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Crystallization-induced asymmetric transformations (CIAT): stereoconvergent acid-catalyzed lactonization of substituted 2-amino-4-aryl-4-hydroxybutanoic acids

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Abstract—Acid-catalyzed lactonization in dilute hydrochloric acid of *N*-substituted 2-amino-4-aryl-4-hydroxybutanoic acids with electron donating aryl substituents is stereoconvergent. The stereochemical outcome is controlled by the precipitation of little soluble *cis*-lactones, starting from both *syn*-2-amino-4-aryl-4-hydroxybutanoic acids and *anti*-2-amino-4-aryl-4-hydroxybutanoic acids or their mixtures. A highly diastereoselective two-step sequence (acid-catalyzed lactonization with CIAT process followed by alkaline hydrolysis) for the transformation of *syn*-**3b–d** to the corresponding *anti*-**3b–d** is reported.

1. Introduction

The γ-hydroxy-α-amino acid unit plays an important role in biologically active substances. Among them the γ-aryl-γ-hydroxy-α-amino acids and the related 4-aryl-substituted 2-aminobutanolides form part of the antifungal agents such as nikkomycines,[1] echinocandins[2–4] or immunosuppressive cymbimycins[5] and have been used as unnatural acids in peptidomimetics and in the site-directed mutagenesis studies.[6]

The preparation of such hydroxy substituted amino acids remains a significant synthetic challenge. The key intermediates for their synthesis are enantiomerically pure aroylalanines. Such alanines are readily available via a chiral pool approach using aspartic acid[7,8] and serine[9] as the source of chirality or alternatively via enantioselective alkylation of 2-imino esters.[10–12] This efficient synthetic method represents a sequence consisting of an *aza*-Michael addition coupled to the crystallization-induced asymmetric transformation (CIAT). This has been used for the synthesis of ACE inhibitors[13,14] as well as the synthesis of enantiomerically pure homophenylalanines.[15] The application of 1-phenylethylamine in such a transformation is especially favorable as both the enantiomers of phenylethylamine are readily available, with both antipodes of the final compounds attainable. Recent applications of *aza*-Michael-based CIAT processes have been elaborated in our laboratory.[16–19]

The reduction of γ-oxo-α-amino acids or their esters was realized with different types of reducing agents. In the case of γ-arylsubstituted γ-oxo-α-aminobutanoic acids or esters, the best diastereoselectivity in favor of the *anti*-isomer was achieved using Et_3SiH under acidic conditions (54:7 or 90:10).[20,21]

We have developed the highly diastereoselective catalytic reduction of *N*-alkyl substituted aroylalanines **2** leading to the corresponding *syn*-γ-aryl-γ-hydroxy-α-amino acids.[22] The stereoselectivity of the reduction can be interpreted in terms of chelate formation with a manganese(II) salt, followed by an axial attack of the hydride on the half-chair transition state, which favors the formation of a chair conformation (Fig. 1).

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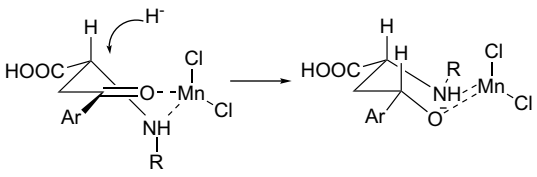
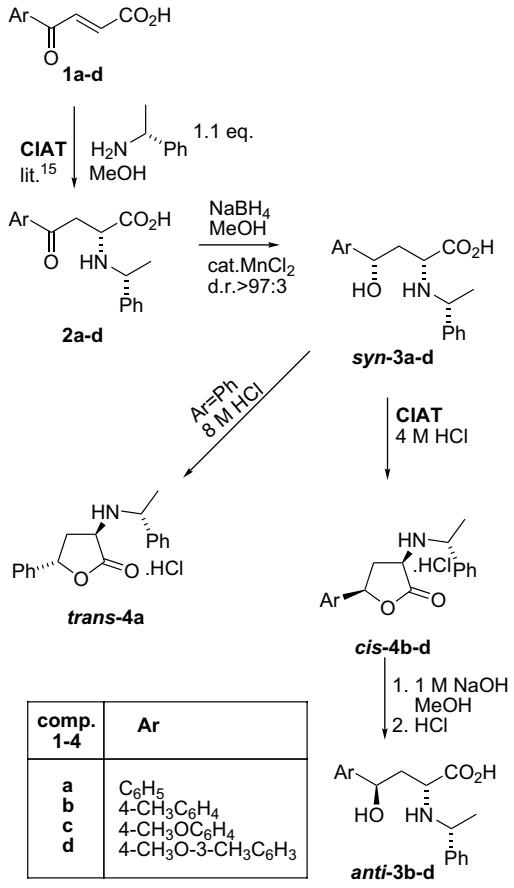


Figure 1.

