Tetrahedron Vol. 47, No. 4/5, pp. 563-572, 1991
Printed in Great Britain

0040-4020/91 $3.00+.00

ANODIC OXIDATION OF *N*-ACYL AND *N*-ALKOXYCARBONYL DIPEPTIDE ESTERS AS A KEY STEP FOR THE FORMATION OF CHIRAL HETEROCYCLIC SYNTHETIC BUILDING BLOCKS

Apostolos Papadopoulos[a], Burhansha Lewall[a], Eberhard Steckhan[a*], Klaus-Dieter Ginzel[a], Falk Knoch[b], and Martin Nieger[c]

[a]Institut für Organische Chemie und Biochemie der Universität Bonn, Gerhard-Domagk-Str. 1, D-5300 Bonn 1, F.R.G.; [b]Institut für Anorganische Chemie II der Universität Erlangen-Nürnberg, Egerlandstraße 1, D-8520 Erlangen, F.R.G., [c]Institut für Anorganische Chemie der Universität Bonn, Gerhard-Domagk-Str. 1, D-5300 Bonn 1, F.R.G.

(*Received in USA* 15 *August* 1990)

Summary: The anodic oxidation of N-protected dipeptide esters using chloride as a redox catalyst can be performed regioselectively at the C-terminal amino acid. With methanol as solvent, glycine as the C-terminal, and L-valine or L-proline as N-terminal amino acid methoxylation at the glycine residue takes place. Deprotection of this product leads to the (3*S*,6*RS*)-6-methoxy-2,5-piperazinedione(3) which can be applied as a chiral cationic glycine equivalent. The exchange of the methoxy group by C-nucleophiles takes place with high *trans*-diastereoselectivity under steric control by the substituent in 3-position. With branched amino acids at the C-terminus of the dipeptide ester the anodic oxidation in acetonitrile/methanol (95:5) as solvent with tetraethylammonium chloride as supporting electrolyte and redox catalyst leads to methyl imidazolidin-4-one-2-carboxylates. The cyclization takes place via the intermediate formation of the *N*-acylimino ester of the C-terminal amino acid.

1. INTRODUCTION

Selective oxidation in the a-position of the N- or C-terminal amino acid residue in protected dipeptides is synthetically interesting. It leads to compounds which are potential chiral electrophilic amino acid equivalents. The introduction of nucleophiles into the oxidized α-position with stereochemical control by the second amino acid residue is therefore possible. Generally, the oxidation in α-position of the nitrogen of dipeptide derivatives leads to the formation of the synthetically important chiral amidoalkylation reagents[1].

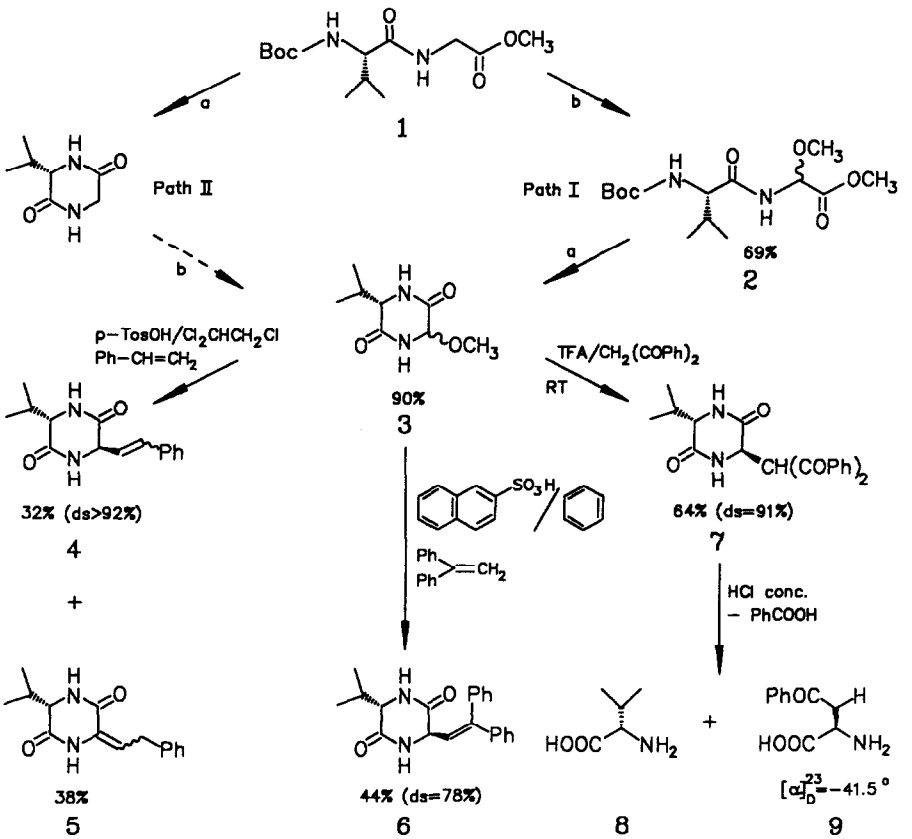
The anodic oxidation of N-protected amino acid esters has proven to be a very efficient way for the synthesis of cationic amino acid equivalents. The use of sodium chloride as a redox catalyst in methanol solution results in high yields of the α-methoxylation products[2]. Previously, we have shown that the indirect electrochemical oxidation using sodium chloride as redox catalyst is equally effective for the α-methoxylation of dipeptide esters. The regioselectivity can be influenced by the N-protecting group and the amino acid side-chains. In this way, total regioselectivity towards the oxidation of the C-terminal amino acid could be obtained[3]. We now report the application of this reaction to the synthesis of chiral heterocyclic compounds and their use as synthetic building blocks.

2. ELECTROCHEMICALLY GENERATED 3-SUBSTITUTED (3*S*,6*RS*)-6-METHOXY 2,5-PIPERAZINEDIONES - CHIRAL CATIONIC GLYCINE EQUIVALENTS FOR THE SYNTHESIS OF ENANTIOMERICALLY PURE α-AMINOACIDS

Presently, the most promising chiral cationic glycine equivalents for the synthesis of enantiomerically pure α-amino acids are the 2-chloro bislactimether of cyclo(L-Val-Gly-)[4], the chiral oxazinone introduced by Williams[5], and Harding's[1b] chiral carbamate of an α-hydroxyglycine ester. As an alternative, the achiral iminoesters, generated from protected glycine esters by NBS bromination followed by HBr elimination, may be acylated by chiral enamines leading to α-amino acids in high dia- and enantioselectivity[6].

