The Synthesis of Amino Acid Bridged Dicatechol Derivatives

Markus Albrecht,* Matthias Napp, Matthias Schneider

Institut für Organische Chemie, Universität Karlsruhe, Richard-Willstätter-Allee, 76131 Karlsruhe, Germany
Fax +49(721)698529; E-mail: albrecht@ochhades.chemie.uni-karlsruhe.de

Received 6 October 2000; revised 29 November 2000

Abstract: Amino acid bridged dicatechol ligands **1a**–**e** are synthesized by a stepwise coupling procedure. First 2,3-dimethoxybenzoic acid (**2**) is coupled with the amino acid (**3a**–**e**) followed by a second coupling step of the obtained derivatives **4a**–**e** with 2,3-dimethoxybenzyl amine (**5**). As coupling reagents for the amide bonds either DDC/NHS or EDC/HOBt are used. In the final step of the reaction sequence the methyl ethers of the ligand precursors **6a**–**e** are cleaved with BBr_3 to obtain the dicatechol ligands **1a**–**e**, which are potential building blocks for metallo-supramolecular chemistry.

Key words: amino acids, catechol, ligands, amides, supramolecular chemistry

Amino acids are the monomeric building blocks of a special class of biopolymers: the peptides. Hereby the structures of peptides are dictated by specific sequences of amino acids. α-Helical, β-sheet, or different turn structures are observed due to intra- and/or interstrand hydrogen bonding in combination with the steric and hydrophilic/hydrophobic influence of different amino acid side chains.[1]

In our work on the formation of helicate-type dinuclear complexes, we found a way to control the diastereoselectivity of the self-assembly process and thus the structure of the complexes by use of simple alkyl-spacers with different chain length (even versus odd).[2] It also should be possible to use amino acids (or short peptides) in the spacer as structure controlling moieties. Upon complex formation two different non-covalent interactions (coordination to the metal, inter- or intramolecular hydrogen bonding) would influence the structure of the obtained complexes.[3] In addition, the use of chiral amino acids will enable the formation of enantiopure metal complexes[4] and the directionality of the amino-acids (N-terminus versus C-terminus) will introduce some further information into the system.[5]

An example of an amino acid bridged dicatecholate ligand **1** is shown in the Figure. The two (deprotonated) catechol moieties are able to bind to two metal ions and are connected by a spacer that contains one amino acid building block. Therefore, two H-bond donors (NH) and two H-bond acceptors (C=O) are present in the strand. The catecholate oxygen atoms can act as additional hydrogen bond acceptors.[6]

In this paper, we present the synthesis of derivatives **1**, using straightforward peptide coupling chemistry.[7] As amino acids, we have chosen glycine, alanine, phenyl alanine, valine and leucine, which do not bear any functionalities in the side chain.

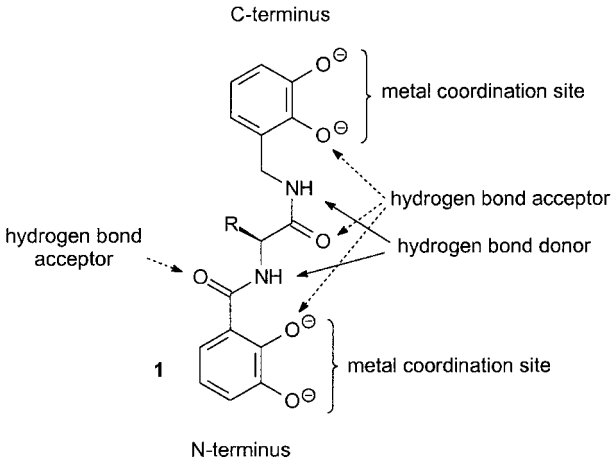


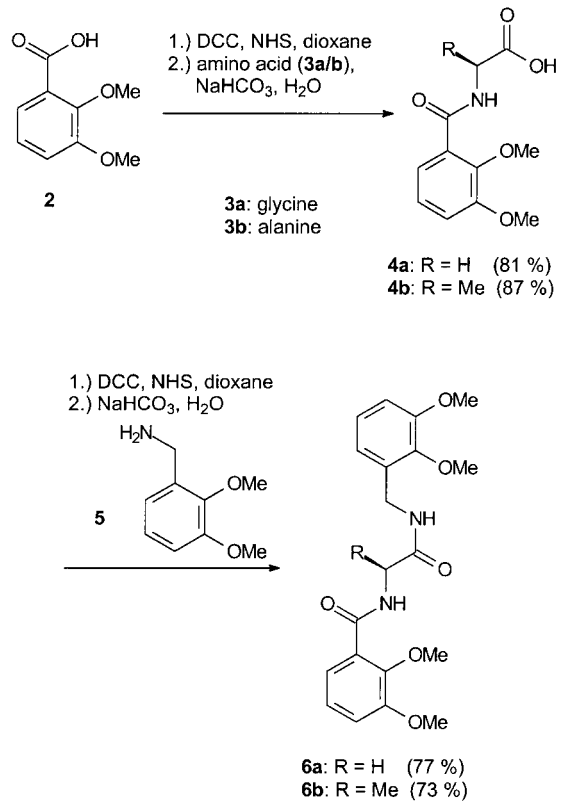
Figure Amino acid bridged dicatechol derivatives **1**

The ligand precursors **6a**, **b** with hydrophilic amino acids in the spacer were synthesized as depicted in Scheme 1, starting with 2,3-dimethoxybenzoic acid (**2**). For the coupling reaction, the benzoic acid **2** was activated with dicyclohexyl carbodiimide (DCC) and *N*-hydroxysuccinimide (NHS).[8] The precipitated dicyclohexyl urea was removed by filtration and the amino acids **3a**, **b**, dissolved in aqueous $NaHCO_3$, were added to obtain the derivatives **4a**, **b**. This procedure by Bergeron et al. has been previously applied to the preparation of the glycine derivative **4a**.[9] We additionally prepared the alanine derivative **4b** using this methodology. After recrystallization, the compounds were obtained as white crystalline solids (**4a** from ethanol: 81%; **4b** from water: 87%).