The chelation increases the solubility of the starting oxoamino acids in reaction media and also augments the reactivity of the carbonyl group. The catalytic amount of $MnCl_2$ was sufficient for the control of stereoselectivity in all the cases studied. Unfortunately, the enantiomerically pure *syn*-γ-hydroxy-α-amino acids **3a**–**d** exhibited a high gelation ability, making their purification a tedious and time consuming operation. Herein, we report their transformation to more convenient derivatives.

2. Results and discussion

The acid-catalyzed lactonization of *syn*-**3a**–**d** in dilute HCl was selected. The conditions of the high yield precipitation of the only slightly soluble hydrochlorides of the corresponding lactones **4a**–**d** (Scheme 1) were optimized. As an aryl substituent becomes progressively more electron donating, the precipitation of solid lactone hydrochlorides proceeds more easily. In the case of 4-methoxysubstituted **3c** and **d**, simple stirring of the reaction mixture in 4 M HCl at 20–25 °C for several hours was sufficient. The tolyl substituted derivative **3b** requires prolonged reaction time and elevated temperature (50 °C). Attempted lactonization of the phenyl derivative **3a** under the above mentioned conditions (*c* 0.05 M in 4 M HCl; 50 °C) gives a mixture of the starting material as well as both *cis*- and *anti*-lactones together with the growing amount of β,γ-unsaturated (*E*)-4-phenyl-2-(1phenylethylamino)but-3-enoic acids.[23] The solid butanolide *trans*-**4a** was obtained in reasonable yield (68%) by increasing both the concentration of **3a** and hydrochloric acid (0.14 M in 8 M HCl; 20 °C) (Scheme 1). Prepared butanolides **4a**–**d**, unlike starting *syn*-hydroxyamino acids **3a**–**d**, are easy to handle and can be further purified by crystallization.

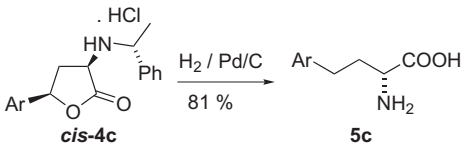


comp. 1-4	Ar
a	C_6H_5
b	4-$CH_3C_6H_4$
c	4-$CH_3OC_6H_4$
d	4-CH_3O-3-$CH_3C_6H_3$

Scheme 1.

The diastereomeric ratio of the precipitated products was high in all cases. However, only with phenyl derivative **3a** was the expected *trans*-**4a** obtained. In all other examples, an inversion of the configuration on C-4 of the starting **3b**–**d** took place and *cis*-butanolides **4b**–**d** were isolated in high yield (70–91%) and excellent diastereoselectivity (d.r. >95:5 in the reaction mixture and up to 99:1 in filtered solid product). The inversion of the configuration on C-4 was unambiguously confirmed by the alkaline hydrolysis of the **4b**–**d** to the corresponding *anti*-**3b**–**d** (Scheme 1) as well as confrontation of the HPLC records with those of the starting *syn*-**3b**–**d**.

In order to establish that no loss of stereochemical integrity at C-2 had occurred during the lactonization process, a sample of lactone **4c** was subjected to catalytic hydrogenation to give 4-methoxyhomophenylalanine **5c** (Scheme 2), which was enantiomerically pure as confirmed by comparison of the specific rotation data with those in the literature[15] as well as with the sample prepared by direct hydrogenolysis of compound **2c**.



Scheme 2.

The 2,4-relationship of lactones **4a**–**d** was further confirmed by the NOE experiments depicted in Figure 2. The butyrolactones are known to exist in the envelope conformation and in the solution an equilibrium of two conformers should be considered.[24] In analogous 3,5-dihydro-2(3*H*)-furanones,[20,25] the cis-isomers were found to be conformationally stable with the substituents taking up pseudo-equatorial positions, causing a very distinct NOE between the H-2 and H-5 protons. In the case of the more conformationally labile *trans*-**4a**, the decoupling at the signals of H-2- and H-5, respectively, led to NOE effect between the H-4α and H-4β only (Fig. 2).

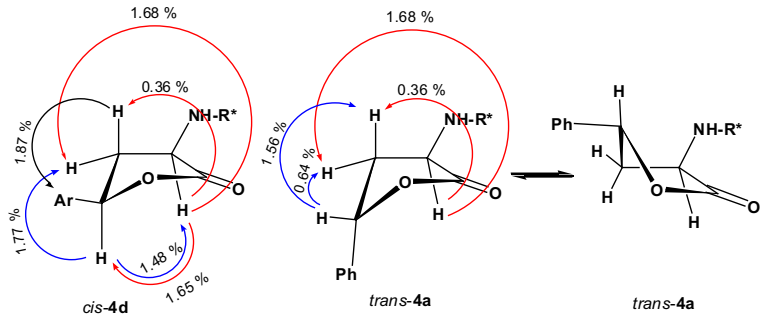


Figure 2. A result of NOE experiments on *cis*-**4d** and *trans*-**4a**, respectively (free base in $CDCl_3$ solution).

