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ELECTROGENERATED CHIRAL CATIONIC GLYCINE EQUIVALENTS - PART 2: CHIRAL 3-METHOXY-2,5-MORPHOLINEDIONES FROM (*S*)-α-HYDROXY ACIDS AND DIMETHYL AMINOMALONATE

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Abstract: Chiral 3-methoxy-2,5-morpholinediones which are cyclic *N,O*-acetals have proved to be excellent chiral cationic amino acid equivalents, especially if larger nucleophiles are employed. They are easily obtained from dipeptolides formed between chiral α-hydroxy acids and dimethyl amino malonate *via* regioselective electrochemical methoxylation followed by intramolecular lactonization after decarboxylation. The lactonization can be performed quantitatively from the open-chain peptolide by condenzation under reduced pressure at elevated temperature. The easy separation of the desired amino acid and the α-hydroxy acid being the chiral auxiliary by extraction is valuable.

INTRODUCTION

In the preceding publication we proved that the cyclic *N,O*-acetal cyclo(*L*-Pro-Gly(OMe)OMe is an excellent chiral electrophilic glycine equivalent[1] also in comparison with existing alternative methods. One disadvantage for the synthesis of non-proteinogenic α-amino acids, however, still exists. This is the cleavage of the cyclic dipeptide to give the desired product. This cleavage not only needs the somewhat drastic conditions of 6N HCl in methanol at 60°C but also generates two amino acids, the desired product and the chiral auxiliary, which have to be separated by chromatography. To solve these problems, we anticipated that chiral 3-methoxy-2,5-morpholinediones should be applicable as chiral cationic glycine equivalents. The advantage of morpholinediones would be the easier hydrolysis of the substitution products to give the desired new amino acid and the α-hydroxy acid used as chiral auxiliary. In addition, the separation of the two acids would be possible by simple extraction. Therefore, we studied the application of such systems as chiral amidoalkylation reagents according to the following concept (Fig. 1).

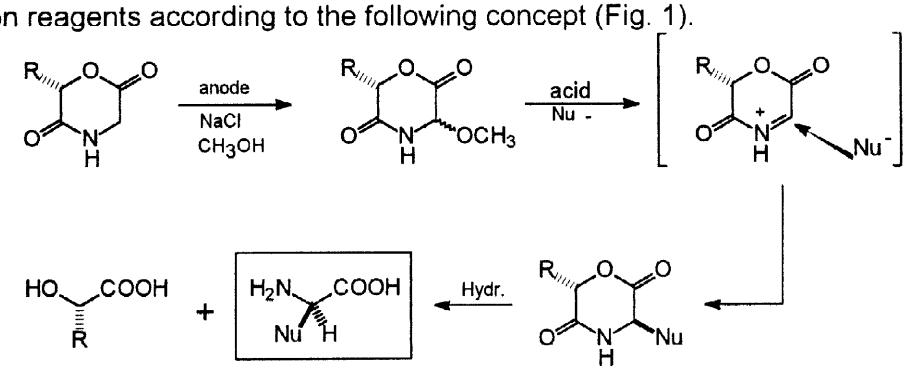

Figure 1: Concept for the application of chiral 3-methoxy-2,5-morpholinediones as cationic glycine equivalents.

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RESULTS AND DISCUSSION

Starting from enantiomerically pure α-hydroxy acids **1**, which are easily obtained directly from the chiral pool or *via* deamination of α-amino acids under retention of the configuration, the sequence to the 6-substituted chiral 2,5-morpholinediones seemed to be straight forward (Fig. 2). However, using mandelic acid as chiral auxiliary resulted in racemization already during the synthesis of the heterocyclic ring due to the stabilization of the enol form by the phenyl substitutent. This observation is in accordance with studies by *Schöllkopf*.[2] We therefore concentrated on α-hydroxy acids with alkyl substituents which do not favor the enolization like (*S*)-2-hydroxyisovaleric acid (**1a**, obtained *via* deamination from *L*-valine), (*S*)-2-hydroxy-3,3-dimethylbutyric acid (**1b**, obtained via deamination from *L-tert*-leucine) and (*S*)-hexahydro mandelic acid (**1c**).

The synthesis acording to Fig. 2 starting from **1a** went smoothly until the electrochemical methoxylation (according to method C in the preceding publication). Under the slightly acidic conditions of the indirect electrochemical oxidation of the chiral morpholinedione, the lactone is opened and the open-chain peptolide is subsequently transformed into the iminoester which intramolecularly cyclizes to the undesired methyl 5-isopropyl-4-oxazolidinone-2-carboxylate.

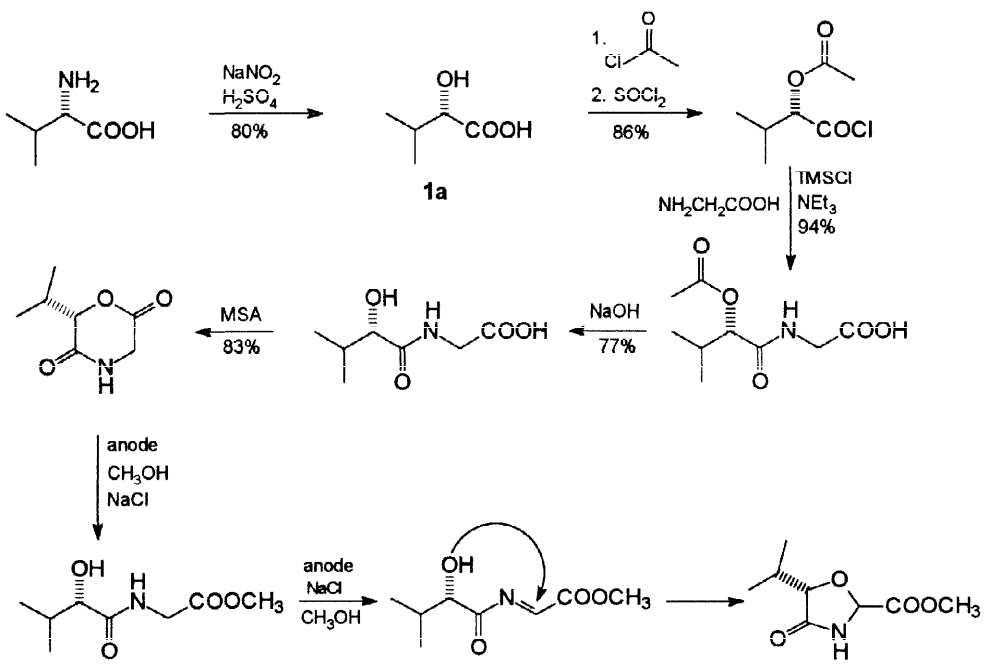


Figure 2: Attempted synthesis of a 6-substituted chiral 3-methoxy-2,5-morpholinedione via indirect electrochemical methoxylation of a cyclic dipeptolide.