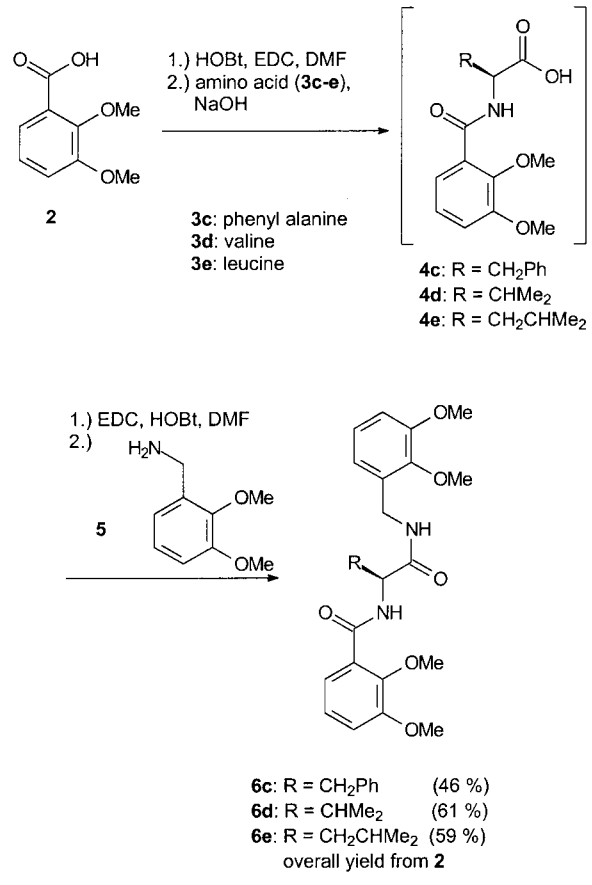
The derivatives **4a**, **b** bear an acid function, which again can be activated by use of DCC and NHS. Addition of 2,3-dimethoxybenzyl amine (**5**) to the in situ formed NHS derivative resulted in the formation of the methyl protected ligand precursors **6a** (77%) and **6b** (73%).

For the preparation of the ligand precursors with the hydrophobic amino acids phenyl alanine (**3c**), valine (**3d**), and leucine (**3e**), the coupling with DCC/NHS led to some problems in the purification steps. Therefore, we used hydroxybenztriazole (HOBt) in the presence of ethyl(dimethylaminopropyl)carbodiimide (EDC) for the activation of the carboxylic acid functions of **2** as well as of **4c**–**e**.[10]

After coupling of the benzoic acid **2** with the amino acids **3c**–**e**, the compounds **4c**–**e** were formed but could not be obtained in analytically pure form. However, the purity was high enough to perform a subsequent activation of the acid functions with HOBt/EDC followed by reaction with



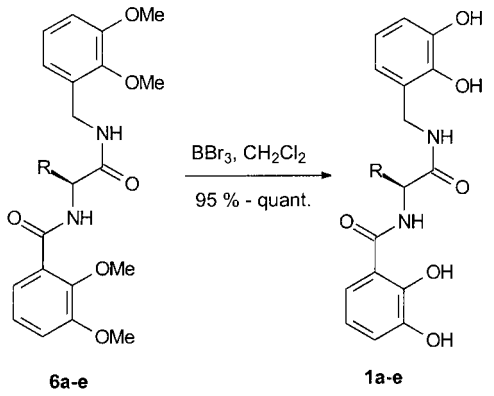
Scheme 1



Scheme 2

the benzyl amine **5**. After chromatographic work up, the ligand precursors were obtained in 46% (**6c**), 61% (**6d**), and 59% yield (**6e**) over two steps.

In the final step, the ligand precursors **6a**–**e** were deprotected to obtain the dicatechol derivatives **1a**–**e** (Scheme 3).



Scheme 3

Ether cleavage was achieved by reaction of the tetramethoxy derivatives **6a**–**e** with BBr_3 in dichloromethane at 0 °C followed by stirring over night at room temperature.[11] After quenching of the crude mixture, the solvent was removed and the residue was either dissolved several times in methanol and volatile components removed in vacuum to obtain the glycine **1a** or alanine derivatives **1b** in 95% yield each, or the residue was dissolved in ethyl acetate and washed with water. In this case the organic phase contained the phenylalanine **1c**, valine **1d**, or leucine derivative **1e**, which after evaporation of the solvent were obtained in quantitative yield. The amino acid bridged dicatechol compounds **1a**–**e** were isolated as hygroscopic solid materials.

One of the catechol units of **1** was attached to the N-terminus of the amino acid as a catechol amide like it is observed for some naturally occurring siderophores.[12] To the C-terminus a non-natural dihydroxy benzyl group was linked via an amide group.