The configuration on the newly formed stereogenic centers in relation to the 1-phenylethylamino moiety has been validated by X-ray analysis of **4c** (Fig. 3).[26]

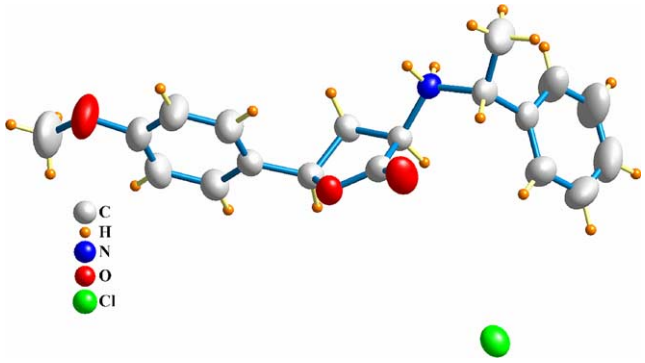
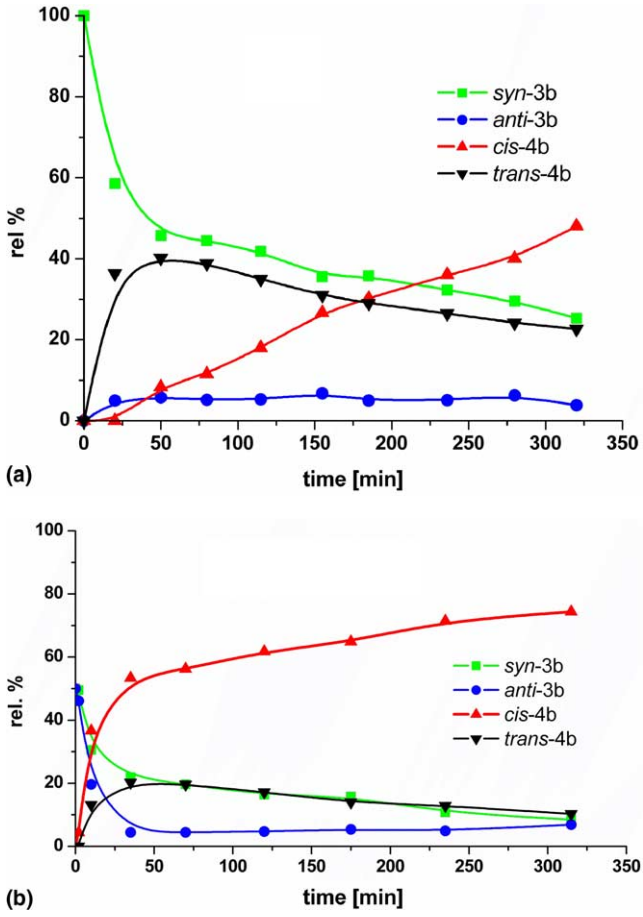


Figure 3. ORTEP drawing of *cis*-butanolide hydrochloride **4c** with thermal ellipsoids drawn at the 50% probability level.†

In order to gain a deeper understanding of the lactonization process, we carried out a series of HPLC-monitored experiments of the cyclization of the hydroxyamino acids **3a**–**c**.

In the case of phenyl derivative **3a**, the cyclization was straightforward with the formation of *trans*-**4a**, with small epimerization on C-4 only. HPLC study of lactonization of **3b** was more illustrative. It has demonstrated the rapid formation of *trans*-butanolide *trans*-**4b**, which reached the maximum concentration when the precipitation of little soluble *cis*-butanolide *cis*-**4b** started (Graph 1a). From this point on, the stereoselectivity was fully controlled by the slow precipitation of *cis*-**4b**, which after the relevant time was filtered off in high diastereo- and enantiomeric purity. Surprisingly, the same result was obtained from the mixture of the hydroxyamino acids (*syn*-**3b**:*anti*-**3b** = 1:1). The precipitation of the solid was more rapid and the predominance of *cis*-**4b** was unequivocal after the first 20 min of the reaction time (Graph 1b).



Graph 1. The distribution of hydroxyamino acids **3b** and their lactones **4b** in the reaction mixture (a) starting from the *syn*-**3b**; (b) from the mixture of *syn*-**3b**:*anti*-**3b** (1:1).

In the case of the 4-methoxysubstituted derivative **3c**, the lactonization was even more rapid. The precipitation of the *cis*-**4c** started within 3–4 min of the reaction, and within one hour the conversion was practically complete. The result is independent of the stereochemistry of the starting hydroxyamino acid. Both *syn*-**3c** and *anti*-**3c** produce the same *cis*-**4c** in high diastereomeric purity (Fig. 4).