We would like to propose an effective and simple alternative in which an electrochemical methoxylation is the key step. Ben-Ishai[1e,f] and ourselves[2] have shown that the methoxy group in N-protected α-methoxylated glycine methyl esters may be exchanged by nucleophiles like arenes, alkenes, and CH-acidic compounds under catalysis of protons or by enamines, silyl enol ethers, or enolacetates under Lewis acid catalysis[2]. Therefore we anticipated that it should be possible to exchange the methoxy group in (3*S*)-3-isopropyl-6-methoxy 2,5-piperazinedione(3), the methoxylated form of cyclo(L-Val-Gly-), in the same way. The stereochemical course of this exchange should be directed by the isopropyl side-chain of the L-valine residue. As illustrated in Scheme 1, it should be possible to synthesize enantiomerically pure new α-amino acids in a very simple way. Access to compound 3 should be possible either by the anodic oxidation, deprotection, and cyclization sequence (path I) or the reversed sequence (path II).

Scheme 1



a = HCOOH (deprotection, cyclization)
b = $-2e^{\ominus}$, $-2H^{\oplus}$, $+CH_3OH$(NaCl)

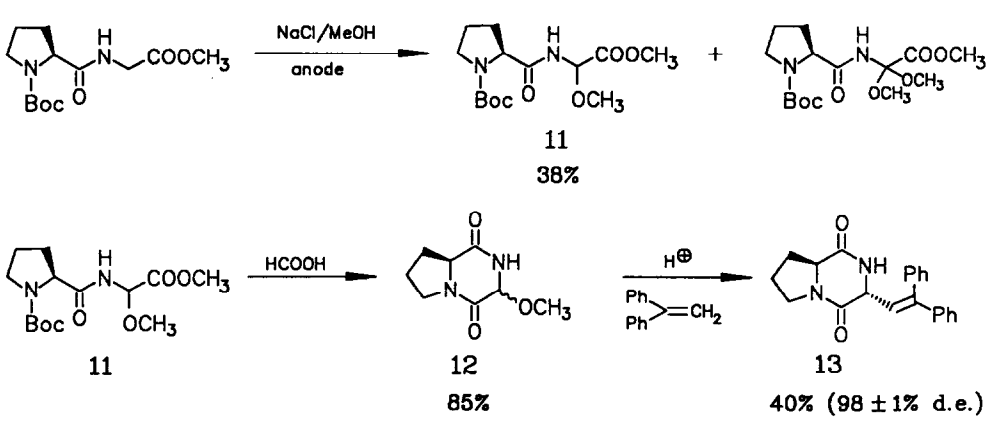
In our previous studies[3] we had developed a method for the regioselective indirect electrochemical oxidation of dipeptides in α-position to the N-terminus using NaCl as redox catalyst. Thus we were able to methoxylate *N*-Boc-L-Val-GlyOMe(1) at the glycine residue with total regioselectivity and in high yield. Electrolysis of 1 (3.5 mmol) in MeOH/$LiClO_4$(0.1 M) containing

NaCl at a Pt-anode until the consumption of 3 F/mol resulted in the formation of 69 % **2** (mixture of diastereoisomers in a ratio of 2:1). We were able to expand the electrolysis to a larger scale (30 mmol **1**) using a Sigraflex^R carbon foil. Thus **2** was received in 70 % yield. With compound **2** in hand, we followed path I in **scheme 1**. Compound **2** was deprotected and cyclized to **3** (mixture of diastereoisomers) by HCOOH (98 %) in isobutanol/toluene in 90% yield.

First examples of the methoxy group exchange by nucleophiles in **3** were performed. Thus, treatment of **3** as a mixture of diastereoisomers with dibenzoyl methane in trifluoroacetic acid gave **4** in a ratio of diastereoisomers of better than 10:1. Separation by flash chromatography gave the pure diastereoisomers in 57 % respectively 5.6 % yield. The major diastereomer may also be separated by simple recrystallisation from EtOH/H_2O (5:1). The diastereomeric excess was determined by ^1H NMR spectroscopy from the product before separation to give 82 +/- 3 % de. The introduction of olefins as nucleophiles was studied in the case of styrene and 1,1-diphenylethene. Treatment of **3** and styrene with *para*-toluene sulfonic acid in 1,1,2-trichloroethane gave the styryl substituted compound **5** as a mixture with **6**, formed by double bond shift. The formation of **5** occured with about 85% de. Introduction of 1,1-diphenylethene into **3** was obtained using β-naphthalene sulfonic acid in benzene to give compound **7** in 47.5% yield with 57% de. In all cases, the *trans*-configuration was favored.

Better diastereoselectivity was expected with L-proline instead of L-valine as chiral inductor. Thus, starting from *N*-Boc-L-Pro-GlyOMe (**10**) we first followed the cyclization, oxidation sequence (path II in **Scheme 1**). However, anodic methoxylation of cyclo(L-Pro-Gly-) in presence of NaCl was not regioselective and resulted in the formation of two mono- and one dimethoxylated 2,5-piperazinediones. Following path I, anodic methoxylation of the open-chain dipeptide ester **10** (3.5 mmol) in methanol/$LiClO_4$ (0.1 M) in presence of NaCl at a platinum anode until the consumption of 3 F/mol resulted in the formation of 32% of the desired product **11**, monomethoxylated at the glycine residue. As a side-reaction, dimethoxylation at the glycine residue was observed. Larger scale electrolysis of 28 mmol of **10** at a Sigraflex^R carbon foil anode gave 38% **11** together with the dimethoxylated product (**Scheme 2**). Currently, we are investigating an improved access to **11** starting from the *N*-Boc protected dipeptide of L-proline and dimethyl aminomalonate. After the formation of the halfester anodic decarboxylation (Hofer-Moest reaction) should selectively lead to **11**.

Scheme 2



As illustrated in **Scheme 2**, the separated **11** was deprotected and cyclized to **12** by HCOOH (98%) in isobutanol/toluene in 85%

yield. To compare the diastereoselectivity of the methoxy group exchange in **3** and **12**, **12** was refluxed with 1,1-diphenylethene and β-naphthalene sulfonic acid in benzene to give **13** in 40% yield with 98% de.

The predominant formation of the *trans*-configuration was confirmed by a 200 MHz ^{1}H NOE experiment. The diastereoselectivity was determined by integration of the ^{1}H NMR signals of the methine ring protons. Thus, the proline residue in **12** leads to an unexpected high diastereoselectivity in the nucleophilic methoxy group exchange by 1,1-diphenylethene as compared with **3** (98% vs. 57% de = 99% vs. 78.5% ds). **12** is also more promising as a chiral cationic glycine equivalent because the proline residue results in a much better solubility in organic solvents making the methoxy group exchange under Lewis acid catalysis possible[7]. Further applications of **12** for amidoalkylation reactions are under way.