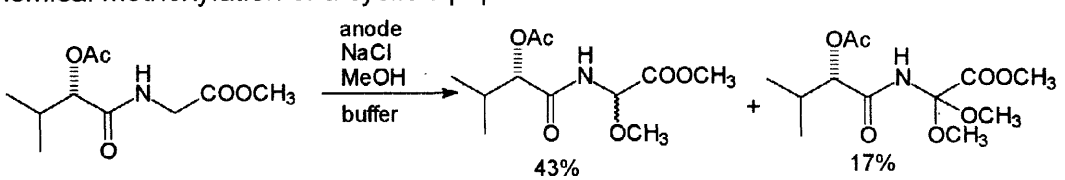


Figure 3: Indirect electrochemical methoxylation of the protected dipeptolide from (*S*)-2-hydroxy-isovaleric acid and glycine methyl ester

To avoid this problem, instead of performing the electrochemical methoxylation on the stage of the chiral cyclic dipeptolide, we already did it on the stage of the protected open-chain dipeptolide using the NaCl-mediated process. However, as in the case of *N*-Boc-*L*-Pro-GlyOMe (see preceding

paper) dimethoxylation can not be avoided giving the monomethoxylated product in 43% and the dimethoxylated compound in 17% yield (Fig. 3).

Therefore alternatively, we went through the dipeptolide **3** from the α-hydroxy acid **1** and dimethyl amino malonate (AMDM) which could be methoxylated selectively and effectively by method C to give **4** in high yield. The desired monomethoxylated dipeptolide **5** was formed from **4** *via* decarboxylative hydrolysis in practically quantitative yield (Fig. 4).

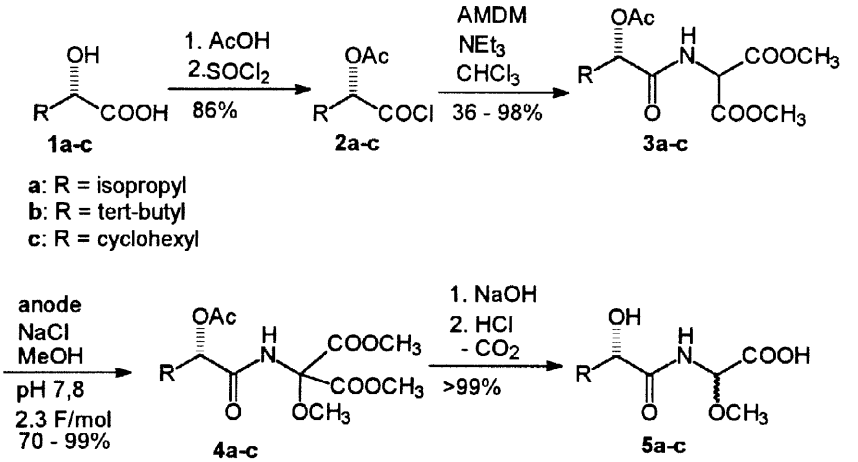


Figure 4: Selective formation of monomethoxylated dipeptolide **5**. (AMDM = amino malonic acid dimethyl ester).

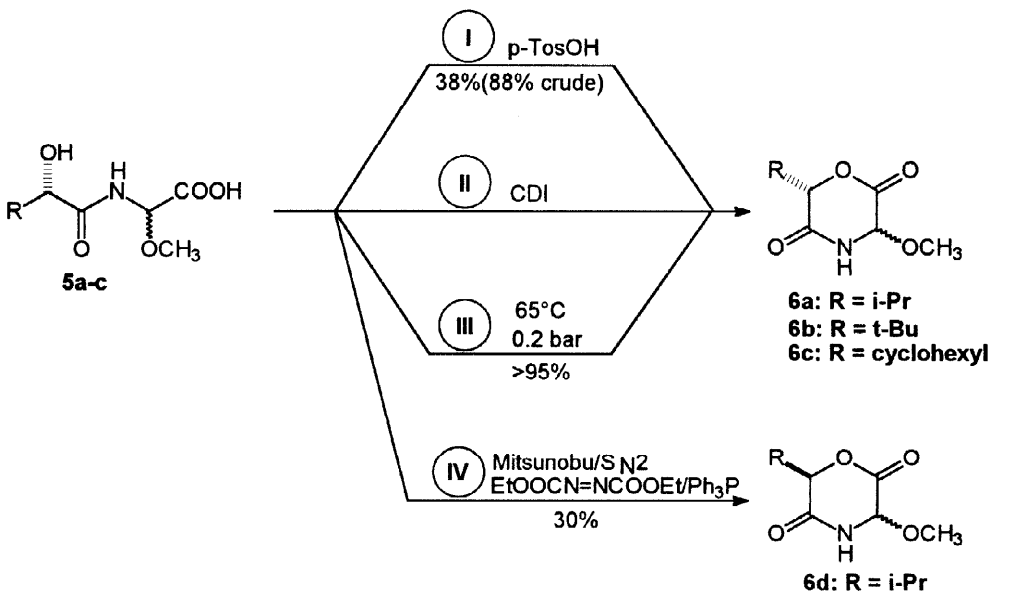
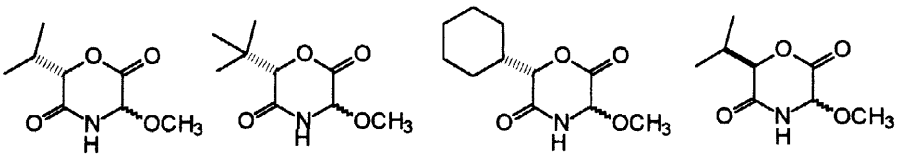


Figure 5: Cyclization methods for the open-chain methoxylated dipeptolide **5** (p-TosOH = p-toluene sulfonic acid; CDI = carbonyl diimidazole).

The cyclization of **5** can be performed in four different ways. The acid catalyzed reaction (p-TosOH = *p*-toluene sulfonic acid; method **I**) gives the cyclized product **6** in 38 % yield. Cyclization by carbonyl diimidazole (CDI, method **II**) is quantitative, however the separation of the product from imidazole is tedious and results in large product losses. Therefore, for method II we did not separate and purify **6** but used the crude product directly for the following nucleophilic exchange

reaction to give **7**. We found, that most simply and effectively **5** cyclizes spontaneously under reduced pressure and elevated temperature (method **III**). Thus, practically quantitative yields of the cyclized products could be obtained. Under *Mitsunobu*[3] conditions (method **IV**) inversion of the configuration occurs. The yields of 30% are unoptimized yet. Thus, starting from only one chiral hydroxy acid both configurations at C-6 can be obtained (Fig 5).

Thus, the following methoxylated cyclic dipeptolides **6a-d** could be obtained.



6a **6b** **6c** **6d**

We used the chiral electrophilic glycine equivalents **6a-d** to compare the diastereoselectivities in amidoalkylation reactions. As a test reaction, we employed the $TiCl_4$ catalyzed reaction with allyl trimethyl silane and ally triphenyl silane.

The diastereoselctivities are somewhat lower as compared with the methoxylated cyclic *N,O*-acetal cyclo(*L*-Pro-Gly(OMe)OMe.[1] The 6-*tert*-butyl group in **6b** does not improve the diastereoselectivity as compared with the 6-isopropyl group in **6a** and **6d**. However, the 6-cyclohexyl group in **6c** results in a higher stereoselectivity. By increasing the size of the nucleophile from allyl trimethylsilane to allyl triphenylsilane the stereoselectivity is drastically enhanced from 73% *de* to 90% *de*. Starting from **6a** or **6d**, both obtained from *L*-hydroxy valeric acid, the enantiomeric products **7a** and **7d** can both be obtained (Figure 6).