It has herein been demonstrated that the level of the observed stereoselectivity is ultimately determined by the

† CCDC 260109 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

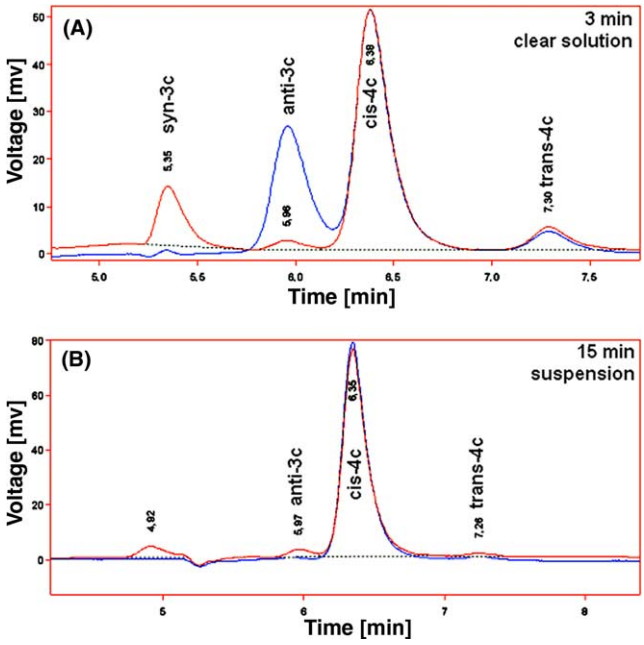
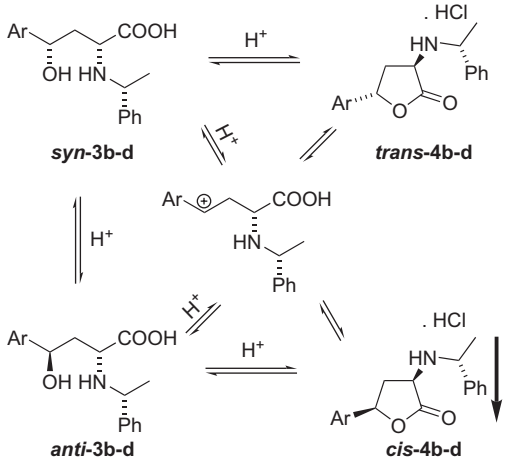


Figure 4. A typical HPLC chromatogram of a reaction mixture of **3c** lactonization (*c* 0.02 M in 4 M HCl; 20 °C). Red line—starting from the *syn*-**3c** (d.r. 97:3), blue line—starting from the *anti*-**3c** (d.r. 99:1). (A) Within the first 3 min of the reaction—clear solution; (B) After 15 min—a suspension. Mobile phase 1.5% (v/v) solution of triethylamine in a mixture of acetonitrile–water (1:2) adjusted to pH 2.9, 0.9 ml/min, other conditions as in the experimental part.

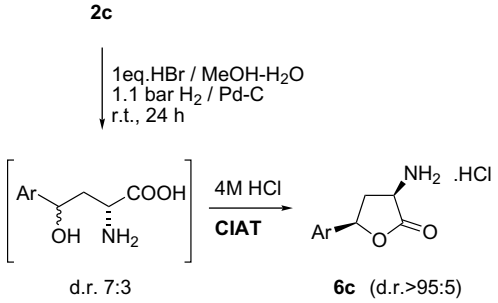
electronic nature of the aryl substituents. The electronic nature of the aryl substituents has previously been shown to effect the stereoselectivity of benzylic substitution reactions with the stereoselectivity being attributed to variations of the cationic nature, and S_N1 versus S_N2 character of the reaction pathway.[27,28]

The acid catalyzed lactonization of the hydroxyamino acids **3b–d** provides selective formation of *cis*-butanolides **4b–d** and can be rationalized by the presence of a rapid equilibrium between the diastereomers in the solution, realized via a stabilized benzylic cation. Without consideration of all the other possible equilibria in the reaction (Scheme 3), the stereoselectivity is fully controlled by the precipitation of the less soluble cis-isomer. Furthermore, the final *cis*-**4b–d**:*trans*-**4b–d** ratio in the solution does not depend on the *syn*-/*anti*-ratio of the starting hydroxyamino acids **3b–d**. It follows that the lactonization is stereoconvergent for all *syn*- and *anti*-hydroxyamino acids **3b–d** with aryl substituents capable or stabilizing the putative benzylic cation and providing less soluble crystalline *cis*-butanolides **4b–d**. The stereochemical outcome of the lactonization is controlled by crystallization and represents an efficient example of the crystallization-induced asymmetric transformation. This CIAT approach could also explain some discrepancies in the earlier experiments on lactonization of racemic γ-aryl-γ-hydroxy-α-amino butanoic acid derivatives.[29]



Scheme 3. Proposed mechanism for the tandem lactonization followed by CIAT.