As an example, the cleavage of a 6-substituted 2,5-piperazinedione was performed in the case of **4** after separating the two diastereoisomers. Treatment of **4** with 6 N HCl for 20 h at 90°C resulted in the formation of L-valine with correct specific rotation together with D-2-amino-4-oxo-4-phenylbutanoic acid (**9**) and benzoic acid. The formation of benzoic acid and **9** is due to the acidic ketone cleavage of the 1,3-dicarbonyl compound. The L-form of **9** is known. It was synthesized via the achiral *N*-acetyl iminoester and the trimethylsilyl enol ether of acetophenone followed by enzymatic deprotection with hog renal acylase[6]. By comparison of the specific rotation of compound **9** being $[\alpha]_D^{23} = -41.5^\circ$ (c = 0.105 in 6 N HCl) with the L-derivative ($[\alpha]_D^{20} = +42.9^\circ$)[6] we could prove that **9** is enantiomerically pure and that the predominating diastereoisomer of **4** has the *trans*-configuration.

3. ELECTROCHEMICAL GENERATION OF METHYL IMIDAZOLIDIN-4-ONE-2-CARBOXYLATES BY INDIRECT ELECTROCHEMICAL DIPEPTIDE CYCLIZATION

Starting from dipeptides, imidazolidin-4-ones without a 2-carboxy group may either be obtained by diastereoselective cyclization of a dipeptide azomethine[8], by cylization of an α-amino acid amide with an aldehyde[9], or by anodic decarboxylation of an unprotected dipeptide followed by intramolecular trapping of the intermediate *N*-acyliminium ion[10]. To our knowledge, the formation of imidazolidin-4-ones with a carboxy group at the C-2 has only been reported reacting 2-benzylidene-4-methyl-5(2*H*) oxazolone with α-amino acid derivatives which are cyclized under alkaline conditions[11].

Previously, we had shown[3], that during the anodic oxidation of N-protected dipeptide esters **14** in methanol using NaCl as redox catalyst not only the expected methoxylated dipeptide derivatives were formed but in some cases also methyl imidazolidin-4-on-2-carboxylates **15** could be isolated as side-products. These products, obviously, were generated by intramolecular attack of the nitrogen of the N-terminal amino acid onto the intermediate *N*-acylimino ester of the C-terminal amino acid. We were now able to form **15** selectively in one step and mostly good yields. Thus, **14** is electrochemically oxidized in an undivided cell using acetonitrile/methanol (95:5) as solvent mixture and tetraethylammonium chloride as redox catalyst as illustrated in **Scheme 3**. For good results, the C-terminal amino acid has to carry a side-chain (see **Table**).

In most cases satisfying yields could be obtained. Only, if carbamate protecting groups are combined with dipeptides containing alkyl side-chains also in the N-terminal amino acid, the yields are low or the cyclization does not occur at all. The diastereoselectivity of the cyclization is relatively low (between 2.6:1 and 1.5:1). For the two regioisomeric compounds **15c** and **15d** the relative configuration was determined by x-ray crystallography. While in compound **14c** the *cis*-configuration of methyl and phenyl group is

favored (*trans*-**14c**), in compound **14d** their prefered trans-configuration is observed (*cis*-**14d**). Further electrochemical and chemical transformations of the methyl imidazolidin-4-one-2-carboxylates and their application as synthetic building blocks are currently under way[10].

Scheme 3

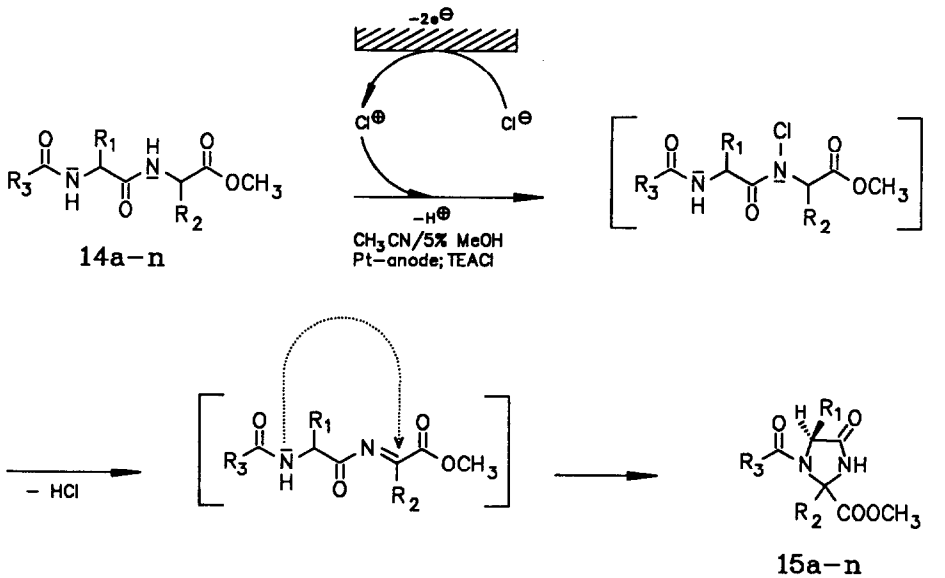


Table: Results of the chloride mediated electrooxidative cyclization of N-protected dipeptide methyl esters **14a-n** acetonitrile/methanol (95:5) using tetraethylammonium chloride as redox catalyst[a]

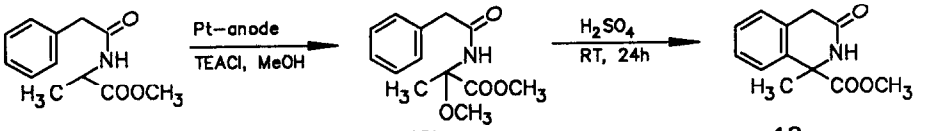
	Starting Material 14			Product 15	Ratio of
	R^3	R^1	R^2	[% yield][b]	Diastereo-isomers
a:	Ph	H	CH_3	79	---
b:	Ph	CH_3	CH_3	84	1.5:1
c:	Ph	Ph	CH_3	67	1.6:1[c]
d:	Ph	CH_3	Ph	70	2.0:1[c]
e:	$PhCH_2$	H	CH_3	48	---
f:	$PhCH_2$	CH_3	CH_3	42	1.5:1
g:	$(CH_3)_3C$-O	CH_3	Ph	70	1.7:1
h:	$(CH_3)_3C$-O	H	CH_3	45	---
i:	$(CH_3)_3C$-O	$CH(CH_3)_2$	CH_3	13	2.6:1
k:	$(CH_3)_3C$-O	CH_3	CH_3	--	---
l:	MeO	H	CH_3	60	---
m:	MeO	CH_3	CH_3	--	---
n:	MeO	CH_3	Ph	61	1.5:1

[a] Undivided cell; anode material: Pt-foil; catode material: Pt-wire; electrolyte: 50 mL CH_3CN/MeOH (95:5) containing 0.5 to 1.5g TEACl; yields determined after 3-4 F/mol by liquid chromatography on flash silica gel with ethyl acetate, n-heptane, or cyclohexane, methanol mixtures as eluents. [b] Material yield. [c] In the case of compounds **14c** and **14d** the diastereoisomers could be separated and the configuration be determined by x-ray crystallography indicating that *trans*-**14c** and *cis*-**14d** are favored.