Herein, we have presented the straightforward synthesis of five amino acid bridged dicatechol derivatives **1a**–**e**, which should be potential ligands for the self-assembly of oligonuclear metal complexes. Also, we added NHS or HOBt as a racemization reducing agent during the amide coupling reactions,[7,8,10] we cannot rule out that some racemization occurred. As amino acids, we used glycine, alanine, phenyl alanine, valine and leucine. We were able to introduce these amino acids without the use of protecting groups. At present, we are performing coordination studies with the ligands to obtain, in self-assembly processes, oligonuclear metallo-supramolecular coordination compounds. Also, the synthesis of further derivatives with other amino acids and with short peptides in the spacer is underway.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 500 spectrometer using DEPT techniques for the assignment of the multiplicity of carbon atoms (internal standard: $CHCl_3$ or CHD_2OD). FT-IR spectra were recorded by diffuse reflection (KBr) on a Bruker IFS spectrometer. EI/HRMS (70 eV) mass spectra were taken on a Finnigan MAT 90 mass spectrometer. The optical rotation was detected on a Perkin−Elmer 241 polarimeter. Elemental analyses were obtained with a Heraeus CHN-O-Rapid analyzer. Solvents were purified by standard methods. Mps: Büchi 535 (uncorrected).

***N*-2,3-Dimethoxybenzoyl-glycine (4a)**
The glycine derivative **4a** was synthesized as described in the literature; yield: 81% (Lit.: 91%).[9]

***N*-2,3-Dimethoxybenzoyl-L-alanine (4b)**
A mixture of the benzoic acid **2** (1.00 g, 5.49 mmol) and NHS (760 mg, 6.62 mmol) was dissolved in dioxane (35 mL) and DCC (1.37 g, 6.62 mmol) in dioxane (30 mL) was added slowly. After 17 h at r.t., the precipitated urea was removed by filtration and a solution of $NaHCO_3$ (610 mg, 7.29 mmol) and L-alanine (650 mg, 7.29 mmol) in H_2O (20 mL) was added. After stirring for additional 19 h, solvents were removed in vacuum and the residue was recrystallized from H_2O; yield: 1.21 g (87%); white solid; mp: 80 °C.

$[\alpha]_D^{20}$ = +10.6° (*c* 1, MeOH).

^{1}H NMR ($CDCl_3$, 296 K): δ = 9.61 (br, 1H), 8.77 (d, 1H, *J* = 6.9 Hz), 7.66 (dd, 1H, *J* = 8.0, 1.5 Hz), 7.15 (pseudo t, 1H, *J* = 8.0 Hz), 7.06 (dd, 1H, *J* = 8.0, 1.5 Hz), 4.81 (m, 1H), 3.93 (s, 3H), 3.89 (s, 3H), 1.56 (d, 3H, *J* = 7.2 Hz).

^{13}C NMR ($CDCl_3$, 296 K): δ = 176.6 (C), 165.5 (C), 152.7 (C), 147.9 (C), 125.5 (C), 124.5 (CH), 122.7 (CH), 116.0 (CH), 61.5 (CH_3), 56.1 (CH_3), 48.6 (CH_3), 18.1 (CH).

IR (KBr): ν = 3338, 3017, 2944, 1941, 1750, 1574, 1459, 1308, 1223, 1189, 1146, 1063, 981, 938, 818 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 253 (13) [M]$^+$, 165 (100).

HRMS (EI, 70 eV): *m/z* calcd for $C_{12}H_{15}NO_5$ (M$^+$, 253.26): 253.0950. Found: 253.0937.

Anal. Calcd for $C_{12}H_{15}NO_5 \cdot H_2O$ (271.26): C, 53.13; H, 6.32; N, 5.16. Found: C, 53.19; H, 5.85; N, 6.56.

Glycine Derivative 2-(2,3-Dimethoxyphenyl)carbonyl Amino-*N*-(2,3-dimethoxybenzyl) Acetamide (6a); Typical Procedure
DCC (260 mg, 1.26 mmol) in dioxane (30 mL) was added to a mixture of the glycine derivative **4a** (250 mg, 1.05 mmol) and NHS (145 mg, 1.26 mmol) in dioxane (35 mL). After 16 h at r.t., the precipitated urea was removed by filtration and a solution of $NaHCO_3$ (117 mg, 1.39 mmol) and benzyl amine **5** (234 mg, 1.39 mmol) in H_2O (20 mL) was added. The mixture was stirred for 20 h, solvents were removed in vacuum and the residue was recrystallized from H_2O; yield: 312 mg (77%); white solid; mp: 133 °C.

^{1}H NMR ($CDCl_3$, 296 K): δ = 8.65 (br, 1H), 7.68 (dd, 1H, *J* = 8.1, 1.6 Hz), 7.14 (t, 1H, *J* = 8.1 Hz), 7.06 (dd, 1H, *J* = 8.1, 1.6 Hz), 7.00 (pseudo t, 1H, *J* = 7.9 Hz), 6.88 (dd, 1H, *J* = 7.9, 1.3 Hz), 6.51 (br, 1H), 4.50 (d, 2H, *J* = 5.9 Hz), 4.16 (d, 2H, *J* = 5.5 Hz), 3.94 (s, 3H), 3.90 (s, 3H), 3.85 (s, 3H), 3.84 (s, 3H).

^{13}C NMR ($CDCl_3$, 296 K): δ = 168.8 (C), 165.8 (C), 152.7 (C), 148.0 (C), 147.3 (C), 131.5 (C), 125.9 (C), 125.8 (C), 124.4 (CH), 124.3 (CH), 122.8 (CH), 121.3 (CH), 115.9 (CH), 112.1 (CH), 61.5 (CH_3), 60.7 (CH_3), 56.2 (CH_3), 55.8 (CH_3), 43.9 (CH_2), 39.1 (CH_2).

IR (KBr): ν = 3322, 3006, 2936, 1642, 1528, 1439, 1273, 1123, 979, 745 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 388 (47) [M$^+$].

HRMS (EI, 70 eV): *m/z* calcd for $C_{20}H_{24}N_2O_6$ (M$^+$, 388.42): 388.1634. Found: 388.1620.