The efficiency of the CIAT approach is shown in Scheme 4. Regardless of the low selectivity of catalytic hydrogenation of **2c**, which provides a 7:3 mixture of both *syn*- and *anti*-2-amino-4-hydroxy-4-(4-methoxyphenyl)butanoic acids, the following one-pot stereoconvergent lactonization with CIAT allows isolation of butanolide **6c**,[30] which precipitated from the reaction mixture in good yield and high diastereo- and enantiomeric purity.



Scheme 4.

3. Conclusion

We have reported herein a direct and inexpensive preparation of the *N*-substituted *cis*-3-amino-5-aryldihydrofuran-2(3*H*)-ones and *anti*-2-amino-4-aryl-4-hydroxybutanoic acids, with a high degree of diastereomeric purity. The high diastereoselectivity of this lactonization is independent of the bulkiness of the substituents on the nitrogen atom and initial d.r. of the hydroxyamino acids. Approximately equal d.r.s were obtained in both lactonizations **4b–d** and **6c**. Conversely, the π-donor ability of the aryl substituents had a vital influence on the selectivity.

4. Experimental

Melting points were obtained using a Kofler hot plate and are uncorrected. Optical rotations were measured with a Perkin–Elmer 241 polarimeter and a POLAR L-μP polarimeter (IBZ Messtechnik) with a water-jack-

eted 10.000 cm cell at the wavelength of sodium line D (λ = 589 nm). Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 ml. Elemental analyses were performed by the Microanalytical Service of Slovak University of Technology. ^{1}H NMR spectra were recorded on a Varian VXR-300 (299.94 MHz) spectrometer. Chemical shifts (δ) are quoted in ppm and are either referenced to tetramethylsilane (TMS) as internal standard (δ_{Me} = 0.00 ppm for 299.94 MHz) or the residual protic solvent (CH_3OH, δ_H = 3.34 ppm for 299.94 MHz) was used as the internal reference. Coupling constants (J) are recorded in hertz. The following abbreviations were used to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), b (broad). The COSY and transition-NOESY techniques were used in the assignment of proton–proton relationships and the determination of the relative configuration. ^{13}C NMR spectra were recorded on a Varian VXR-300 (75.43 MHz) spectrometer. The multiplicities of carbons were assigned from a broadband decoupled analysis used in conjunction with either APT or DEPT programs. Chemical shifts are quoted in ppm and are either referenced to the tetramethylsilane (TMS) as internal standard (δ = 0.00 ppm for 75.43 MHz) or the central resonance of CD_3OD (δ = 49.0 ppm for 75.43 MHz) was used as the internal reference.

HPLC experiments were carried out using a chromatography system Pye Unicam with PU4225 UV detector. Detection was carried out at 210 nm. The HPLC column used was Spherisorb 5 ODS-2, 250 × 4.6 mm (Varian). The mobile phase was a 1.5% (v/v) solution of triethylamine in a mixture of acetonitrile and water (from 1:2 to 1:4) adjusted to pH 2.9 with *o*-phosphoric acid, which was pumped through the system at 0.5–1.5 ml/min at room temperature. The amount injected was 20 μl. All data were collected and analyzed using CSW 1.7 software (DATAAPEX). (*R*)-Phenylethylamine (99+%, 99% ee) was obtained from ACROS.

4.1. (2*R*)-4-Aryl-4-oxo-2-{[(1*R*)-1-phenylethyl]amino}-butanoic acids 2a–d

To the solution of aroylacrylic acids **1a**–**d** (25 mmol) in methanol (100 ml), (*R*)-1-phenylethylamine (3.33 g, 27.5 mmol) was added under stirring. The mixture was stirred at 45 °C for 20–40 h in the dark. The course of the CIAT process was monitored by HPLC. The precipitate was filtered off, washed with methanol (10 ml) and ether (2 × 10 ml), and dried under reduced pressure to give the corresponding adduct as a white powder with d.r. >96:4. Small quantity of diastereommerically pure crystals has been obtained by crystallization from the acetonitrile–water mixture.

4.1.1. (2*R*)-4-Oxo-4-phenyl-2-{[(1*R*)-1-phenylethyl]amino}-butanoic acid 2a. Yield 5.3 g (71%; d.r. 97:3); mp 194–196 °C (CH_3CN/H_2O); $[\alpha]_D^{20} = -36.5$ (*c* 0.5; MeOH/1 M H_2SO_4 = 3:1); ^{1}H NMR (D_2O/DCl): δ 7.90 (d, 2H, J = 7.2 Hz, H-2″, H-6″), 7.70 (m, 1H, H-4″), 7.45–7.60 (m, 7H, Ph, H-3″, H-5″), 4.70 (q, 1H, J = 6.9, H-1′), 4.28 (m, 1H, H-2), 3.63–3.91 (m, 2H, H-3), 1.76 (d, 3H, J = 6.9, H-2′). ^{13}C NMR (D_2O/DCl): δ 201.4 (s, C-4), 173.7 (s, C-1), 65.2 (C-2), 56.6 (C-1′), 41.5 (C-3), 21.9 (C-2′), C_{Ar} 137.9 (s), 137.5 (s), 137.8 (d), 133.0 (d), 132.5 (d), 131.9 (d), 131.2 (d), 130.9 (d). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.44; H, 6.49; N, 4.44.