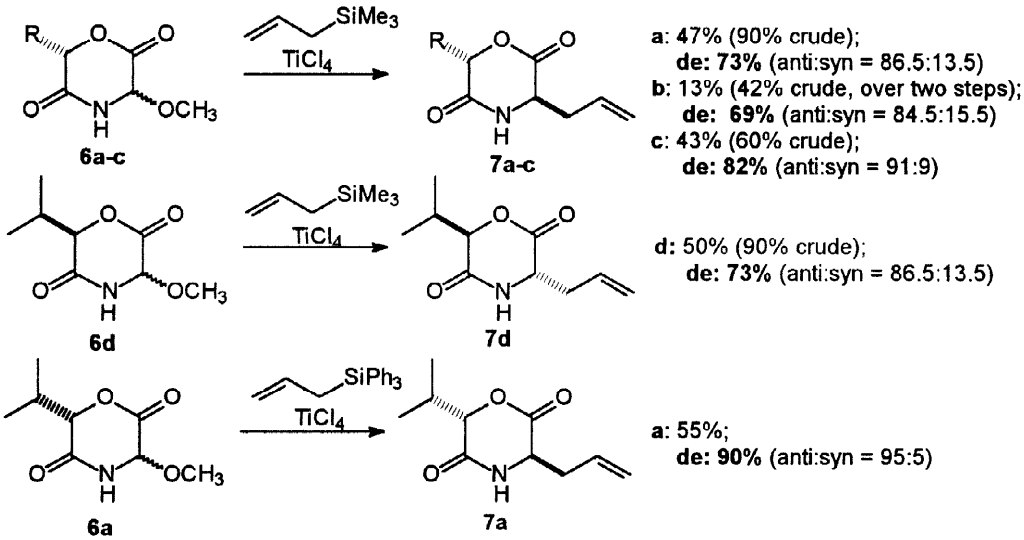
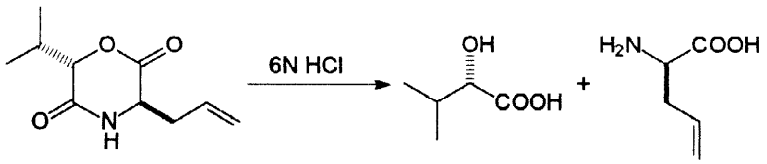


Figure 6: Methoxy group exchange in compounds **6a-d** by allyltrimethyl and triphenyl silane.

As expected, the cleavage of the products like **7a** occurs under mild conditions and the separation of the starting chiral hydroxy acid and the *D*-allyl glycine **8** can be performed easily and effectively by extraction. **8** was purified over a short cation exchange column to give the amino acid in 71% yield. The optical purity of **8** was determined by measuring the specific rotation giving a value of $[\alpha]_D^{21}$ = +33.5° (c = 1, H_2O) which compares well with the literature value of $[\alpha]_D^{24}$ = +37.8.[4] (*S*)-2-

hydroxyisovaleric acid was obtained in 71% and showed a specific rotation of $[\alpha]_D^{21}$ = +17.4° (c = 1, $CHCl_3$). Literature values are +19.1°,[5] 16.9°,[6] and 18.0°.[7]



7a 71% **8** (62%)

Figure 7: Hydrolysis of **7a** to give *D*-allyl glycine **8**.

It is obvious that the 3-methoxy-2,5-morpholinediones prove to be excellent chiral cationic amino acid equivalents, especially if larger nucleophiles are employed. The easy separation of the amino acid and the α-hydroxy acid by extraction is valuable. The possibility to obtain both enantiomers of the new amino acid from only one chiral precursor is advantageous.

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, Überlingen. Mass spectra: A.E.I., Manchester, MS-9, MS-30, and MS-50. Melting points were recorded on a Reichert, Wien, melting point apparatus and are uncorrected. R_f values were obtained by using thin-layer chromatography (TLC) on silica gel-coated aluminium sheets (Merck silica gel F_{254}). The plates were inspected by UV light prior to development with ninhydrin 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 distiled 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 cyclindrical Pt-foil (25cm^2 or 44 cm^2) anode, a coaxial Pt-wire cathode, and a magetic 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.

General procedure for the protection and activation of the a-hydroxy acids **1a-c**:
The hydroxy acids **1a-c** are initially introduced into a 50 mL three-necked flask equipped with a reflux condenser and freshly distilled acetyl chloride is added. The reaction starts after heating the mixture slightly with a drying pistol. After the evolution of gas bubbles has subsided the mixture is heated for further 15 minutes under reflux and then excess acetyl chloride is removed by distillation. Thionyl chloride is added to the obtained acetoxylated hydroxy acid and refluxed for 2 hours. Excess thionyl chloride is distilled off *in vacuo* and the residue is dissolved in absolute chloroform for the subsequent reaction.
(*S*)- Acetoxyisovaleric acid chlorid (**2a**). According to the general procedure (11.81g, 100 mmol) of **1a** reacted with (19.8 mL, 46 mmol) of acetyl chloride and (21.8 mL, 300 mmol) of thionyl chloride to give 14.25g (80%) of **2a**. M.p 84°C/1 Torr. ^{1}H NMR ($CDCl_3$, 200 MHz): δ =1.07 (d, *J* = 7Hz, 3H, CH_3), 1.13 (d, *J* = 7Hz, 3H, CH_3), 2.17 (s, 3H, O=CCH_3), 2.45 (qqd, *J* = 7; 4Hz, 1H, CH), 4.90 (d, *J* = 4Hz, 1H, OCH) ppm.
(*S*)-2-Acetoxy-3,3-dimethylbutyric acid chlorid (**2b**). According to the general procedure (2.01g, 15.2 mmol) of **1b** reacted with (3.3 mL, 46 mmol) of acetyl chloride and (3.3 mL, 45.5mmol) of thionyl chloride to give 2.31g (80%) of **2b**. M.p 45°C/1 Torr. ^{1}H NMR ($CDCl_3$, 90 MHz): δ = 1.11 (s, 9H, C $(CH_3)_3$), 2.18 (s, 3H, O=CCH_3), 4.75 (s, 1H, OCH) ppm.
(*S*)-2-Acetoxyhexaydromandelic acid chlorid (**2c**). According to the general procedure (5g, 31.65 mmol) of **1c** reacted with (6.96 mL, 94.95 mmol) of acetyl chloride and (6.65 mL, 95mmol) of thionyl chloride to give

5.2 g (76%) of **2c** .^{1}H NMR ($CDCl_3$, 200 MHz): δ =1.02-1.36, 1.55-1.82 (m, 10H, cyclohexyl), 1.97-2.14 (m, 1H, cyclohexyl), 2.12 (s, 3H, $O(CO)CH_3$), 4.91 (d, *J* = 3.7 Hz, 1H, OCH) ppm.