In a similar way, we tried to perform the electrochemical cyclization of a *N*-phenylacetyl amino acid ester via its intermediate imino ester. Under nucleophilic attack of the phenylring of the protecting group we anticipated the formation of a tetrahydro isoquinoline derivative. The indirect electrolysis of *N*-phenylacetyl alanine methyl ester (**16**) with tetraethylammonium chloride

as redox catalyst in acetonitrile/methanol (95:5), however, did not yield the desired cyclization product. Instead, small amounts of *N*-phenylacetyl α-methoxyalanine methyl ester (**17**) could be obtained. If the electrolysis was performed in methanol at a platinum anode, **17** could be obtained in 62% yield. Cyclization to the desired compound **18** was possible with sulfuric acid in 40% yield in a separate step (**Scheme 4**). Compared with results of Ben-Ishai[1f], the yield of the cyclization is relatively good.

Scheme 4



16 **17** 62% **18** 40%

EXPERIMENTAL

All compounds are identified by microanalysis or high resolution mass spectrometry. ^1H NMR-, ^{13}C NMR-, IR-, and mass spectrometry. ^1H NMR spectra: Bruker WH 90 and AC 200 (d values, TMS internal standard). - IR spectra: Pye Unicam SP 1100. - Mass spectra: A.E.I. MS-9, MS-30, and MS-50. - Melting points (uncorrected): Kofler micro heating plate (Reichert). - Microanalyses: Perkin-Elmer CH-Analyzer 240 and Haraeus CHNO-Rapid. - TLC Analyses: TLC alumina sheets, silica gel 60 F_{254} (Merck, Riedl-de Haen) and Chiralplate (Macherey-Nagel). Preparative LC separations: Silica gel for flash chromatography 30-60 um (Baker) or 36-62 mesh (Woelm).

Ethyl acetate (Merck) was dried over K_2CO_3 and Na_2SO_4 and subsequently distilled from P_2O_5. Cyclohexane (Merck), triethylamine (Merck), n-heptane (BASF), and THF (Baker, p.a.) were purified by distillation. Methanol (Merck, Aldrich, p.a., stored over 4 A molecular sieve), acetonitrile (Merck, Aldrich, p.a., stored over 4 A molecular sieve), glycine (Janssen), glycyl glycine (Janssen), L-alanine (Janssen, DEGUSSA), L-valine (DEGUSSA), L-proline (DEGUSSA), L-(+)-a-phenylglycine (Fluka), glycine methylester hydrochloride (Merck), L-valine methylester hydrochloride (Merck), 2-(*tert*-butyl-oxycarbonyloximino)-2-phenylacetonitrile (BOC-ON, Janssen), 1-Hydroxybenzotriazol (1-HOBT, Janssen), N,N'-dicyclohexylcarbodiimid (DCC, Janssen), benzoyl chloride (Janssen), phenylacetyl chloride (Aldrich), diazald (Janssen), carbitol (Janssen), dibenzoyl methane (Merck), 1,1-diphenylethene (Merck), styrene (Aldrich), p-toluene sulfonic acid (Janssen), b-naphthalene sulfonic acid (Janssen), methyl chloroformate (Aldrich), hydrazine hydrate (99%, Janssen) were used as obtained.

N-Acyl- and *N*-alkoxycarbonyl protected dipeptide esters were prepared by standard procedures using the the DCC/1-HOBT method[12] starting from the N-protected amino acids[13] and the amino acid methyl ester hydrochlorides (**1, 10, 14a-n**).

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 freuqency conversion.

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

Procedure for the Methoxylation of N-Boc Dipeptide esters **1** and **10** in Methanol in the Presence of NaCl:
a) Small scale electrolysis: 3.4 (**1**), respectively 3.5 mmol (**10**) of the starting materials were dissolved in 35 mL MeOH (0.1 M $LiClO_4$) containing 250 mg NaCl and electrolized in cell 1 at constant current (200 mA) until consumption of 3 F/mol. For workup, the solvent was evaporated at 40°C. After addition of 40 mL of water to the residual oil, the organic phase was extracted with 4x80 mL of chloroform, dried with $MgSO_4$, filtered, and the solvent evaporated. The products were separated by flash chromatography on silica gel with ethyl acetate/cyclohexane mixtures as eluents. **2** and **11** were obtained in 69.1% (2.38 mmol), respectively 32% (1.1 mmol) yield.
b) Large scale electrolysis: 27.7 (**1**), respectively 28 mmol (**10**) of the starting materials were dissolved in 350 mL MeOH (0.1 M $LiClO_4$) containing 1750 mg NaCl and electrolyzed in cell 2 at constant current (400 mA) until consumption of 4.5, respectively 4.0 F/mol. After the usual workup, **2** and **11** were obtained in 70% (19.4 mmol), respectively 38% (10.6 mmol) yield.

Procedure for the Synthesis of the 6-Methoxy-2,5-piperazinediones **3** and **12**:
Compounds **2** (2.4 mmol) or **11** (0.5 mmol) were dissolved in 65 mL, respectively 40 mL of formic acid (95%). After standing for 2 h at room temperature, the formic acid was evaporated in vacuo at 30°C. The residual formate was dissolved in an

isobutanol/toluene mixture (3:1, respectively 4:1) and refluxed for 3 h. The formic acid was removed by azeotropic distillation. After evaporation of the remaining isobutanol and toluene, the cyclic dipeptides crystallized. Separation of the diastereomers was possible by flash chromatography on silica gel. **3** and **12** were obtained in 87% (*trans*-3*S*,6*R*:*cis*-3*S*,6*S* = 2:1), respectively 85% (*trans*-3*S*,6*R*:*cis*-3*S*,6*S* = 1:1). The relative configuration was determined by NOE experiments. For the *cis*-diastereoisomer ^{1}H NMR signals for H-3, respectively H-6 were enhanced, if the signals for H-6, respectively H-3 were saturated. The same experiment did not show any enhancement for the corresponding signals of the *trans*-diastereoisomer.