4.1.2. (2*R*)-4-(4-Methylphenyl)-4-oxo-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid 2b. Yield 6.1 g (78%; d.r. 97:3); mp 199–200 °C (CH_3CN/H_2O); $[\alpha]_D^{20} = -52.5$ (*c* 0.5, MeOH/1 M H_2SO_4 = 3:1); ^{1}H NMR (CD_3OD/DCl): δ 7.88 (d, 2H, J = 8.1 Hz, H-2″, H-6″), 7.42–7.62 (m, 5H, Ph), 7.35 (d, 2H, J = 8.0 Hz, H-3″, H-5″), 4.73 (q, 1H, J = 6.9 Hz, H-1′), 4.11 (m, 1H, H-2), 3.59–3.83 (m, 2H, H-3), 2.42 (s, 3H, CH_3), 1.78 (d, 3H, J = 6.3 Hz, H-2′). ^{13}C NMR (CD_3OD/DCl): δ 196.6 (C-4), 170.8 (C-1), 60.4 (C-2), 54.7 (C-1′), 39.8 (C-3), 21.7 (CH_3), 20.3 (C-2′), 146.6 (s), 136.7 (s), 134.0 (s), 131.0 (d), 130.7 (d), 130.5 (d), 129.5 (d), 129.1 (d). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.01; H, 6.99; N, 4.14.

4.1.3. (2*R*)-4-(4-Methoxyphenyl)-4-oxo-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid 2c. Yield 5.8 g (71%; d.r. 98:2); mp 191–192 °C (CH_3CN/H_2O); $[\alpha]_D^{20} = -64.0$ (*c* 0.5, MeOH/1 M H_2SO_4 = 3:1); ^{1}H NMR (CD_3OD/DCl): δ 7.98 (d, 2H, J = 8.8 Hz, H-2″, H-6″), 7.45–7.60 (m, 5H, Ph), 7.05 (d, 2H, J = 8.7 Hz, H-3″, H-5″), 4.75 (q, 1H, J = 6.9 Hz, H-1′), 4.11 (dd, 1H, J = 6.1 Hz, J = 4.0 Hz, H-2), 3.90 (s, 3H, OCH_3), 3.62–3.82 (m, 2H, H-3), 1.79 (d, 3H, J = 6.3 Hz, H-2′). ^{13}C NMR (CD_3OD/DCl): δ 195.4 (C-4), 170.8 (C-1), 60.4 (C-2), 56.3 (OCH_3), 54.8 (C-1′), 39.5 (C-3), 20.4 (C-2′), 165.9 (C-4″), 136.7 (s), 131.9 (s), 131.0 (d), 130.7 (d), 129.5 (d), 129.2 (d), 115.1 (d). Anal. Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.47; H, 6.33; N, 4.29.

4.1.4. (2*R*)-4-(4-Methoxy-3-methylphenyl)-4-oxo-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid 2d. Yield 6.3 g (74%; d.r. 98:2); mp 188–192 °C (CH_3CN/H_2O); $[\alpha]_D^{20} = -63.3$ (*c* 0.5, MeOH/1 M H_2SO_4 = 3:1); ^{1}H NMR (CD_3OD/DCl): δ 7.89 (dd, 1H, J = 8.7 Hz, J = 2.4 Hz, H-6″), 7.8 (d, 1H, J = 2.4 Hz, H-2″), 7.45–7.55 (m, 5H, Ph), 7.05 (d, 1H, J = 8.7 Hz, H-5″), 4.73 (q, 1H, J = 6.9 Hz, H-1′), 4.10 (dd, 1H, J = 6.4 Hz, J = 4.2 Hz, H-2), 3.94 (s, 3H, OCH_3), 3.54–3.80 (ABx, 2H, J = 6.4 Hz, J = 4.2 Hz, H-3), 2.25 (s, 3H, CH_3), 1.79 (d, 3H, J = 6.9 Hz, H-2′). ^{13}C NMR (NaOD/D_2O): δ 195.7 (C-4), 170.9 (C-1), 164.2 (C-4″), 136.7 (C-Ph), 129.0, 128.2 (q), 131.7, 131.1, 130.1, 110.8 (CH), 130.7, 129.1 (CH), 60.3 (C-2), 56.4 (C-1′), 54.9 (OCH_3), 39.4 (C-3), 20.3 (C-2′), 16.3 (CH_3). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.39; H, 6.54; N, 3.97.