General procedure for the coupling of dimethyl aminomanolate with acetoxy acid chlorides **2a-c.** The acid chloride dissolved in a small quantity of chloroform and the triethylamine are added dropwise to the dimethyl aminomalonate hydrochloride suspended in 150 mL of absolute chloroform and cooled to -20°C (methanol/dry ice) without allowing the temperature to rise above -15°C. After 6 hours, the cooling bath is removed and the reaction solution is stirred for another 2 hours at room temperature. Then, extraction is carried out twice with water, four times with a saturated sodium hydrogen carbonate solution and again with water until the aqueous phase has a neutral pH. After drying the organic phase over $MgSO_4$ and concentrating in *vacuo* a white powder is obtained which is recrystallzed from petroleum ether (40-60)/ethanol (20:1 v/v) to give **3a-c**.

Dimethyl (*S*)-*N*-2-acetoxy-3-methylbutanoyl aminomalonate (**3a**). According to the general procedure, (6g, 33.6 mmol) of **2a** and (9 mL, 64.6 mmol) of triethylamine reacted with (6.17g, 33.6 mmol) of dimethyl aminomalonate hydrochloride to give 9.5g (98%) of **3a**. M.p 101-103°C. $[\alpha]_D^{21}$ = - 17.5° (c = 1 in $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ =0.96 (d, *J* = 6.3 Hz, 6H, 2 CH_3), 2.19 (s, 3H, O=CCH_3), 2.25 (d, *J* = 6.3; 3.8 Hz, 1H CH), 3.80 (s, 6H, 2 $COOCH_3$), 5.10 (d, *J* = 3.8 1H, OCH), 5.15 (d, *J* = 6.3 Hz, 1H, NCH), 6.95 (d broad, *J* = 6.3 Hz, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 22,5 MHz): δ = 16.86 (CH_3), 18.57 (CH_3), 20.77 ($OCCH_3$), 30.81 (CH), 53.47 ($COOCH_3$), 53.56 ($COOCH_3$), 55.67 (NCH), 77.68 (OCH) 166.46 (2CO), 169.38 (CO), 169.83 (CO) ppm. MS: *m/z* =290 (M^+ + H, 0,1%), 289 (M^+ 0,25%), 247 (47), (205 (35), 174 (43), 148 (23), 146 (58), 143 (20), 115(34), 88 (29), 43 (100). IR (KBr): ν_{max} = 3431 cm^{-1} (m), 2975 (s), 1746 (s), 1685 (m), 1518 (m) 1422 (m), 1334(m), 1236 (s), 1198 (m), 1044 (s). HRMS calcd for $C_{12}H_{19}NO_7$: 289.1161 (M^+); found: 289.1166.

Dimethyl (*S*)-*N*-2-acetoxy-3,3-dimethylbutanoyl aminomalonate (**3b**). According to the general procedure, (1.08g, 5.6 mmol) of **2b** and (1.5 mL, 10.8 mmol) of triethylamine reacted with (1.03g, 5.6 mmol) of dimethyl aminomalonate hydrochloride to give 1.14g (67%) of **3b**. M.p 62 - 64°C. ^{1}H NMR ($CDCl_3$, 200 MHz) : δ =1.03 (s, 9H, C $(CH_3)_3$), 2.18 (s, 3H, O=CCH_3), 3.82 (s, 6H, 2 $COOCH_3$), 4.88 (s, 1H, OCH), 5.15 (d, *J* = 6,2 Hz, 1H, NCH), 6.86 (d broad, *J* = 6.2 Hz, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 22,5 MHz): δ = 20.77 ($OCCH_3$), 26.08 ($C(CH_3)_3$), 34.27 ($C(CH_3)_3$, 53.47 ($COOCH_3$), 53.56 ($COOCH_3$), 55.70 (NCH), 80.59 (OCH), 166.56 (CO), 168.47 (CO), 169.80 (CO) ppm. MS: *m / z* =304 (M^+ + H, 0,6%), 247 (M^+ + H - C_4H_9, 69%), 205 (72), 174 (43), 157 (35), 148 (73), 146 (50), 129 (40), 88 (54), 87 (58), 69 (20), 57 (23), 43 (100). IR (KBr): ν_{max} = 3367 cm^{-1} (m), 2958 (s), 1743 (s), 1689 (s), 1513 (m) 1436 (m), 1371(m), 1232 (s), 1026 (m), 736 (w). HRMS calcd for $C_{13}H_{21}NO_7$: 304.1390 (M^+ + H) ; found: 304.1390.

Dimethyl (*S*)-*N*-2-acetoxy-2-cyclohexylethanoyl aminomalonate (**3c**). According to the general procedure, (7.45g, 31.65 mmol) of **2c** and (8.55 mL, 63.6 mmol) of triethylamine reacted with (5.82g, 31.65 mmol) of dimethyl aminomalonate hydrochloride to give 6.56g (63%) of **2c**. M.p 125 - 127°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.94-1.38; 1.55-1.82 (m, 10H, cyclohexyl), 1.84-2.03 (m, 1H, cyclohexyl), 2.18 (s, 3H, $O(CO)CH_3$), 3.81 (s, 6H, 2 $COOCH_3$), 5.10 (d, *J* = 4,4Hz, 1H, OCH), 5.18 (d, *J* = 6.6 Hz, 1H, NCH), 6.96 (d broad, *J* = 6,6 Hz, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 50,3 MHz): δ = 20.81 ($O(CO)CH_3$), 25.89 (CH_2), 25.99 (2 CH_2), 27.15 (CH_2), 29.00 (CH_2), 40.23 (CH, cyclohexyl), 53.50 ($COOCH_3$), 53.56 ($COOCH_3$), 55.67 (NCH), 77.39 (OCH), 166.46 (CO), 169.34 (CO), 169.80 (CO) ppm. MS: *m / z* = 330 (M^+ + H, 1%), 329 (M^+, 0,2%), 298 (6%), 269 (5), 247 (100%), 205 (96), 174 (17), 148 (56), 146 (37), 122 (26), 95 (69), 88 (41), 67 (14), 59 (12), 55 (22). IR (KBr): ν_{max} = 3292 cm^{-1} (m, NH), 2926 (m, CH), 1745 (s, CO), 1658 (s, $CO_{Amide\ I}$), 1547 (m, $CO_{Amide\ II}$) 1438 (m CH), 1371(m), 1239 (m), 1167 (m). Found: C, 54.56; H, 6.99; N, 4.24. $C_{15}H_{23}NO_7$ requires C, 54.70; H, 7.04; N, 4.25.

General procedure for the electrolyses of compounds **3a-c**.

Starting material, supporting electrolyte and solvent are placed in an undivided water-cooled beaker type glass cell (cell 1) with a cyclindrical Pt-foil (25cm^2 or 44 cm^2) anode, a coaxial Pt-wire cathode , and a magnetic stirrer. The starting materials are dissolved in MeOH containing NaCl, Na_2HPO_4, KH_2PO_4 . The electrolysis is carried out under galvanostatic conditions. The reaction is monitored by TLC. For work-up, the solvent is stripped off in a rotary evaporator and the residue is dissolved in 200 mL of water and four times extracted, with 150 mL of chloroform. The combined organic phases are dried over Na_2SO_4, filtered, and the solvent evaporated. The products are separated by flash chromatography on silica gel to give **4a-c**.