Substitution of the Methoxy Group in **3** and **12** by C-Nucleophiles:

a) Dibenzoyl methane as nucleophile: 1000 mg (5.4 mmol) of **3** and 1500 mg (6.4 mmol) of dibenzoyl methane were dissolved in mL of trifluoroacetic acid and stirred for 3 h at 0°C and 48 h at room temperature. The trifluoroacetic acid was evaporated and t residual mixture separated by flash chromatography with $CHCl_3$/MeOH (250:1, 160:1, 80:1) as eluents. 1280 mg (3.4 mmol; 64 of **4** was obtained in an *trans*/*cis* ratio of better 91:9 (determined by ^{1}H NMR measurement before separation).

b) Styrene as nucleophile: 50 mg (0.27 mmol) of **3**, 0.5 mL (4.0 mmol) of styrene, and 20 mg of p-toluene sulfonic acid were dissolved in 5 mL of 1,1,2-trichloroethane. The mixture was refluxed for 18 h, the solvent evaporated, and the mixture separated by flash chromatography with ethyl acetate/cyclohexane (6:4) as eluent. 22 mg (0.085 mmol; 32%) of **5** was obtained in an *trans*/*cis* ratio of better 92.5:7.5 (determined by ^{1}H NMR measurement before separation).

c) 1,1-Diphenylethene as nucleophile: 811 mg (4.0 mmol) of **3**, 3300 mg (18 mmol) of 1,1-diphenylethene, and 120 mg (0.5 mmol) b-naphthalene sulfonic acid were dissolved in 30 mL benzene and refluxed for 18 h. The solvent was evaporated, the residue dissolved in 30 mL dichloromethane, the organic phase washed with 50 mL aqueous sodium carbonate (200 mg) solution, and dried with $MgSO_4$. After filtration and evaporation of the solvent, purification was performed by chromatography on silica gel with ethyl acetate/cyclohexane (9:1) as eluent. 640 mg (1.9 mmol; 47.5%) of **7** was obtained in an *trans*/*cis* ratio of 78.5:21.5 (determined by ^{1}H NMR measurements before separation).

Using the same procedure, 120 mg (0.66 mmol) of **12**, 300 mg (1.7 mmol) of 1,1-diphenylethene, and 10 mg (0.04 mmol) of b-naphthalene sulfonic acid were refluxed in 30 mL of benzene. After flash chromatography on silica gel with ethyl acetate/cyclohexane (6:4) as eluent 88 mg (0.27 mmol; 41%) of **13** was obtained in an *trans*/*cis* ratio of 98.5:1.5.

The configuration of the products was determined by NOE experiments as described for **3** and **12**, and by hydrolysis of **4** (40 mL 6*N* HCl, 20 h, 90°C, sovirel glass reactor under elevated pressure) to give the amino acid (2*R*)-2-amino-4-oxo-4-phenylbutyric acid (**9**). It's specific rotation of $[a]_D^{23}$ = -41.5° (c = 1 in 6*N* HCl) compared well with the reported one for the corresponding (2*S*)-enantiomer of $[a]_D^{20}$ = +42.9°[6]. Besides **9**, enantiomerically pure L-valine was obtained.

General Procedure for the Synthesis of Methyl Imidazolidin-4-one-2-carboxylates by Indirect Electrochemical Dipeptide Cyclization:

Between 3 and 7 mmol of the N-protected dipeptide esters **14a-n** and 500 to 1500 mg tetraethylammonium chloride were dissolved in acetonitrile/methanol (95:5) and electrolyzed in cell 1 at a constant current (120 mA) until the consumption of 3 to 4 F/mol. Workup was identical with that for compounds **2** and **11**. The products were separated by flash chromatography on silica gel with ethyl acetate/n-heptane or cyclohexane/EtOH mixtures as eluents.

Selected Spectroscopic Data

Spectroscopic data of **2** and **3** are described elsewhere[3].

N-*tert*-Butoxycarbonyl-L-prolyl-D,L-a-methoxyglycine Methyl Ester (N-Boc-L-Pro-D,L-Gly(OMe)OMe) (**11**). Oil (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); ^{1}H NMR ($CDCL_3$, 90 MHz): 1.75-2.3 (m, 6H, 2 CH_3), 3.3 (s, 3H, OCH_3), 3.4 (t, 2H, CH_2 perturbed by methoxy signal), 3.73 (s, 3H, OCH_3), 4.24 (dd, broad, 1H, CH), 5.46 (d, *J* = 9 Hz, 1H, CH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 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; *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).

(3*S*,6*RS*)-6-Methoxy-1,3-trimethylene-2,5-piperazinedione [cyclo(L-Pro-Gly(OMe)-] (**12**): 2 Diastereoisomers in a ratio of 1:1 were separated by flash chromatography [ethyl acetate/acetone/H_2O (18:6:1)]. (3*S*,6*R*)-Enantiomer (*trans*-**12**): R_f = 0.4; oil (Found: M^+, 184.0847. $C_8H_{12}N_2O_3$ requires *M*, 184.0848); ^{1}H NMR ($CDCL_3$, 90 MHz): 1.6-2.5 (m, 4H, 2 CH_2), 3.3 (s, 3H, OCH_3), 3.6 (m, 2H, CH_2), 4.1 (dd, *J* = 9 Hz, 8 Hz, 1H, CH), 4.6 (d, *J* = 4.6 Hz, 1H, CH),7.5 (d, broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 22.43 (CH_2), 28.35 (CH_2), 45.41 (CH_2), 55.96 (OCH_3), 58.22 (CH), 84.2 (CH), 162.26 (CO), 171.97 (CO) ppm; *m*/*z* = 184 (M^+, 12.8%), 154 (34), 152 (9), 125 (9), 70 (93), 69 (27), 68 (13), 60 (100). (3*S*,6*S*)-Enantiomer (*cis*-**12**): R_f = 0.31; oil (Found: C, 51.76; H, 6.47; N, 14.89. $C_8H_{12}N_2O_3$ requires C, 52.16; H, 6.56; N, 15.21); ^{1}H NMR ($CDCl_3$, 90 MHz): 1.68-2.4 (m, broad, 4H, 2CH_2), 3.46 (s, 3H, OCH_3), 3.57 (perturbed by methoxy signal, 2H, CH_2), 4.01 (dd, *J* = 9.0 Hz, 7.0 Hz, 1H, CH), 5.07 (s, broad, 1H, CH), 7.08 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 22.1 (CH_2), 28.54 (CH_2), 44.99 (CH_2), 55.34 (OCH_3) 59.23 (CH), 81.82 (CH), 162.38 (CO), 168.18 (CO) ppm.