4.2. *syn*-(2*R*,4*S*)-4-Aryl-4-hydroxy-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid *syn*-3a-*syn*-3d

To a presonicated (1 min) stirred suspension of **2a**–**d** (8 mmol) and $MnCl_2 \cdot 4H_2O$ (320 mg, 1.6 mmol) in MeOH (120 ml) at 15 °C, $NaBH_4$ (2 × 296 mg, 2 × 8 mmol) was added slowly (20 min). The reaction

mixture was stirred for an additional 30 min, after which water (40 ml) followed by 5 ml of 10% solution of potassium carbonate was added. Methanol was removed under reduced pressure and the remaining volume adjusted to 100 ml with water. The precipitated $MnCO_3$ was filtered off and the pH of the remaining solution adjusted to 6.0 with 1 M HCl. The precipitate‡ was filtered off, washed with EtOH, ether, and dried under reduced pressure (50 Pa, 50 °C) to afford crude *syn*-**2a**–**d** as white powders (*syn*-**2a**–**d**:*anti*-**2a**–**d** >97:3).

4.2.1. *syn*-(2*R*,4*S*)-4-Hydroxy-4-phenyl-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid *syn*-3a. Yield 1.72 g (72%); mp 194–195 °C (70% EtOH; d.r. 98:2); $[\alpha]_D^{20} = -14.0$ (*c* 1, 0.1 M NaOH); ^{1}H NMR (NaOD/D_2O): δ 7.32–7.50 (m, 8H, H_{Ar}), 7.18–7.25 (m, 2H, H_{Ar}), 4.69 ('t', 1H, $J \cong 6.9$, H-4), 4.70 (q, 1H, *J* 6.6, H-1′), 2.82 ('t', 1H, $J \cong 6.9$, H-2), 1.93 ('t', 2H, $J \cong 6.9$, H-3), 1.42 (d, 3H, $J \cong 6.6$, H-2′). ^{13}C NMR (NaOD/D_2O): δ 184.7 (s, C-1), 75.6 (d, C-4), 62.7 (d, C-2), 59.5 (d, C-1′), 44.3 (t, C-3), 26.0 (q, C-2′), 146.6, 146.7 (s, C_{ipso} of Ph), 130.7, 130.4 (d, C-4″ of Ph), 131.6, 131.5, 130.3, 129.1 (d, CH of Ph). Anal. Calcd for $C_{18}H_{21}NO_3$: C, 72.22; H, 7.07; N, 4.68. Found: C, 70.48; H, 7.27; N, 4.48.

4.2.2. *syn*-(2*R*,4*S*)-4-Hydroxy-4-(4-methylphenyl)-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid *syn*-3b. Yield 1.90 g (76%); mp 196–199 °C; $[\alpha]_D^{20} = +2.3$ (*c* 1, 0.1 M NaOH); ^{1}H NMR (NaOD/D_2O): δ 7.3–7.5 (m, 5H, Ph), 7.17 (d, 2H, *J* 8.1, H_{Tol}), 7.06 (d, 2H, *J* 8.1, H_{Tol}), 4.64 ('t', 1H, $J \cong 6.9$, H-4), 3.66 (q, 1H, *J* 6.6, H-1′), 2.76 ('t', 1H, $J \cong 6.9$, H-2), 2.31 (s, 3H, CH_3), 1.90 ('t', 2H, $J \cong 6.6$, H-3), 1.40 (d, 3H, *J* 6.6, H-2′). ^{13}C NMR (NaOD/D_2O): δ 184.8 (s, C-1), 75.4 (d, C-4), 62.7 (d, C-2), 59.5 (d, C-1′), 44.3 (t, C-3), 26.0 (q, C-2′), 23.0 (CH_3), 146.6 (s, C_{ipso} of Ph), 130.4 (d, C-4″ of Ph), 142.6, 140.8 (s, C_{Tol}), 132.0, 131.6, 130.3, 129.2 (d, CH_{Ar}). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47.‡