Dimethyl(*S*)-*N*-2-acetoxy-3-methylbutanoyl-α-methoxy aminomalonate (**4a**). According to the general procedure, (1.7g, 5.87 mmol) of **3a** and (5.5g, 23.36 mmol) of NaCl, (1.82g, 12.82 mmol) of Na_2HPO_4, (3.82g, 28.07 mmol) of KH_2PO_4 in 200 mL MeOH were electrolyzed at a current density of 9.5 mA/cm^2 until the

consumption of 2.5 F/mol. The product requires no further purification. After work-up, 1.87mg (100%) of **4a** as an oil were obtained. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.97 (d, *J* = 7.5 Hz, 6H, $2CH_3$), 2.19 (s, 3H, $O=CCH_3$), 2.23 (d, *J* = 7.5; 4.5 Hz, 1H CH), 3.31 (s, 3H, OCH_3), 3.82 (s, 6H, 2 $COOCH_3$), 5,01 (d, *J* = 4.5 1H, OCH), 7.56 (broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 22,5 MHz): δ = 16.99 (CH_3), 18.48 (CH_3), 20.71 ($OCCH_3$), 30.61 (CH), 52.50 (OCH_3), 53.89 (2 $COOCH_3$), 77.77 (OCH), 83.89 ($C_{quart.}$), 165.78 (CO), 165.95 (CO), 169.41 (CO), 169.93 (CO) ppm. MS: *m / z* = 260 (M^+ - $C_2H_3O_2$, 8%), 245 (5), 203 (3) 161 (13), 143 (42), 118 (29), 115 (52), 83 (5), 43 (100). IR (KBr): ν_{max}, 3392 cm^{-1} (m, NH), 2963 (m CH), 1752 (s, CO_{Ester}), 1696 (m CO_{AmidI}), 1497 (m CO_{AmidII}), 1259 (m), 1118 (m), 1025 (w), 755 (m).

Dimethyl(*S*)-*N*-2-acetoxy-3,3-dimethylbutanoyl-α-methoxy aminomalonate (**4b**). According to the general procedure, (0.93g, 3.06 mmol) of **3b** and (5.5g, 23.36 mmol) of NaCl, (1.82g, 12.82 mmol) of Na_2HPO_4, (3.82g, 28.07 mmol) of KH_2PO_4 in 200 mL MeOH were electrolyzed at a current density of 9.5 mA/cm^2 until the consumption of 2.1 F/mol. The products were separated by flash chromatography on silica gel with diethyl ether/cycloexane (1:1v/v) as eluent. After work-up, 717mg (70%) of **4b** as an oil were obtained. ^{1}H NMR ($CDCl_3$, 250 MHz): δ =1.05 (s, 9H, $C(CH_3)_3$), 2.18 (s, 3H, $O=CCH_3$), 3.33 (s, 3H, OCH_3), 3.82 (s, 3H, $COOCH_3$), 3.83 (s, 3H, $COOCH_3$), 4.77 (s, 1H, OCH), 7.47 (s, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 22,5 MHz): δ = 20.86 ($OCCH_3$), 26.08 ($C(CH_3)_3$), 34.18 ($C(CH_3)_3$, 59.29 (OCH3), 53.85 ($COOCH_3$), 53.92 ($COOCH_3$), 80.69 (OCH), 83.89 (C_{quart}), 165.78 (CO), 166.11 (CO), 168.66 (CO), 169.99 (CO) ppm. MS: *m/z* =334 (M^+ + H, 1%), 277 (16), 274 (30), 245 (25), 203 (45), 171 (27), 162 (21), 161 (51), 157 (59), 146 (33), 129 (62), 87 (69), 69 (40), 57 (25), 43 (100). IR (KBr): ν_{max} =3445 cm^{-1} (m), 2970 (s), 1729 (m), 1638 (s), 1543 (m) 1368 (m), 1295 (s), 1061 (m), 709 (w). HRMS calcd for $C_{14}H_{23}NO_8$: 333.1417 (M^+) ; found: 333.1417.

Dimethyl(*S*)-*N*-2-acetoxy-2-cyclohexylethanoyl-α-methoxy aminomalonate (**4c**). According to the general procedure, (3.28g, 10 mmol) of **3c** and (5g, 85.5 mmol) of NaCl, (1.82g, 12.8 mmol) of Na_2HPO_4, (3.82g, 28.1 mmol) of KH_2PO_4 in 200 mL MeOH were electrolyzed at a current density of 9.5 mA/cm^2 until the consumption of 2.1 F/mol. The products were separated by flash chromatography on silica gel with diethyl ether/cycloexane (1:1 v/v) as eluent. After work-up, 3.31g (92%) of **4c** were obtained. M.p 63-65°C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.01-1.32; 1.53-1.80 (m, 10H, cyclohexyl), 1.83-2.01 (m, 1H, cyclohexyl), 2.20 (s, 3H, $O(CO)CH_3$), 3.32 (s, 3H, OCH_3), 3.82 (s, 3H, $COOCH_3$), 3.83 (s, 3H, $COOCH_3$), 5.01 (d, *J* = 4.8 Hz, 1H, OCH), 7.59 (broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 20.68 ($O(CO)CH_3$), 25.75 (CH_2), 25.85 ($2CH_2$), 27.21 (CH_2), 28.72 (CH_2), 39.92 (CH, cyclohexyl), 53.37 (OCH_3), 53.83 ($COOCH_3$), 53.85 ($COOCH_3$), 77.33 (OCH), 83.76 (C_{quart}), 165.78 (CO), 169.32 (CO) ppm. MS: *m / z* = 360 (M^+ + H, 18%), 328 (8), 183 (100), 155 (44), 146 (29), 118 (11), 95 (51). IR (KBr): ν_{max} = 3332 cm^{-1} (m, NH), 2942 (m, CH), 1784 (s, CO), 1752 (s, CO), 1709 (s, CO) 1512 (m, NH), 1431 (m CH), 1253 (s), 1118 (s). Found: C, 53.48; H, 7.02; N, 3.84. $C_{16}H_{25}NO_8$ requires C, 53.67; H, 7.01; N, 3.90.

General procedure for deprotection and decarboxylation of dipeptolides **4a-c**.

The protected dipeptolide and the sodium hydroxide are dissolved in water and stirred for 3 hours at room temperature. For the complete extraction of the product into the organic phase the aqueous phase is acidified with HCl to a pH value of 1.5 - 2.0 and then continously extracted for 48 hours with diethyl ether in a continous light phase perforator. After drying the ether phase with Na_2SO_4 and distilling off the solvent, the products **5a-c** are obtained.

