - 81,6° (c = 1 in $CHCl_3$) ^1H NMR ($CDCl_3$, 400 MHz): δ =1.70 - 2.10 (m, 3H, $2CH_2$), 2.33 - 2.40 (m, 1H, $2CH_2$), 2.45 - 2.61 (m, 2H, CH_2), 3.50 (ddd, *J* =12; 9; 3 Hz, 1H, NCH_2) 3.60 - 3.69 (m, 1H, NCH_2), 3.97 (dtd, *J* = 8; 4; 0,8 Hz, 1H NCH), 4.07 (dd, *J* = 10; 6 Hz, 1H, NCH), 5.15 - 5.30 (m, 2H, CH_2), 5.77 (dddd, *J* = 16.5; 10.5; 7.5; 7Hz, 1H, CH), 7.00 (broad, d, *J* = 3Hz 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 22.5 MHz): δ = 22.01 (CH_2), 29.16 (CH_2), 38.81 (CH_2), 45.57 (NCH_2), 57.55 (CH), 58.39 (CH), 120.44 (CH_2) 131.90 (CH), 165.34 (CO), 169.38 (CO) ppm. IR (KBr): ν_{max} =3240 cm^{-1} (m, NH), 2980 (w, CH),1670 (s, CO_{AmidI}), 1630 (s, CO_{AmidII}),1450 (m), 1430(w), 1410(w), 1340 (w), 1320 (w), 1300 (w), 1210 (w), 1140 (w), 1110 (w), 1070 (w), 1010 (w), 1000 (w), 990 (w), 920 (w), 880 (w), 800 (w), 760 (w), 720 (w). MS: *m/z* =194 (M^+, 35%) 153 ($M^+ C_3H_5$, 50%), 133 (38), 125 (100), 104 (78), 76(51), 70 (96). HRMS calcd for $C_{10}H_{14}N_2O_2$: 194.1055; found: 194.1050.

Hydrolytic clevage of **9** to give enantiomerically pure *L*-proline and *D*-allyl glycine (**10**). The diketopiperazine **9** (188mg, 0.97 mMol) is dissolved in 10 mL of 6N HCl and heated in a pressure resistant glass tube for 10 hours at a bath temperature of 90°C. Then the slightly yellow-colored solution is distilled and the residue dissolved in a small quantity of water, adjusted to a pH value of 6 using a 10% NH_3 solution and extracted with $CHCl_3$. The aqueous phase is concentrated and the amino acids dissolved therein separated by chromatography using silica gel (63-200 μm; eluent: $CHCl_3/CH_3OH$/conc. NH_3 = 5:4:1). 89 mg (80 %) of *D*-allyl glycine and 71 mg (62 %) of *L*-proline were obtained. Commercially obtained authentic samples of allyl glycine and *L*-proline were identical to the isolated products as determined by GLC and GLC/MS. The specific rotation of the obtained *D*-allyl glycine of $[\alpha]_D^{21}$ =+ 33.5° (c =1 in H_2O) compared well with literature data[21]. The recovered *L*-proline had the same specific rotation as the starting material (Degussa).

Determination of the enantiomeric purity of the separated amino acids. The enantiomeric purities of the obtained *D*-allyl glycine and *L*-proline were also determined by using a literature method[20] for the formation of the diasteriomeric dipeptides with *N*-trifluoroacetyl-*L*-prolyl chloride. Because the reagent was found to be impure, containing also small amounts of the *D*-proline derivative, the dipeptides were not only prepared with the obtained products but also with enantiomerically pure authentic samples of *D*-allyl glycine and *L*-proline in the following way. 1 - 2 mg of of the amino acids are introduced into screw cap jars, 1 mL of a 3% methanolic acetyl chloride solution is added and the mixture is heated to dryness in a heating block at 90°C. After cooling, 1 mL of a 0.1 M N-trifluoroacetyl-*L*-prolyl chloride solution in CH_2Cl_2 (an approx. 5-10 times excess) is added to the residue. Then a few drops of triethylamine are added until a pH value of 10 - 12 is reached. The screw cap glass is closed and left to stand for 2 hours at room temperature during which the pH value is constantly monitored. Then the mixture is vigorously extracted with 1 mL of 6 N HCl, the phases are separated with the aid of a centrifuge and the organic phase is dried over Na_2SO_4, filtered off and the solvent evaporated at room temperature under a stream of nitrogen. The remaining dipeptide ester is dissolved in 1 mL of absolute ether. Samples can now be taken from this solution for detection by GC/MS using a Hewlett-Packard HP-1

capillary column (12m, 0.2mm diameter, 0.33μm film thickness) with helium as a carrier gas starting at 100° C (1 min, heating with 30°C/min up to 250°C (10 min). The area ratios of the depeptide diastereomers for the obtained products and the authentic samples were identical. Retention times: *N*-trifluoroacetyl -*D*-prolyl -*L*-allylglycine methyl ester =8.8 min; *N*-trifluoroacetyl -*L*-prolyl -*L*-allylglycine methyl ester =9.1 min; *N*-trifluoracetic -*D*-prolyl -*L*-proline methyl ester =10.1 min; *N*-trifluoracetic -*L*-prolyl -*L*-proline methyl ester =10.3 min.

Acknowledgements: Financial support by the Deutsche Forschungsgemeinschaft (Ste 227/19-1,2,3), the Fonds der Chemischen Industrie, and the BASF Aktiengesellschaft, the supply of chemicals by the DEGUSSA AG and a graduation fellowship (P.B.) by the state of Nordrhein Westfalen are gratefully acknowledged.