Anal. Calcd for $C_{20}H_{24}N_2O_6$ (388.42): C, 61.85; H, 6.23; N, 7.21. Found: C, 62.01; H, 6.38; N, 7.40.

L-Alanine Derivative (2*S*)-2-(2,3-Dimethoxyphenyl)carbonyl Amino-*N*-(2,3-dimethoxybenzyl) Ethyl Amide (6b)
Compound **6b** was prepared similar to the synthesis of **6a**. Purification of the crude product was done by column chromatography (silica gel, EtOAc); yield: 302 mg (73%); white solid; mp: 138 °C.

$[\alpha]_D^{20}$ = +22.6° (*c* 1, MeOH).

^{1}H NMR ($CDCl_3$, 296 K): δ = 8.66 (d, 1H, *J* = 7.2 Hz), 7.52 (dd, 1H, *J* = 7.9, 1.5 Hz), 7.16 (br, 1H), 7.06 (pseudo t, 1H, *J* = 7.9 Hz), 7.01 (dd, 1H, *J* = 7.9, 1.5 Hz), 6.94 (pseudo t, 1H, *J* = 7.9 Hz), 6.85 (dd, 1H, *J* = 7.9, 1.2 Hz), 6.79 (dd, 1H, *J* = 7.9, 1.2 Hz), 4.79 (m, 1H), 4.49 (m, 2H), 3.89 (s, 3H), 3.85 (s, 3H), 3.80 (s, 6H), 1.46 (d, 3H, *J* = 7.0 Hz).

^{13}C NMR ($CDCl_3$, 296 K): δ = 172.2 (C), 164.9 (C), 152.6 (C), 152.5 (C), 147.9 (C), 147.0 (C), 131.7 (C), 126.0 (C), 124.2 (CH), 124.1 (CH), 122.5 (CH), 121.0 (CH), 115.7 (CH), 111.8 (CH), 61.3 (CH_3), 60.6 (CH_3), 56.1 (CH_3), 55.7 (CH_3), 49.2 (CH), 38.5 (CH_2), 18.5 (CH_3).

IR (KBr): ν = 3323, 3081, 2836, 1578, 1482, 1308, 1225, 1064, 753 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 402 (23) [M$^+$], 165 (100).

HRMS (EI, 70 eV): *m/z* calcd for $C_{21}H_{26}N_2O_6$ (M$^+$, 402.45): 402.1791. Found: 402.1777.

Anal. Calcd for $C_{21}H_{26}N_2O_6$ (402.45): C, 62.67; H, 6.51; N, 6.96. Found: C, 62.27; H, 6.69; N, 6.90.

Compounds 4c−e; General Procedure
Benzoic acid **2** (1.00 g, 5.49 mmol), HOBt (816 mg, 6.04 mmol) and EDC (1.05 g, 5.49 mmol) were dissolved in DMF (60 mL) under Ar at 0 °C, and were stirred at r.t. for 17 h. A mixture of the amino acid **3c−e** (5.49 mmol) and NaOH (220 mg, 5.49 mmol) in H_2O (10 mL) was added. After stirring for additional 14 h, the solvent was removed in vacuum, the residue was dissolved in EtOAc, washed with sat. NH_4Cl, dried ($MgSO_4$), and solvent was removed again. The compounds **4c−e** could not be obtained in analytically pure form by this procedure but were sufficiently pure for further reactions.

***N*-2,3-Dimethoxybenzoyl-L-phenyl Alanine (4c)**
^{1}H NMR (CD_3OD, 296 K): δ = 7.46 (dd, 1H, *J* = 7.6, 1.9 Hz), 7.27 (m, 2H), 7.20 (m, 3H), 7.13 (m, 2H), 4.90 (m, 1H, hidden under the signal of HOD), 3.85 (s, 3H), 3.59 (s, 3H), 3.31 (dd, 1H, *J* = 13.9, 6.6 Hz), 3.20 (dd, 1H, *J* = 13.9, 6.6 Hz).

^{13}C NMR (CD_3OD, 296 K): δ = 174.4 (C), 167.2 (C), 154.3 (C), 149.3 (C), 137.9 (C), 130.5 (CH), 130.5 (CH), 129.6 (CH), 129.6 (CH), 128.0 (CH), 127.1 (C), 125.3 (CH), 122.9 (CH), 117.2 (CH), 61.7 (CH), 56.6 (CH_3), 55.1 (CH_3), 38.1 (CH_2).

MS (EI, 70 eV): *m/z* (%) = 329 (2) [M]$^+$, 165 (100).

HRMS (EI, 70 eV): *m/z* calcd for $C_{18}H_{19}NO_5$ (M$^+$, 329.35): 329.1263. Found: 329.1256.

***N*-2,3-Dimethoxybenzoyl-L-valine (4d)**
^{1}H NMR (CD_3OD, 296 K): δ = 7.49 (dd, 1H, *J* = 7.9, 1.8 Hz), 7.20 (dd, 1H, *J* = 7.9, 1.8 Hz), 7.16 (pseudo t, 1H, *J* = 7.9 Hz), 4.62 (d, 1H, *J* = 4.7 Hz), 3.95 (s, 3H), 3.90 (s, 3H), 2.31 (m, 1H), 1.04 (d, 3H, *J* = 7.3 Hz), 1.02 (d, 3H, *J* = 7.3 Hz).

^{13}C NMR (CD_3OD, 296 K): δ = 174.5 (C), 167.5 (C), 154.3 (C), 149.2 (C), 127.3 (C), 125.5 (CH), 122.9 (CH), 117.2 (CH), 62.2 (CH_3), 59.0 (CH), 56.6 (CH_3), 32.2 (CH), 19.6 (CH_3), 18.2 (CH_3).

MS (EI, 70 eV): *m/z* (%) = 281 (0.4) [M]$^+$, 182 (100).