(*S*)-*N*-(2-Hydroxy-3-methylbutanoyl)-α-methoxyglycine (**5a**). According to the general procedure, the protected dipeptolide **4a** (0.6g, 1.88 mmol) and the sodium hydroxide (0.24g, 6 mmol) reacted to give 386 mg (100%) of **5a** as a white powder. M.p 78-80° C. ^{1}H NMR (D_2O, 200 MHz): δ = 0.85 (d, *J* = 7.2 Hz, 3H, CH_3), 0.96 (d, *J* = 7.2 Hz, 3H, CH_3), 2.06 (septet, d, *J* = 7.2; 3.6 Hz, 1H CH), 3.38 (s, 3H, OCH_3) 4.03 (d, *J* = 3.6 Hz, 1H, OCH), 5.28 (s, 1H, NCH) ppm; ^{13}C NMR (CD_3OD, 50.3 MHz): δ = 16.28 (CH_3), 19.52 (CH_3), 32.96 (CH), 56.35 (OCH_3), 76.96 (CH), 79.19 (CH,) 170.77 (CO), 177.45 (CO) ppm.

(*S*)-*N*-(2-Hydroxy-3,3-dimethylbutanoyl)-α-methoxyglycine (**5b**). According to the general procedure, the protected dipeptolide **4b** (496 mg, 1.49 mmol) and the sodium hydroxide (200 mg, 5 mmol) reacted to give 327mg (100%) of **5b** as a viscous oil. ^{1}H NMR (CD_3OD, 200 MHz): δ = 0.9 (s, 9H, $C(CH_3)_3$), 3.27 (s, 3H, OCH_3), 3.68 (s, 1H, OCH), 5.35 (s, 1H, NCHO) ppm; ^{13}C NMR (CD_3OD, 50.3 MHz): δ = 26.51 ($C(CH_3)_3$), 36.12 ($C(CH_3)_3$, 56.37 (OCH_3), 79.97(CH), (80.12 (CH), 168.31 (CO), 175.52 (CO) ppm. IR (KBr): ν_{max} = 3388 cm^{-1} (s), 2973 (s), 1731(s), 1666 (s), 1503 (m), 1367 (m), 1268 (m), 1108 (m), 1021 (w).

(S)-*N*-(2-Hydroxy-2-cyclohexylethanoyl)-α-methoxyglycine (**5c**). According to the general procedure, the protected dipeptolide **4c** (3.31g, 9.2 mmol) and the sodium hydroxide (1.6g, 40 mmol) reacted to give 2.25g (100%) of **5c** as a glassy solid. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.12-1.35; 1.51-1.84 (m, 10H, cyclohexyl), 2.04 (s, 1H, cyclohexyl), 3.27 (s, 1H, OCH_3), 3.81 (s, 1H, CH), 3.96 (d, *J* = 3.2 Hz, CH) ppm; ^{13}C NMR

($CDCl_3$, 62.9 MHz), partial signal doubling because of distereomers: δ = 26.98 (CH_2), 27.02 (CH_2), 27.21 (CH_2), 30.18 (CH_2), 42.78 and 42.81 (CH, cyclohexyl), 52.08 and 52.21 (OCH_3), 54.38 (CH), 76.51 and 76.56 (CH), 168.44 and 168.48 (CO), 176.54 and 176.62(CO) ppm;

Procedure for the cyclization of hydroxy acid **5a** directly from **4a** with a Broensted acid (Method I).
The protected dipeptolide **4a** (2.04g, 7.8 mmol) and sodium hydroxide (0.79g, 19.7 mmol) are dissolved in 100 mL of water and deprotected according to the preceding section. The cyclization to form the morpholine dione is carried out directly without isolation of the product by acid-catalyzed intramolecular lactonization with toluene sulphonic acid (0.1g, 0.06 mmol) in 273 mL of absolute chloroform and 30 mL of absolute benzene. This mixture is refluxed in a Soxhlet apparatus the vial being filled with 3 A° molecular sieves to reflux until no more reactant can be detected by TLC. The solvent is removed in a rotary evaporator and the residue is dissolved in 25mL of ethyl acetate and washed four times with 10 mL of phosphate buffer solution. After drying the organic phase with Na_2SO_4 and distilling off the solvent, 1.28g (88%) of the crude product *(trans:cis* = 5:1*)* is obtained. The diastereomeric products are separated by flash chromatography on silica gel using diethyl ether: cyclohexane (2:1 v/v) as the eluent. Only the product with the *trans* configuration (0.55g, 38 %) is obtained as colorless oil.
(3RS, 6S)-6-Isopropyl-3-methoxymorpholine-2,5-dione **6a**. ^1H NMR $CDCl_3$, 200 MHz): δ = 0.95 (d, *J* = 7 Hz, 3H, CH_3), 1.13 (d, *J* = 7 Hz, 3H, CH_3), 2.53 (qqd, *J* = 7; 7; 2.5 Hz, 1H, CH), 3.50 (s, 3H, OCH_3) 4.85 (d, *J* = 2.5 Hz, 1H, OCH), 4.80 (d, *J* = 4.5 Hz, 1H, NCH), 7.06 (broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 15.37 (CH_3), 18.60 (CH_3), 28.85 (CH), 56.11 (OCH_3), 80.86 (CH), 81.33 (CH), 163.02 (CO), 169.88 (CO) ppm. MS: *m / z* =188 (M^+ + H, 6%), 187 (M^+ ,0.02%), 156 (3), 145 (18), 143 (18), 128 (40), 116 (46), 115 (48), 100 (14), 60 (100), 43 (31). IR (KBr): ν_{max} = 3580 cm^{-1} (w), 3400 (m), 3080 (m CH), 1850 (s, CO_{Ester}), 1800 (s CO_{Amidl}), 1560(w), 1460 (w), 1420 (m), 1360 (w), 1320 (w), 1170 (m, C-O), 1120 (m), 1090 (w), 1060 (w), 1010(w). HRMS calcd for $C_8H_{13}NO_4$: 187.0845; found: 187.0813.

General procedures for the cyclization of hydroxy acids **5a** and **5b** to the morpholine-2,5diones **6a** and **6b** by reaction with *N,N*-carbonyldiimidazole without isolation (Method II).
In a flask which has been flame dried and purged with argon the free dipeptolide (1.6 mmol) is dissolved in 20 mL of absolute THF and reacted with *N,N'*-carbonyldiimidazole (322 mg, 2 mmol) dissolved in 3 mL of absolute THF. The evolution of gas bubbles indicates the spontaneously commencing reaction. After 10 min, the reaction is complete giving only the desired product quantitatively according to GC/MS. The solvent is removed in a rotary evaporator and the residue dissolved in 15 mL of absolute CH_2Cl_2. Because the isolation and purification of the product was not possible without a dramatic loss in yield, the crude product dissolved in dichloromethane was directly used for the nucleophilic substitution. (See nucleophilic exchange reaction).