REFERENCES

1 Williams, R. M. *Synthesis of Optically Active α-Amino Acids*, Pergamon Press, Oxford 1989.
2 a) Speckamp, W.N.., Hiemstra, H. *Comprehensive Organic Synthesis*, Vol. 2, Pergamon Press, Oxford 1991, 1045; Hiemstra, H., Speckamp, W.N. *The Alkaloids*, Brossi, A., Ed., Vol. 32, Academic Press Inc., London 1988, 271; b) Shono. T. *Electroorganic Synthesis*, Academic Press, London, 1991, 63; Shono T. *Topics Curr.Chem.* 148, 131 (1988).
3 Fiaud, J. C.; Kagan, H. B. *Tetrahedron Lett.* **1970**, *11*, 1813; **1971**, *12*, 1019.
4 Yamamoto, Y.; Ito, W.; Marujama, K. *J. Chem. Soc., Chem. Commun.* **1985**, 1131; Yamamoto, Y.; Ito, W. *Tetrahedron* **1988**, *44*, 5415.
5 Ermert, P.; Meyer, J.; Stucki, C.; Schneebeli, J.; Obrecht, J.-P. *Tetrahedron Lett.* **1988**, *29*, 1265.
6 Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W. *Tetrahedron* **1985**, *41*, 1693; Bretschneider, T.; Miltz, W.; Münster, P.; Steglich, W. *Tetrahedron* **1988**, *44*, 5403; Bretschneider, T., Ph.D. thesis, Bonn 1990.
7 Harding, K. E.; Davis, C. S. *Tetrahedron Lett.* **1988**, *29*, 1891.
8 Enders, D.; Funk, R.; Klatt, M.; Raabe, G.; Hovestreydt *Angew. Chem.* **1993**, *105*, 418; *Angew.* Chem. Int. Ed. Engl. **1993**, *32*, 418.
9 Schöllkopf, U.; Neubauer, H. J.; Hauptreif, M. *Angew. Chem.* **1985**, *97*, 1065; *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1066-1067; Schöllkopf, U.; Grüttner, S.; Anderskewitz, R.; Egert, E.; Dyrbusch, M. *Angew. Chem.* **1987**, *99*, 717-718; *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 683; Schöllkopf, U., Hupfeld, B.; Kuper, S.; Egert, E.; Dyrbusch, M. *Angew. Chem.* **1988**, *100*, 438; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 433.
10 Schickli, C. P.; Seebach, D. *Liebigs Ann. Chem.* **1991**, 655; Seebach, D.; Bürger, H.-M.; Schickli, C. P. *Liebigs Ann. Chem.* **1991**,, 669.
11 Sinclair, P. J.; Zhai, D.; Reibenspies, J.; Williams, R. M. *J. Am. Chem. Soc.* **1986**, *108*, 1103; Williams, R. M.; Sinclair, P. J.; Zhai, D.; Chen, D. *J. Am. Chem. Soc.* **1988**, *110*, 1547; Willimas, R. M.; Aldous, D. J.; Aldous, S. C. *J. Org. Chem.* **1990**, *55*, 4657; Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723; Williams, R. M.; Im, M.-N. *Tetrahedron Lett.* **1988**, *29*, 6075.
12 Agami, C.; Couty, F.; Daran, J.-C.; Prince, B.; Puchot, C. *Tetrahedron Lett.* **1990**, *31*, 2889.
13 Altenbach, H.-J.; Kottemnhahn, M.; Matthäus, M. S. P. Vogt, A. (Degussa AG) Ger. Offen. DE 19,533,617 (13. März 1997); *CA* **1997**, *126*, 264352f.
14 Ross, S.D., Finkelstein, M., Peterson, R.C., *J.Am.Chem.Soc.* **1964**, *86*, 2745; Shono, T. *Tetrahedron*, **1984**, *40*, 811.
15 Seebach, Renaud, P., *Angew.Chem.* **1986**, *98*, 836, *Angew.Chem.Int.Ed.Engl.* **1986**, *25*, 843; Mori, M., Kagechika, K., Sasai, H., Shibasaki, M., *Tetrahedron*, **1991**, *47*, 531; Schäfer,H.-J. *Topics Curr. Chem.* (Steckhan,E. ed.) **1990**, *152*, 91.
16 a) Shono, T., Matsumura, Y., Inoue, K., *J.Org.Chem.* **1983**, *48*, 1388; b) Ginzel, K.D., Brungs, P., Steckhan, E., *Tetrahedron* **1989**, *45*, 1691; c) Papadopoulos, A., Heyer, J., Ginzel, K.D., Steckhan, E., *Chem.Ber.* **1989**, *122*, 2159-64; d) Papadopoulos, A., Lewall, B., Steckhan, E., Knoch, F., Nieger, M., *Tetrahedron* **1991**, *47*, 563.
17 Steckhan, E.; Brungs, P.; Zietlow, A.; Stahl, A.; Lewall, B.; Kardassis, G.; Papadopoulos, A. in: *Modern Methodology in Organic Syntheis*, (T. Shono, ed), Kodansha, Tokyo, VCH, Weinheim 1994, pp. 323.
18 Brungs, P.; Danielmeier, K.; Jakobi, J.; Nothelfer, C.; Stahl, A.; Zietlow, A.; Steckhan, E. *J. Chim. Phys.* **1996**, *93*, 575.
19 Kardassis, G.; Brungs, P.; Nothhelfer, C.; Steckhan, E., following paper.
20 Hoopes, E. A.; Peltzer, E. T.; Bada, J. L. *J. Chromat. Sci.* **1978**, *16*, 556.
21 Beilstein 4, E IV, 2852.