HRMS (EI, 70 eV): *m/z* calcd for $C_{14}H_{19}NO_5$ (M$^+$, 281.31): 281.1263. Found: 281.1258.

***N*-2,3-Dimethoxybenzoyl-L-leucine (4e)**

^{1}H NMR (CD_3OD, 296 K): δ = 7.41 (dd, 1H, *J* = 7.7, 1.9 Hz), 7.18 (dd, 1H, *J* = 8.2, 1.9 Hz), 7.15 (pseudo t, 1H, *J* = 7.7 Hz), 4.71 (dd, 1H, *J* = 8.7, 5.3 Hz), 3.91 (s, 3H), 3.89 (s, 3H), 1.75 (m, 3H), 0.99 (d, 6H, *J* = 6.1 Hz).

^{13}C NMR (CD_3OD, 296 K): δ = 175.8 (C), 167.8 (C), 154.3 (C), 149.0 (C), 128.1 (C), 125.4 (CH), 122.6 (CH), 117.0 (CH), 62.0 (CH_3), 56.6 (CH_3), 52.5 (CH), 42.3 (CH_2), 26.2 (CH), 23.3 (CH_3), 22.2 (CH_3).

MS (EI, 70 eV): *m/z* (%) = 295 (2) $[M]^+$, 165 (100).

HRMS (EI, 70 eV): *m/z* calcd for $C_{15}H_{21}NO_5$ (M^+, 295.34): 295.1420. Found: 295.1410.

Compounds 6c–e; General Procedure

The crude amino acid derivative **4c**–**e** (4.55 mmol), HOBt (737 mg, 5.46 mmol) and EDC (960 mg, 5.01 mmol) were dissolved in DMF (60 mL) under Ar, and the benzylamine **5** (4.55 mmol) was added with ice cooling. The mixture was stirred for 21 h at r.t. before the solvent was removed in vacuum. The residue was dissolved in EtOAc, washed with sat. NH_4Cl and $NaHCO_3$, dried ($MgSO_4$), and solvent was removed again. The crude product was purified by column chromatography (silica gel, hexane/EtOAc, 1:1 for **6c**; 2:1 for **6d**, **e**).

L-Phenyl Alanine Derivative (2*S*)-2-(2,3-Dimethoxyphenyl)carbonyl Amino-*N*-(2,3-dimethoxybenzyl)-3-phenylethylamide (6c)

Yield: 46% over 2 steps; white solid, mp: 123 °C.

$[\alpha]_D^{20}$ = −5.7° (*c* 1, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 296 K): δ = 8.57 (d, 1H, *J* = 7.4 Hz), 7.62 (dd, 1H, *J* = 1.6, 8.0 Hz), 7.22–7.15 (m, 5H), 7.10 (t, 1H, *J* = 8.0 Hz), 7.02 (dd, 1H, *J* = 1.6, 8.0 Hz), 6.95 (t, 1H, *J* = 8.0 Hz), 6.82 (dd, 1H, *J* = 1.2, 8.2 Hz), 6.74 (d, 1H, *J* = 7.7 Hz), 6.42 (t, 1H, *J* = 5.5 Hz) 4.91 (dd, 1H, *J* = 7.2, 14.2 Hz), 4.42 (m, 2H), 3.86 (s, 3H), 3.83 (s, 3H), 3.74 (s, 3H), 3.66 (s, 3H), 3.20 (m, 2H).

^{13}C NMR ($CDCl_3$, 296 K): δ = 170.7 (C), 165.2 (C), 152.6 (C), 152.5 (C), 148.0 (C), 147.1 (C), 136.8 (C), 131.5 (C), 129.3 (CH), 129.3 (CH), 128.6 (CH), 128.6 (CH), 126.8 (CH), 125.9 (C), 124.2 (CH), 124.1 (CH), 122.7 (CH), 121.1 (CH), 115.8 (CH), 112.0 (CH), 61.2 (CH_3), 60.6 (CH_3), 56.1 (CH_3), 55.8 (CH_3), 55.0 (CH), 38.7 (CH_2), 38.2 (CH_2).

IR (KBr): ν = 3270, 2941, 1640, 1530, 1232, 750 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 478 (9) $[M]^+$, 165 (100).

HRMS (EI, 70 eV) *m/z* calcd for $C_{27}H_{30}N_2O_6$ (M^+, 478.55): 478.2104. Found: 478.2098.

Anal. Calcd for $C_{27}H_{30}N_2O_6$ (478.55): C, 67.77; H, 6.32; N, 5.85. Found: C, 67.36; H, 6.30; N, 5.73.

L-Valine Derivative (2*S*)-2-(2,3-Dimethoxyphenyl)carbonyl Amino-*N*-(2,3-dimethoxybenzyl)-3-methylbutylamide (6d)

Yield: 61% over 2 steps; colorless oil.

$[\alpha]_D^{20}$ = −2.1° (c 0.95, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 296 K): δ = 8.64 (d, 1H, *J* = 8.6 Hz), 7.52 (dd, 1H, *J* = 7.9, 1.9 Hz), 7.26–7.02 (m, 2H), 6.99 (dd, 1H, *J* = 10.1, 1.9 Hz), 6.92 (pseudo t, 1H, *J* = 7.9 Hz), 6.85 (dd, 1H, *J* = 7.9, 1.4 Hz), 6.76 (dd, 1H, *J* = 7.9, 1.4 Hz), 4.63 (m, 1H), 4.50 (dd, 1H, *J* = 14.8, 5.8 Hz), 4.41 (dd, 1H, *J* = 14.8, 5.8 Hz), 3.90 (s, 3H), 3.84 (s, 3H), 3.78 (s, 3H), 3.76 (s, 3H), 2.23 (m, 1H), 0.97 (d, 3H, *J* = 5.8 Hz), 0.96 (d, 3H, *J* = 5.8 Hz).