General procedure for the cyclization of hydroxy acids **5a** and **5c** to the morpholine 2,5 diones **6a** and **6c** in a drying pistol *in vacuo* (Method III) The open-chain dipeptolides **5a** and **5c** are introduced into a specimen jar with a height of 10 cm. This is heated slowly to 65°C in a drying pistol in vacuo (0.2 bar). Samples are taken to examine the progress of the cyclization by GC. After 5-6 days the reaction is complete. The product is dissolved in absolute dichloromethane under an inert gas atmosphere for the subsequent reactions.
(3RS, 6S)-6-Isopropyl-3-methoxymorpholine-2,5-dione **6a**. According to the general procedure 1.25g (6 mmol) of the open-chain dipeptolide **5a** are cyclized in a drying pistol. After 6 days, 1.12g (100 %) of **6a** are obtained. M.p 70°C. The spectroscopic data are identical to those obtained for the same compound by cyclization method I(see above).
(3RS, 6S)-6-Cyclohexyl-3-methoxymorpholine-2,5-dione **6c**. According to the general procedure 964 mg (3.9 mmol) of the open-chain dipeptolide **5c** are cyclized in a drying pistol. After 5 days, 886mg (100 %) of **6c** are obtained. M.p 80°C. ^1H NMR ($CDCl_3$, 200 MHz): δ = 1.01-1.37; 1.44-1.93 (m, 10H, cyclohexyl), 2.01-2.18 (m, 1H, cyclohexyl), 3.47 and 3.51 (s, 3H, OCH_3), 4.47 (d, *J* = 5.4 Hz, 1H, OCH), 4.79 and 4.84 (d, *J* = 2.7 Hz, 1H, NCH), 7.76 and 7.86 (d, *J* = 2.7 Hz, 1H, NH) ppm (because of the *3R,S* diastereomers, some signals are doubled).^{13}C NMR ($CDCl_3$, 100.6 MHz): δ = 25.46 and 25.51 (CH_2), 25.67 and 25.77 (CH_2), 25.83 and 26.33 (CH_2), 28.28 and 28.78 (CH_2), 38.56 (CH_2), 41.78 (CH, cyclohexyl), 56.28 and 56.75 (OCH_3), 80.04 and 80.86 (CH), 81.28 and 83.90 (CH), 162.23 and 162.84 (CO), 169.35 and 169.97(CO) ppm (because of the *3R,S* diastereomers, some signals are doubled). MS: *m/z* =183 (M^+-CO_2, 2.6%), 155 (7.9), 145 (47.4), 124 (5.3), 117 (13.2), 95 (10.5), 80 (15.8), 60 (100), 55 (21), 41 (19). HRMS calcd for $C_{11}H_{17}NO_4$ 227.117; found: 227.108.

Procedure for the cyclization of hydroxy acid **5a** under Mitsunobu conditions (Method IV). Triphenylphosphine (420 mg, 1.6 mmol) is dissolved in 5 mL of absolute THF and transferred into a Schlenk tube which has been

flame dried, purged with argon, and cooled to -70°C. After adding diethyl azodicarboxylate (0.25 mL, 1.6 mmol) and stirring for 10 min. **5a** (251 mg, 1.43 mmol) dissolved in 5 mL of absolute THF is added. After 30 min, the cold bath is removed and the reaction mixture is stirred for 14 hours at room temperature. The THF is distilled off and the residue purified by chromatography on silica gel using diethyl ether/cyclohexane (3:1v/v) as the eluent. Only the product with the *trans* configuration (*3S,6R*)-6-isopropyl-3-methoxymorpholine-2,5-dione (**6d**), 76 mg (28%) is obtained. The spectroscopic data are identical to those obtained for the *3R,6S* enantiomer **6a** by cyclization methods I and III (see above).

General procedure for the nucleophilic exchange of the methoxy group in **6a-d** by allylsilane under Lewis-acid catalysis.

The Lewis acid, dissolved in 5 mL of absolute dichloromethane, is initially introduced into a Schlenk tube which is flame dried and purged with argon and then cooled to -65°C. Then the 3-methoxymorpholine-2,5-dione, also dissolved in dichloromethane, and the nucleophile are added dropwise in succession. The reaction solution is stirred at -65°C for an additional 3 hours and then slowly warmed to 0°C. In order to carry out the reaction to completion the solution is stirred for further 12 hours at room temperature. 20 mL of water are then added to the reaction solution and the organic phase is washed with a 1M aqueous $NaHCO_3$ solution, dried over Na_2SO_4, and then the dichloromethane is evaporated with a rotary evaporator and the residue purified by chromatography on silica gel.

(*3R,6S*)-Isopropyl-3-(2-propenyl)morpholine-2,5-dione (**7a**) starting from **6a**. *Allyl trimethylsilane as nucleophile*: According to the general procedure, a 1M solution of $TiCl_4$ (1.6 mL, 1.6 mmol) was introduced into the Schlenk tube and reacted with 3-3-methoxy morpholine-2,5-dione **6a** (118 mg, 0.63 mmol) and allyl trimethylsilane (0.23 mL, 1.6 mmol) to give **7a** with a *trans:cis* ratio of 86.5:13.5 (de: 73%). After work-up, 112 mg (90%) of the crude product were obtained. Purification by column chromatography an SiO_2 diethyl ether/cyclohexane (3:1v/v) as the eluent gave only the *trans*-product **7a** with (*3R, 6S*)-configuration (58 mg, 47%). M.p.115°C. $[\alpha]_D^{21}$ = -34.7° (c =1 in $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz): δ = 0.980 (d, *J* = 6.8 Hz, 3H, CH_3), 1.090 (d, *J* = 6.8 Hz, 3H, CH_3), 2.380 (qqd, *J* = 6.8; 6.8; 4.2 Hz, 1H, CH), 2.575 (dddt, *J* = 14; 7.8; 7.2; 1Hz, 1H, CH_2), 2.705 (dddt, *J* = 14; 6.8; 4.4; 1.2 Hz, 1H, CH_2), 4.200 (ddd, *J* = 7.2; 4.4; 1.5; 1.5 Hz, 1H, NCH), 4590 (d, *J* = 4.2 Hz, 1H, OCH) 5.20 - 5.26 (m, 2H, CH_2), 5.735 (dddd, *J* = 16.5; 10.5; 7.8; 6.8 Hz, 1H, CH), 7.30 (s, broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$ 50.3 MHz): δ = 16.20 (CH_3), 18.45 (CH_3), 31.36 (CH), 37.72 (CH_2), 52.85 (NCH), 83.18 (OCH), 121.20 (CH_2), 130.81 (CH), 166.72 (CO), 167.67 (CO) ppm. MS: *m/z* =197 (M^+, 24%), 156 (45), 155 (26), 128 (86), 86 (9), 83 (19), 73 (100), 70 (48), 55 (30), 43 (28) 41 (42). IR (KBr): ν_{max} = 3400 cm^{-1} (w, NH), 3190 (w), 3080 (w), 2960 (m CH), 1750 (s, CO_{Ester}), 1680 (s CO_{Amidl}), 1460(w), 1430 (w), 1370 (w, CH_3), 1320 (m), 1260 (w), 1180 (m, C-O), 1150 (w), 1050 (m), 930(w), 790 (m). HRMS calcd for $C_{10}H_{15}NO_3$: 197.1051; found: 197.1051. *Allyl triphenylsilane as nucleophile*: According to the general procedure, **6a** (137mg, 0.73mmol) is reacted with allyl triphenylsilane (440 mg, 1.5mmol). After work-up and purification by column chromatography on SiO_2 with diethyl ether/cyclohexane (3:1v/v) as eluent. 80 mg (55 %) of **7a** with a *trans/cis* -ratio of 95:5 (90% *de*) are obtained. The spectroscopic data are identical to the preceding ones.