(3*S*,6*RS*)-6-Dibenzoylmethyl-3-isopropyl-2,5-piperazinedione (**4**): ^{13}C NMR ($CDCl_3$/DMSO, 200 MHz): 16.65, 18.3 (2 CH_3), 31.5 (CH), 58.2 (CH), 59.4 (CH), 128.3 (2 arom. CH), 133.2, 133.4 (2 arom. CH), 136.1, 136.29 (2 arom. C), 166.3, 167.2 (2 CO), 194.3, 194.9 (2 CO) ppm; *m*/*z* = 378 (M^+, 0.97%), 274 (8), 273 (45), 225 (29), 224 (36), 223 (38), 154 (11), 147 (22), 105 (100), 77 (50), 72 (13). (3*S*,6*R*)-Enantiomer (*trans*-**4**): R_f = 0.2 [$CHCl_3$/MeOH (160:1)]; m.p. 229°C [EtOH/H_2O (5:1)] (Found: C,

69.73; H, 5.52; N, 7.50. $C_{22}H_{22}N_2O_4$ requires C, 69.83; H, 5.85; N, 7.40; Found: M^+, 378.1595. $C_{22}H_{22}N_2O_4$ requires *M*, 378.1579); $[\alpha]_D^{23}$ = -25.3° [c = 1, CH_2Cl_2/CF_3COOH (10:1); ^1H NMR ($CDCl_3$/DMSO, 200 MHz): 0.83 (d, *J* = 6.6 Hz, 3H, CH_3), 0.95 (d, *J* = 6.6 Hz, 3H, CH_3), 2.1-2.3 (m, 1H, CH), 3.82 (d, broad, 1H, CH), 4.68 (d, *J* = 5.1 Hz, 1H, CH), 6.14 (d, *J* = 5.1 Hz, 1H, CH), 7.42-8.2 (m, 12H, 10 arom. H, 2NH) ppm. (3*S*,6*S*)-Enantiomer (*cis*-4): R_f = 0.25 [$CHCl_3$/MeOH (80:1); m.p. 232°C [EtOH/H_2O (5:1)] (Found: C, 69.70; H, 5.90; N, 7.49. $C_{22}H_{22}N_2O_4$ requires C, 69.83; H, 5.85; N, 7.40); $[\alpha]_D^{23}$ = -113.6° [c = 1, CH_2Cl_2/CF_3COOH (10:1)]; ^1H NMR ($CDCl_3$/DMSO, 200 MHz): 0.75 (d, *J* = 6.6 Hz, 3H, CH_3), 0.92 (d, *J* = 6.6 Hz, 3H, CH_3), 2.05-2.25 (m, 1H, CH), 3.75 (dt, *J* = 3 Hz, 1.3 Hz, 1H, CH), 4.89 (dt, *J* = 5.2 Hz, 1.3 Hz, 1H, CH), 6.09 (d, *J* = 5.2 Hz, 1H, CH), 7.4-8.1 (m, 12H, 10 arom. CH, 2NH) ppm.

(3*S*,6*R*)-3-Isopropyl-6-(1-phenylethenyl)-2,5-piperazinedione (*trans*-5): R_f = 0.25 [ethyl acetate/cyclohexane (3:2)]; m.p. 110-115°C (EtOH/H_2O) (Found: M^+, 258.1377. $C_{15}H_{18}N_2O_2$ requires *M*, 258.1372); ^1H NMR ($CDCl_3/CF_3COOH$, 200 MHz): 1.06 (d, *J* = 7.6 Hz, 3H, CH_3), 1.16 (d, *J* = 7.6 Hz, 3H, CH_3), 2.4-2.65 (m, 1H, CH), 4.20-4.28 (m, 1H, CH), 5.0 (d, broad, *J* = 8 Hz, 1H, CH), 6.2 (dd, *J* = 8 Hz, 15.6 Hz, 1H, CH), 6.78 (d, *J* = 15.6 Hz, 1H, CH), 7.3-7.45 (m, 5H, arom. H), ppm; *m/z* = 259 (M^+ +1, 16%), 258 (M^+, 44), 215 (36), 187 (13), 177 (43), 163 (19), 156 (83), 154 (19), 130 (11), 128 (20), 127 (15), 121 (70), 113 (35), 107 (100), 91 (27).

(3*S*,6*RS*)-3-Isopropyl-6-(1,1-diphenylethenyl)-2,5-piperazinedione (7): R_f = 0.3 [ethyl acetate/cyclohexane (9:1)]; m.p. 294°-298°C (EtOH/H_2O) (Found: M^+, 334.164. $C_{21}H_{22}N_2O_2$ requires M, 334.1681); *m/z*: 334 (M^+, 100%), 291 (41), 263 (27), 248 (20), 235 (11), 220 (9), 208 (32), 207 (31), 206 (80), 192 (38), 191 (60), 179 (21), 178 (27), 165 (44), 130 (41), 128 (20), 103 (28), 91 (30), 77 (38), 72 (80), 57 (40), 55 (38). (3S,6R)-Enantiomer (trans-7): ^1H NMR ($CDCl_3$/DMSO, 200 MHz): 0.78 (d, *J* = 6.3 Hz, 3H, CH_3), 0.9 (d, *J* = 6.3 Hz, 3H, CH_3), 2.1 (m, broad, 1H, CH), 3.64 (broad, 1H, CH), 4.39 (d, *J* = 9.6 Hz, 1H, CH, H6), 5.9 (d, *J* = 9.6 Hz, 1H, olefin.-CH), 7.08-7.45 (m, 10H, arom. H), 8.25 (d, broad, 1H, NH) ppm; for the *cis*-enantiomer (*cis*-7) the signal for H6 is observed at 4.45 and that for the olefinic H at 5.8 ppm.

(3*S*,6*R*)-6-(1,1-Diphenylethenyl)-1,3-trimethylene-2,5-piperazinedione (*trans*-13): R_f = 0.2 [ethyl acetate/cyclohexane (3:2)]; oil (Found: M^+, 332.1550. $C_{21}H_{20}N_2O_2$ requires *M*, 332.1525); ^1H NMR ($CDCl_3$, 200 MHz): 1.8-2.5 (m, 4H, s CH_2), 3.45-3.71 (m, 2H, CH_2), 4.23 (dd, *J* = 10 Hz, 7.5 Hz, 1H, CH), 4.64 (dd, *J* = 12 Hz, 5.4 Hz, 1H, CH), 5.96 (d, *J* = 12 Hz, 1H, CH), 6.46 (d, *J* = 5.4 Hz, 1H, NH), 7.12-7.48 (m, 10H, arom. H) ppm; ^{13}C NMR ($CDCl_3$, 200 MHz): 22.03 (CH_2), 22.9 (CH_2), 45.6 (CH_2), 56.47 (CH), 58.09 (CH), 121.58 (CH), 127.5, 127.7, 127.8, 127.9, 128.0, 128.1, 128.2, 128.3, 129.6, 130.2 (10 arom. CH), 141.24 (arom. C), 164.4 (CO), 169.4 (CO) ppm; *m/z* = 333 (M^+ +1, 19%), 323 (M^+, 17), 248 (6), 208 (19), 207 (21), 206 (85), 192 (27), 191 (78), 165 (11), 152 (28), 124 (11), 77 (14), 70 (100).