^{13}C NMR ($CDCl_3$, 296 K): δ = 171.1 (C), 165.1 (C), 152.6 (C), 152.4 (C), 147.8 (C), 147.0 (C), 131.7 (C), 126.1 (C), 124.1 (CH), 124.0 (CH), 122.6 (CH), 121.0 (CH), 115.6 (CH), 111.7 (CH), 61.5 (CH_3), 60.5 (CH_3), 58.7 (CH), 56.0 (CH_3), 55.6 (CH_3), 38.4 (CH_2), 31.1 (CH), 19.4 (CH_3), 18.0 (CH_3).

IR (KBr): ν = 3316, 2964, 1643, 1578, 1429, 1224, 1265 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 430 (14) $[M]^+$, 165 (100).

HRMS (EI, 70 eV) *m/z* calcd for $C_{23}H_{30}N_2O_6$ (M^+, 430.50): 430.2104. Found: 430.2098.

L-Leucine Derivative (2*S*)-2-(2,3-Dimethoxyphenyl)carbonyl Amino-*N*-(2,3-dimethoxybenzyl)-4-methylpentylamide (6e)

Yield: 59% over 2 steps; colorless oil.

$[\alpha]_D^{20}$ = −3.8° (*c* 1.32, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 296 K): δ = 8.38 (d, 1H, *J* = 8.0 Hz), 7.53 (dd, 1H, *J* = 8.0, 1.7 Hz), 7.05 (m, 2H), 6.99 (dd, 1H, *J* = 8.0, 1.4 Hz), 6.91 (pseudo t, 1H, *J* = 8.0 Hz), 6.83 (d, 1H, *J* = 8.0 Hz), 6.76 (d, 1H, *J* = 8.0 Hz), 4.74 (m, 1H), 4.47 (dd, 1H, *J* = 14.9, 6.0 Hz), 4.41 (dd, 1H, *J* = 14.9, 6.0 Hz), 3.85 (s, 3H), 3.83 (s, 3H), 3.78 (s, 3H), 3.78 (s, 3H), 1.76 (m, 1H), 1.67 (m, 2H), 0.91 (d, 6H, *J* = 6.2 Hz).

^{13}C NMR ($CDCl_3$, 296 K): δ = 171.9 (C), 165.1 (C), 152.5 (C), 152.4 (C), 147.7 (C), 147.0 (C), 131.7 (C), 126.1 (C), 124.2 (CH), 124.0 (CH), 122.5 (CH), 120.9 (CH), 115.6 (CH), 111.7 (CH), 61.3 (CH_3), 60.5 (CH_3), 56.0 (CH_3), 55.6 (CH_3), 52.0 (CH), 41.3 (CH_2), 38.4 (CH_2), 24.8 (CH), 22.9(CH_3), 22.0 (CH_3).

IR (KBr): ν = 3311, 2955, 1645, 1578, 1429, 1225, 1264 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 444 (13) $[M]^+$, 165 (100).

HRMS (EI, 70 eV) *m/z* calcd for $C_{24}H_{32}N_2O_6$ (M^+, 444.53): 444.2260. Found: 444.2256.

Compounds 1a–e; General Procedure

The ligand precursors **6a**–**e** (0.30 mmol) were dissolved in CH_2Cl_2 (30 mL) and a 1 M solution of BBr_3 in CH_2Cl_2 (2 mL) was added at 0 °C under Ar. The mixture was stirred for 18 h at r.t. before MeOH (5 mL) was added, and the solvent was removed under vacuum. The purification of **1a**, **b** was done by dissolution of the residue followed by removal of volatile components under vacuum several times. The compounds **1c**–**e** were purified by dissolution in EtOAc, washing with H_2O, drying ($MgSO_4$), and removal of the solvent under vacuum.

Glycine Bridged Derivative 2-(2,3-Dihydroxyphenyl)carbonyl Amino-*N*-(2,3-dihydroxybenzyl) Acetamide (1a)

Yield: 95%; slightly brown solid; mp: 78 °C (dec.).

^{1}H NMR (CD_3OD, 296 K): δ = 7.26 (dd, 1H, *J* = 7.8, 1.5 Hz), 6.94 (dd, 1H, *J* = 7.8, 1.5 Hz), 6.74 (pseudo t, 1H, *J* = 7.8 Hz), 6.71 (dd, 1H, *J* = 7.8, 1.5 Hz), 6.69 (dd, 1H, *J* = 7.8, 1.5 Hz), 6.63 (pseudo t, 1H, *J* = 7.8 Hz), 4.37 (s, 2H), 4.07 (s, 2H).

^{13}C NMR (CD_3OD, 296 K): δ = 171.1 (C), 170.8 (C), 149.2 (C), 146.3 (C), 145.6 (C), 143.6 (C), 125.2 (C), 120.3 (CH), 119.6 (CH), 118.8 (CH), 118.7 (CH), 118.1 (CH), 115.7 (C), 114.6 (CH), 42.5 (CH_2), 38.9 (CH_2).

IR (KBr): ν = 3331, 1638, 1589, 1458, 1077, 785 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 332 (48) $[M]^+$, 137 (100).

HRMS (EI, 70 eV) *m/z* calcd for $C_{16}H_{16}N_2O_6$ (M^+, 332.31): 332.1008. Found: 332.1018.

Anal. Calcd for $C_{16}H_{16}N_2O_6 \cdot H_2O$ (350.31): C, 54.86; H, 5.18; N, 8.00. Found: C, 55.13; H, 5.47; N, 7.48.