(*3S,6R*)-6-Cyclohexyl-3-(2-propenyl)morpholine-2.5-dione (**7c**) starting from **6c**. According to the geneneral procedure, **6c** (440 mg, 1.93 mmol) reacted with allyl trimethylsilane (0.72mL, 5 mmol). After work-up and purification by column chromatography on SiO_2 with diethyl ether/cyclohexane (2:1 v/v) as eluent only *trans*-**7c** (195mg, 42.5%) was obtained, while the crude product (270 mg, 60%) showed a *trans/cis* ratio of 91:9 (82% *de*). M.p. 124-127°C. ^1H NMR ($CDCl_3$, 200 MHz): δ =1.03-1.45; 1.58-1.85 (m, 10H, cyclohexyl), 1.92-2.13 (m, 1H, cyclohexyl), 2.54 (dddt, *J* =14.2; 8.1; 2.7; 1.4 Hz, 1H, CH_2), 2.77 (dddt, *J* =14.2; 6.1; 4.1, 1.4 Hz, 1H, CH_2), 4.18 (ddd, *J* = 8.1; 4.1, 1.4 Hz, 1H, NCH), 458 (d, *J* = 4.7 Hz, 1H, OCH) 5.18-5.31 (m, 2H, CH_2), 5.74 (dddd, *J* =21.6; 13.5; 8.1; 6.1 Hz, 1H, CH), 6.60 (s, broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 26.27 (CH_2), 26.53 (CH_2), 27.42 (CH_2), 29.36 (CH_2), 38.36 (CH_2), 41.82 (CH, cyclohexyl), 53.08 (NCH), 84.00 (OCH), 122.09 (CH_2), 131.69 (CH), 167.27 (CO), 167.90 (CO) ppm; MS: *m/z* =237 (M^+, 1%), 200 (6), 173 (36), 168 (9) 155 (20), 123 (21), 95 (100), 74 (86), 70 (62), 60 (45), 55 (47). IR (KBr): ν_{max} = 3326 cm^{-1}(s, NH), 3088 (m, C=C), 2929 (s, CH), 1720 (s, CO), 1629 (s CO_{Amidl}), 1544 (m, CO_{AmidII}), 1449 (m CH), 1211 (s), 1103 (s), 990 (m), 923 (m), 706 (m).

(*3R,6S*)-6-*tert*-Butyl-3-(2-propenyl)morpholine-2,5-dione (**7b**) from **5b** without isolation of **6b**. In a flask which has been flame dried and purged with argon, the free dipeptolide **5b** (250 mg, 1.1 mmol) is first cyclized according to the general procedure (method II) with *N,N'*-carbonyldiimidazole (215 mg, 1.32 mmol) dissolved in 3 mL of absolute THF. The evolution of gas bubbles reveals the spontaneously commencing reaction. The crude product **6b** of the cyclization reacted with allyl trimethylsilane (0.98 mL, 6.16 mmol) according to the general procedure for the allylation with 1M $TiCl_4$ solution (6.16 mmol). After work-up, 59 mg (42% over two steps) of

crude **7b** were obtained. Purification by column chromatography on SiO_2 with diethyl ether: cyclohexane (1:5 v/v) as eluent only gave *trans* **7b** (30 mg, 13% over two steps) while the crude product showed a *trans/cis*-ratio of 84.5:15.5 (69% *de*). M.p. 103°C. ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.10 (s, 9H, $C(CH_3)_3$), 2.50 (m, 1H, CH_2), 2.83 (m, 1H, CH_2),4.17 (dd, *J* = 8.3; 8.3 Hz, 1H, NCH), 4.45 (s, 1H, OCH) 5.21-5.28 (m, 2H, CH_2), 5.73 (m, 1H, CH), 6.50 (s, broad, 1H, NH) ppm; ^{13}C NMR ($CDCl_3$, 50.3 MHz): δ = 26.13 ($C(CH_3)_3$), 37.51 ($C(CH_3)_3$, 37.76 (CH_2), 52.29 (NCH), 87.14 (OCH), 121.45 (CH_2), 131.272 (CH), 166.04 (CO), 166.68 (CO) ppm. MS: *m/z* =212 (M^++H, 5%), 211 (M^+, 17%), 170 (100), 142 (46), 127 (39), 117 (12), 113 (41), 96 (44), 87 (63), 86 (48), 70 (77), 57 (71), 41 (35). IR (KBr): ν_{max} = 3398 cm^{-1}(m), 3082 (s), 2962 (s), 1747 (s), 1684 (s), 1527 (m), 1374 (m), 1265 (m), 994 (s), 739 (s). HRMS calcd for $C_{11}H_{17}NO_3$: 211.1204; found: 211.1209.

(*3S,6R*)-6-Isopropyl-3-(2-propenyl)morpholine-2.5-dione (**7d**) from **6d**. According to the general procedure and identically to the allylation of the *3R,6S* derivative **6a**, the *6R* derivative **6d** (76 mg, 0.41 mmol) reacted with allyl trimethylsilane (0.16 mL, 1.1 mmol) to give 73 mg (0.37 mmol, 90%) of **7d** as a crude product with a *trans/cis* ratio of 86.5:13.5 (73 % *de*). Chromatographic purification according to compound **7a** gave only *trans*-**7d** (42 mg, 0.21 mmol, 50%). $[\alpha]_D^{21}$ = +34.7° (c =1 in $CHCl_3$). The spectroscopic data were identical to those of **7a**.

Hydrolysis of the (*3R,6S*)-Isopropyl-3-(2-propenyl)morpholine-2.5-dione (**7a**) and isolation of enantiomerically pure (*S*)-2-hydroxyisovaleric acid and *D*-allyl glycine.

To the morpholine dione **7a** (70 mg, 0.35 mmol) 10 mL of water are added and the mixture is stirred for 9 hours at 90°C. The reaction solution is evaporated to dryness, the residue dissolved in 8 mL of 6 N HCl and refluxed for 6 hours. After cooling to room temperature, an additional 15 mL of water are added and extraction is carried out twelve times with diethyl ether. The organic phase is dried over Na_2SO_4, concentrated and the remaining crude (*S*)-2-hydroxyisovaleric acid purified by vacuum sublimation to give 30 mg (71%) $[\alpha]_D^{21}$ = + 17.4° (c = 1 in $CHCl_3$). The isolation of the amino acid from the aqueous phase is carried out by chromatography on a cation exchange resin. For this purpose a short column (diameter: 2 cm, length: 12 cm) is filled with the acidic cation exchanger Dowex 50-W X4, 50 - 100 mesh (Fluka AG), washed with water followed by a 5% NH_3 solution, water, dilute HCl and finally once again with water, until the eluate is neutral. Then, the aqueous acidic solution of the amino acid is concentrated to a volume of 2 - 3 mL, applied to the column and subsequently washed with 150 mL of water. The elution of allyl glycine is carried out using a 5% NH_3 solution. The eluate is evaporated *in vacuo* and the allyl glycine obtained is recrystallized from ethanol/water. To give 25 mg (63 %), $[\alpha]_D^{21}$ = + 33.5° (c = 1 in H_2O).

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