Spectroscopic data of compounds **15a-i** and **15l,n** are all very similar. Therefore, the data of compunds **15c** and **15d** are given as typical examples.

Methyl 1-Benzoyl-2-methyl-t-5-phenyl-imidazolidin-4-one-r-2-carboxylate (*trans*-15c):

0.41 g (42%) after separation of the diastereomers by flash chromatography on silica gel with n-heptane/ethyl acetate (4:3) as eluent; m.p. 232-234°C (Found: C, 67.35; H, 5.34; N, 8.24. $C_{19}H_{18}N_2O_4$ requires C, 67.44; H, 5.36; N, 8.27); ^1H NMR ($CDCl_3$, 90 MHz): 2.11 (s, 3H, CH_3), 3.82 (s, 3H, CH_3O), 5.13 (s, 1H, CH), 7.42 (s, 1H, NH), 7.00-7.22 (m, 10H, arom. H) ppm; ^{13}C NMR ($CDCl_3$/DMSO, 90 MHz): 23.04 (CH_3), 52.78 (OCH_3), 64.37 (CH), 75.67 (C), 125.5, 126.4, 128.7, 127.6, 129.1 (10 arom. CH), 135.29 (arom. C), 137.04 (arom. C), 169.4 (CO), 169.8 (CO), 170.64 (CO) ppm; *m/z*: 339 (M^+ +1, 0.16%), 279 (0.4%), 106 (9), 105 (100), 77 (30), 42 (5). X-ray crystallographic structure determination of *trans*-**15c**: Colorless single crystals suitable for the collection of X-ray diffraction data were obtained by recrystallization from ethanol/n-heptane. A crystal (dimension 0.40x0.20x0.10 mm) was selected for data collection and mounted on a Nicolet R3m/V automated fourcircle diffractometer. The crystal was found to be monoclinic, and unit cell parameters and the orientation matrix were obtained. Data collection was carried out using ω-scan technique with 3.0-15°/min.: space group $P2_1/c$; a = 1254.2(8) pm; b = 1109.3(10) pm; c = 1341.4(5) pm; β = 110.86°(4); V = 1744(2)x10^6 pm^3; $d_{calcd.}$ = 1.29 g/cm^3 (Z = 4); radiation Mo-K_α; graphite monochromator; 2 Θ limits $4° < 2\Theta < 54°$; total reflections scanned 5694; 3930 unique structure factors, 2354 "observed" reflections with $F > 6\sigma$ (F); R = 0.087; R_w = 0.058; 269 refined parameters. The structure was solved by SHELXTL-PLUS, a direct-methods program. The non-hydrogen atoms were refined anisotropically. The position of the phenyl hydrogens were calculated for ideal geometry and fixed during refinement. The hydrogens of the methyl groups were calculated for an ideal tetraeder and rotated around the central C-atom during refinement. Hydrogen atoms with common isotropic temperature factor. Further details of the crystal structure analysis are available from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen, on quoting the depository number CSD-320141, the name of the authors, and the literature citation.

Methyl 1-Benzoyl-2-methyl-c-5-phenyl-imidazolidin-4-one-r-2-carboxylate (*cis*-15c):

0.26 g (26%) after separation of the diastereomers by flash chromatography on silica gel with n-heptane/ethyl acetate (4:3) as eluent; m.p. 185°C (Found: C, 67.30; H, 5.73; N, 8.05. $C_{19}H_{18}N_2O_4$ requires C, 67.44; H, 5.36; N, 8.27); ^1H NMR ($CDCl_3$, 90 MHz): 1.89 (s, 3H, CH_3), 3.77 (s, 3H, CH_3O), 5.17 (s, 1H, CH), 8.0 (s, 1H, NH), 7.06 (m, 10H, arom. H) ppm; ^{13}C NMR ($CDCl_3$/DMSO, 90 MHz): 23.14 (CH_3), 53.21 (OCH_3), 64.51 (CH), 75.74 (C), 126.23 128.1, 128.56, 128.64, 130.1 (10 arom. CH), 135.52 (arom. C), 135.94 (arom. C), 169.2 (CO), 169.7 (CO), 170.93 (CO) ppm; *m/z*: 339 (M^+ +1, 0.24%), 279 (0.4), 106 (16), 105 (100), 77 (53), 42 (6).

Methyl 1-Benzoyl-c-5-methyl-2-phenyl-imidazolidin-4-one-r-2-carboxylate (*cis*-15d):

0.73 g (71%) of the mixture of diastereomers could be obtained by flash chromatography on silica gel with n-heptane/ethanol (8:1 and 6:1) as eluent (cis:trans = 2:1). The diastereomers could be separated by HPLC (ethyl acetate/n-heptane = 5:8). m.p. 220°C

(Found: C, 67.33; H, 5.32; N, 8.18. $C_{19}H_{18}N_2O_4$ requires C, 67.44; H, 5.36; N, 8.24); ^{1}H NMR ($CDCl_3$, 90 MHz): 1.2 (d, J = 7 Hz, 3H, CH_3), 3.86 (s, 3H, CH_3O), 4.57 (q, J = 7 Hz, 1H, CH), 7.5 (broad, 1H, NH), 7.37-7.48 (m, 10H, arom. H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 17.52 (CH_3), 52.83 (OCH_3), 56.16 (CH), 78.85 (C), 126.5, 127.3, 127.7, 128.4, 130.7 (10 arom. CH), 135.08 (arom. C), 136.83 (arom. C), 168.5 (CO), 168.6 (CO), 172.34 (CO) ppm; *m/z*: 279 (0.3%), 106 (8), 105 (100), 77 (34), 42 (1).