L-Alanine Bridged Derivative (2*S*)-2-(2,3-dihydroxyphenyl)carbonyl Amino-*N*-(2,3-dihydroxybenzyl) Ethylamide (1b)

Yield: 95%; slightly brown solid; mp: 112 °C (dec.).

$[\alpha]_D^{20}$ = −15° (*c* 1, MeOH).

^{1}H NMR (CD_3OD, 296 K): δ = 7.32 (dd, 1H, *J* = 8.0, 1.4 Hz), 6.94 (dd, 1H, *J* = 8.0, 1.4 Hz), 6.74 (pseudo t, 1H, *J* = 8.0 Hz), 6.71 (dd, 1H, *J* = 7.7, 1.7 Hz), 6.68 (dd, 1H, *J* = 7.7, 1.7 Hz), 6.63 (pseudo t, 1H, *J* = 7.7 Hz), 4.63 (q, 1H, *J* = 7.1 Hz), 4.39 (d, 1H, *J* = 14.8 Hz), 4.35 (d, 1H, *J* = 14.8 Hz), 1.46 (d, 3H, *J* = 7.1 Hz).

^{13}C NMR (CD_3OD, 296 K): δ = 175.5 (C), 170.8 (C), 149.8 (C), 147.2 (C), 146.6 (C), 144.6 (C), 126.1 (C), 121.2 (CH), 120.6 (CH), 119.8 (CH), 119.7 (CH), 119.5 (CH), 117.0 (C), 115.6 (CH), 50.6 (CH), 40.0 (CH_2), 18.5 (CH_3).

IR (KBr): ν = 3372, 1639, 1589, 1481, 1337, 1079, 788 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 346 (25) $[M]^+$, 137 (100).

HRMS (EI, 70 eV) *m/z* calcd for $C_{17}H_{18}N_2O_6$ (M^+, 346.34): 346.1165. Found: 346.1155.

Anal. Calcd for $C_{17}H_{18}N_2O_6 \cdot 1.25\ H_2O$ (368.84): C, 55.36; H, 5.60; N, 7.59. Found: C, 55.45; H, 5.33; N, 7.32.

L-Phenyl Alanine Bridged Derivative (2*S*)-2-(2,3-Dihydroxyphenyl)carbonyl Amino-*N*-(2,3-dihydroxybenzyl)-3-phenylethylamide (1c)

Yield: quantitative; slightly brown solid; mp: 76 °C.

$[\alpha]_D^{20} = -46.2$ (*c* 1, $CHCl_3$).

^{1}H NMR ($CDCl_3$, 296 K): δ = 9.33 (br, 1H), 7.18 (m, 1H), 7.14 (m, 3H), 7.03 (m, 2H), 6.92 (m, 2H), 6.73 (m, 2H), 6.62 (pseudo t, 1H, *J* = 6.5 Hz), 6.48 (m, 2H), 5.94 (br, 1H), 4.80 (d pseudo t, 1H, *J* = 8.0, 5.4 Hz), 4.28 (dd, 1H, *J* = 14.6, 6.5 Hz), 4.14 (dd, 1H, *J* = 8.6, 6.5 Hz), 3.21 (dd, 1H, *J* = 13.5, 5.4 Hz), 3.02 (dd, 1H, *J* = 13.5, 8.6 Hz).

^{13}C NMR ($CDCl_3$, 296 K): δ = 173.0 (C), 169.7 (C), 149.0 (C), 146.4 (C), 145.8 (C), 142.5 (C), 135.1 (C), 129.1 (CH), 129.1 (CH), 128.9 (CH), 128.9 (CH), 127.5 (CH), 123.7 (C), 121.6 (CH), 120.7 (CH), 119.0 (CH), 118.8 (CH), 116.5 (CH), 115.1 (CH), 113.4 (C), 54.5 (CH), 40.3 (CH_2), 38.9 (CH_2).

IR (KBr): ν = 3376, 1638, 1531, 1263, 738, 702 cm^{-1}.

MS (EI, 70 eV): m/z (%) = 422 (19) $[M]^+$, 120 (100).

HRMS (EI, 70 eV) *m/z* calcd for $C_{23}H_{22}N_2O_6$ (M^+, 422.44): 422.1478. Found: 422.1483.

Anal. Calcd for $C_{23}H_{22}N_2O_6 \cdot 1.5\ H_2O$ (449.44): C, 61.46; H, 5.61; N, 6.23. Found: C, 61.65; H 5.24; N, 5.78.

L-Valine Bridged Derivative (2*S*)-2-(2,3-Dihydroxyphenyl)carbonyl Amino-*N*-(2,3-dihydroxybenzyl)-3-methyl Butylamide (1d)

Yield: quantitative; slightly brown solid; mp: 70 °C (dec.).

$[\alpha]_D^{20} = -31.6°$ (*c* 1, $CHCl_3$).

^{1}H NMR (CD_3OD, 296 K): δ = 7.35 (dd, 1H, *J* = 7.9, 1.3 Hz), 6.95 (dd, 1H, *J* = 7.9, 1.3 Hz), 6.75−6.67 (m, 3H), 6.62 (pseudo t, 1H, *J* = 7.9 Hz), 4.44 (m, 2H), 4.32 (d, 1H, *J* = 15.0 Hz), 2.18 (m, 1H), 0.99 (m, 6H).

^{13}C NMR (CD_3OD, 296 K): δ = 174.1 (C), 170.1 (C), 148.9 (C), 147.0 (C), 146.5 (C), 144.5 (C), 126.0 (C), 121.5 (CH), 120.5 (CH), 120.0 (CH), 119.9 (CH), 119.6 (CH), 117.7 (C), 115.7 (CH), 60.3 (CH), 39.9 (CH_2), 32.2 (CH), 19.7 (CH_3), 18.8 (CH_3).

IR (KBr): ν = 3353, 2968, 1637, 1535, 1262, 1044 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 374 (12) $[M]^+$, 137 (100).

HRMS (EI, 70 eV) *m/z* calcd for $C_{19}H_{22}N_2O_6$ (M^+, 374.39): 374.1478. Found: 374.1472.

Anal. Calcd for $C_{19}H_{22}N_2O_6.1.5\ H_2O$ (401.39): C, 56.85; H, 6.28; N, 6.98. Found: C, 56.51; H, 5.81; N, 6.66.

L-Leucine Bridged Derivative (2*S*)-2-(2,3-Dihydroxyphenyl)carbonyl Amino-*N*-(2,3-dihydroxybenzyl)-4-methylpentylamide (1e)

Yield: quantitative; slightly brown solid; mp: 64 °C (dec.).

$[\alpha]_D^{20} = -41.2$ °(*c* 1, $CHCl_3$).

^{1}H NMR (CD_3OD, 296 K): δ = 7.32 (dd, 1H, *J* = 8.0, 1.4 Hz), 6.94 (dd, 1H, *J* = 8.0, 1.4 Hz), 6.81−6.60 (m, 4H), 4.69 (m, 1H), 4.38 (d, 1H, *J* = 14.7 Hz), 4.33 (d, 1H, *J* = 14.7 Hz), 1.69 (m, 3H), 0.96 (d, 3H, *J* = 6.0 Hz), 0.93 (d, 3H, *J* = 6.0 Hz).

^{13}C NMR (CD_3OD, 296 K): δ = 175.3 (C), 175.3 (C), 170.9 (C), 149.6 (C), 147.1 (C), 146.5 (C), 144.5 (C), 126.1 (C), 121.2 (CH), 120.5 (CH), 119.7 (CH), 119.5 (CH), 117.0 (CH), 115.6 (CH), 53.3 (CH), 42.0 (CH_2), 39.9 (CH_2), 26.1 (CH), 23.4 (CH_3), 22.0 (CH_3).

IR (KBr): ν = 3363, 2960, 1637, 1538, 1263, 1045 cm^{-1}.

MS (EI, 70 eV): *m/z* (%) = 388 (22) $[M]^+$, 137 (100).

Anal. Calcd for $C_{20}H_{24}N_2O_6 \cdot H_2O$ (406.44): C, 59.10; H, 6.45; N, 6.89. Found: C, 59.38; H, 6.45; N, 6.57.

Acknowledgement

This work was supported by the Fonds der Chemischen Industrie and the Deutsche Forschungsgemeinschaft.

References

(1) Schulz, G. E.; Schirmer, R. H. *Principles of Protein Structure;* Springer Verlag: Weinheim, 1979.
Jakubke, H. -D.; Jeschkeit, H. *Aminosäuren, Peptide, Proteine;* VCH: Weinheim, 1982.
(2) Albrecht, M. *Chem. Soc. Rev.* **1998**, *27*, 281.
Albrecht, M. *Chem.–Eur. J.* **2000**, *6*, 3485.
(3) For amino acid substituted chelating ligands see, e. g.:
Imperiali, B.; Prins, T. J.; Fischer, S. L. *J. Org. Chem.* **1993**, *58*, 1613.
Walkup, G. K.; Imperiali, B. *J. Org. Chem.* **1998**, *63*, 6727.
Bishop, B. M.; McCafferty, D. G.; Erickson, B. W. *Tetrahedron* **2000**, *56*, 4629.
(4) For examples of enantiopure helicates see: Carrano, C. J.; Raymond, K. N. *J. Am. Chem. Soc.* **1978**, *100*, 5371.
Corey, E. J.; Cywin, C. L.; Noe, M. C. *Tetrahedron Lett.* **1994**, *35*, 69.
Enemark, E. J.; Stack, T. D. P. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 996.
Albrecht, M. *Synlett* **1996**, 565.
Baum, G.; Constable, E. C.; Fenske, D.; Housecroft, C. E.; Kulke, T. *Chem.–Eur. J.* **1999**, *5*, 1862.
(5) Albrecht, M. *J. Incl. Phen. Macrocycl. Chem.* **2000**, *36*, 127; and references cited therein.
(6) Karpishin, T. B.; Stack, T. D. P.; Raymond, K. N. *J. Am. Chem. Soc.* **1993**, *115*, 6115.
(7) Bodanszky, M.; Bodanszky, A. *The Practice of Peptide Synthesis;* Springer Verlag: Berlin, 1984.
Jones, J. *Synthese von Aminosäuren und Peptiden;* VCH: Weinheim, 1995.
(8) Anderson, G. W.; Zimmerman, J. E.; Callahan, F. M. *J. Am. Chem. Soc.* **1964**, *86*, 1839.
(9) Bergeron, R. J.; Kline, S. J.; Stolowich, N. J.; McGovern, K. A.; Burton, P. S. *J. Org. Chem.* **1981**, *46*, 4524.
(10) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. I. *J. Org. Chem.* **1961**, *26*, 2525.
König, W.; Geiger, R. *Chem. Ber.* **1970**, *103*, 788.
(11) Albrecht, M. *Synthesis* **1996**, 230.
(12) Matzanke, B. F., Müller-Matzanke, G., Raymond, K. N., in Loehr, T. M., Eds., *Iron Carriers and Iron Proteins;* VCH: New York, 1989.
Raymond, K. N. *Coord. Chem. Rev.* **1990**, *105*, 135.

Article Identifier:
1437-210X,E;2001,0,03,0468,0472,ftx,en;T03100SS.pdf