Methyl 1-Benzoyl-t-5-methyl-2-phenyl-imidazolidin-4-one-r-2-carboxylate (*trans*-15d):

0.73 g (71%) of the mixture of diastereomers could be obtained by flash chromatography on silica gel with n-heptane/ethanol (8:1 and 6:1) as eluent (cis:trans = 2:1). The diastereomers could be separated by HPLC (ethyl acetate/n-heptane = 5:8). m.p. 199-200°C (Found: C, 67.43; H, 5.42; N, 8.50. $C_{19}H_{18}N_2O_4$ requires C, 67.44; H, 5.36; N, 8.24); ^{1}H NMR ($CDCl_3$, 90 MHz): 1.06 (d, J = 7 Hz, 3H, CH_3), 3.77 (s, 3H, CH_3O), 4.35 (q, J = 7 Hz, 1H, CH), 7.8 (s, 1H, NH), 7.33 (m, 10H, arom. H) ppm; ^{13}C NMR ($CDCl_3$, 90 MHz): 18.87 (CH_3), 53.63 (OCH_3), 55.96 (CH), 79.25 (C), 126.9, 127.5, 128.0, 128.7, 128.9, 130.1 (10 arom CH), 135.56 (arom. C), 137.14 (arom. C), 168.8 (CO), 169.8 (CO), 173.17 (CO) ppm; *m/z*: 339 (M^++1, 0.23%), 279 (0.3%), 106 (8), 105 (100), 77 (30), 51(4). X-ray crystallographic structure determination of *trans*-**15d**: Colorless single crystals suitable for the collection of X-ray diffraction data were obtained by recrystallization from ethanol/n-heptane. A crystal (dimension 0.3x0.6x0.6 mm) was selected for data collection and mounted on a Nicolet R3m/V automated fourcircle diffractometer. The crystal was found to be monoclinic, and unit cell parameters and the orientation matrix were obtained from 24 reflections in the range $20^o<2\theta<25^o$. Data collection was carried out using ω-scan technique with 4.0-29.3°/min.: space group $P2_1/c$; a=1284.6(4) pm; b=970.3(3) pm; c=1405.9(5) pm;β=98.04°(3); V=1735(1)x10^6 pm^3; $d_{calcd.}$=1.30 g/cm^3 (Z=4); radiation Mo-K_α; graphite monochromator; 2 θ limits $3^o<2\theta<50^o$; total reflections scanned 3301; 3056 unique reflections, 2208 "observed" reflections with $F>4\sigma$ (F); R=0.055; R_w=0.058; 230 refined parameters. The structure was solved by direct methods (SHELXTL). The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were localized by difference electron density determination and refined using a riding model [U(H) = 1.2U_{eq}(C)]. The nitrogen H was refined freely. List of positional and anisotropic thermal parameters of non-hydrogen atoms, positional and thermal parameters of hydrogen atoms, bond distances, and bond angles are available from Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-7514 Eggenstein-Leopoldshafen, on quoting the depository number CSD-54788, the name of the authors, and the literature citation.

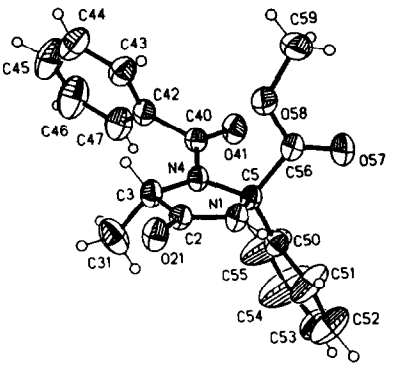


Figure : Molecular structure of *trans*-**15d**

Acknowledgements: Financial support by the Deutsche Forschungsgemeinschaft,the Fonds der Chemischen Industrie,and the BASF Aktiengesellschat, the supply of chemicals by the DEGUSSA AG, and a graduation fellowship (K.D.G.) by the state of Nordrhein Westfalen are gratefully acknowledged.

REFERENCES

1. For leading references: a) Zaugg, H.E. *Synthesis* **1984**, *85*, 181; b) Harding, K.E.; Davis, C.S. *Tetrahedron Lett.* **1988**, *29*, 1891; c) O'Donnell, M.J.; Bennett, W.D.; Polt, R.L. *Tetrahedron Lett.* **1985**, *26*, 695; d) O'Donnel, M.J.; Bennett, W.D. *Tetrahedron* **1988**, *44*, 5389; e) Ben-Ishai, D.; Altmann, J.; Bernstein, Z.; Peled, N. *Tetrahedron* **1978**, *34*, 467-473; f) Ben-Ishai, D.; Sataty, I.; Peled, N.; Goldshare, R. *Tetrahedron* **1987**, *43*, 439-450; g) Mooiweer, H.-H.; Ettema, K.W.A.; Hiemstra, H.; Speckamp, W.N. *Tetrahedron* **1990**, *46*, 2991.
2. Ginzel, K.-D.; Brungs, P.; Steckhan, E. *Tetrahedron* **1989**, *45*, 1691; Shono, T.; Matsumura, Y.; Inoue, K. *J.Org.Chem.* **1983**, *48*, 1388; *J.Chem.Soc., Chem.Commun.* **1983**, 1168.
3. Papadopoulos, A.; Heyer, J.; Ginzel, K.-D.; Steckhan, E. *Chem.Ber.* **1989**, *122*, 2159.

4. Schöllkopf, U.; Neubauer, H.-J.; Hauptreif, M. *Angew.Chem.* **1985**, *97*, 1065-1066; *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*, 683-684.
5. Williams, R.M.; Sinclair, P.J.; Zhai, D.; Chen, D. *J.Am.Chem.Soc.* **1988**, *110*, 1547-1557.
6. a) Bretschneider, T.; Miltz, W.; Münster, P; Steglich, W. *Tetrahedron* **1988**, *44*, 5403-5414; b) Kober, R.; Papadopoulos, K.; Miltz, W.; Enders, D.; Steglich, W. *Tetrahedron* **1985**, *41*, 1693.
7. Brungs, P.; Steckhan, E., unpublished results.
8. Egli, M.; Polt, R.; Seebach, D. *Chimia* **1989**, *43*, 4.
9. Naef, R.; Seebach, D. *Helv.Chim.Acta* **1985**, *68*, 135; Fitzi, R.; Seebach, D. *Tetrahedron* **1988**, *44*, 5277.
10. Seebach, D.; Charczuk, R.; Gerber, C.; Renaud, P. *Helv.Chim.Acta* **1989**, *72*, 401.
11. Lucente, G.; Romea, A.; Schimberni, A.M. *J.Heterocyl.Chem.* **1970**, *7*, 1165.
12. König, W.; Geiger, R. *Chem.Ber.* **1970**, *103*, 788.
13. Itoh, M.; Hagiwara, D.; Kamiya, T. *Tetrahedron Lett.* **1975**, 4393; *Bull.Chem.Soc.Jpn.* **1977**, *50*, 718; Schwyzer, R.; Sieber, P.; Kappeler, H. *Helv.Chim.Acta.* **1959**, *42*, 2622; Irie, H.; Nakanishi, H.; Fujii, N.; Mizuno, Y.; Fushimi. T.; Funakoshi, S.; Yajima, H. *Chem.Lett.* **1980**, 705.