4.2.3. *syn*-(2*R*,4*S*)-4-Hydroxy-4-(4-methoxyphenyl)-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid *syn*-3c. Yield 1.66 g (63%); mp 192–195 °C; $[\alpha]_D^{20} = -4.6$ (*c* 1, 0.1 M NaOH); ^{1}H NMR (NaOD/D_2O): δ 7.28–7.46 (m, 5H, Ph), 7.13 (d, 2H, *J* 8.7, H_{An}), 6.90 (d, 2H, *J* 8.7, H_{An}), 4.64 ('t', 1H, $J \cong 6.9$, H-4), 3.82 (s, 3H, CH_3O), 3.64 (q, 1H, *J* 6.9, H-1′), 2.71 ('t', 1H, $J \cong 6.5$, H-2), 1.90 ('t', 2H, $J \cong 6.8$, H-3), 1.38 (d, 3H, *J* 6.6, H-2′). ^{13}C NMR (NaOD/D_2O): δ 184.8 (s, C-1), 75.0 (d, C-4), 62.6 (d, C-2), 59.4 (d, C-1′), 58.2 (CH_3O), 44.0 (t, C-3), 26.0 (q, C-2′), 146.6 (s, C_{ipso} of Ph), 130.4 (d, C-4″ of Ph), 161.1, 138.1 (s, C_{An}), 131.6, 130.6, 130.3, 116.8 (d, CH_{Ar}). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25.‡

4.2.4. *syn*-(2*R*,4*S*)-4-Hydroxy-4-(4-methoxy-3-methylphenyl)-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid (*syn*-3d). Yield 2.30 g (84%); mp 192–193 °C (70% EtOH; d.r. 98:2); $[\alpha]_D^{20} = -4.7$ (*c* 1, 0.1 M NaOH); ^{1}H NMR (NaOD/D_2O): δ 7.22–7.48 (m, 5H, Ph), 7.00 (br s, 1H, H-2″Ar), 6.99 (d, 1H, *J* 8.1, H_{Ar}), 6.89 (d, 1H, *J* 8.1, H_{Ar}), 4.61 ('t', 1H, $J \cong 6.8$, H-4), 3.83 (s, 3H, CH_3O), 3.63 (q, 1H, *J* 6.6, H-1′), 2.69 ('t', 1H, $J \cong 6.9$, H-2), 2.15 (s, 3H, CH_3), 1.90 ('t', 2H, $J \cong 7.1$, H-3), 1.38 (d, 3H, *J* 6.6, H-2′). ^{13}C NMR (NaOD/D_2O): δ 184.9 (s, C-1), 75.0 (d, C-4), 62.5 (d, C-2), 59.4 (d, C-1′), 58.5 (CH_3O), 44.0 (t, C-3), 26.0 (q, C-2′), 18.3 (CH_3), 146.6 (s, C_{ipso} of Ph), 130.3 (d, C-4″ of Ph), 159.4, 137.8, 129.4 (s, C_{Ar}), 131.6, 131.7, 130.2, 128.0, 113.9 (d, CH_{Ar}). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.2; H, 7.44; N, 4.16.

‡ In the case of *syn*-**3b** and **c** and *anti*-**3c** voluminous gel, no satisfactory elemental analysis was obtained.

4.3. *trans*-(3*R*,5*R*)-5-Phenyl-3-{[(1*R*)-1-phenylethyl]amino}dihydrofuran-2(3*H*)-one hydrochloride 4a

To the well-homogenized (ultrasound) suspension of *syn*-hydroxy acid **3a** (1 g, 3.34 mmol) in water (8 ml), concd hydrochloric acid (16 ml) was added in one portion. Starting material was dissolved and small precipitation of the product started under vigorous stirring at 25 °C. The mixture was stirred for 4 h at 25 °C. The precipitated product was filtered off, washed with 2 × 5 ml 1 M HCl, and dried under the diminished pressure at 60 °C. Raw product (0.88 g, d.r. >96:4) was crystallized from the acetonitrile–ether mixture. Yield : 0.72 g (68%; d.r. 98:2); mp: 160–162 °C (CH_3CN/Et_2O); $[\alpha]_D^{20} = -115.2$ (*c* 0.6, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.60–7.68 (m, 2H, Ph), 7.30–7.50 (m, 8H, Ph), 5.9 (dd, 1H, $J = 7.8$ Hz, $J = 5.8$ Hz, H-4), 4.66 (q, 1H, $J = 6.9$ Hz, H-1′), 4.05 (dd, 1H, $J = 9$ Hz, $J = 6.6$ Hz, H-2), 2.80–2.96 (m, 1H, H-3), 2.37–2.50 (m, 1H, H-3), 1.63 (d, 3H, $J = 6.9$ Hz). ^{13}C NMR (NaOD/D_2O): δ 171.5 (C-1), 138.5, 136.6 (C-$_{Ar}$,q), 129.2, 128.7 (1 × CH_{Ar}), 129.0, 128.8, 128.3, 126.1 (2 × CH_{Ar}), 79.3 (C-4), 56.3 (C-1′), 51.5 (C-2), 32.9 (C-3), 19.7 (C-2″). Anal. Calcd for $C_{18}H_{20}ClNO_2$: C, 68.03; H, 6.34; N, 4.41. Found: C, 68.24; H, 6.48; N, 4.52.

4.4. *cis*-(3*R*,5*R*)-5-(4-Methylphenyl)-3-{[(1*R*)-1-phenylethyl]amino}dihydrofuran-2(3*H*)-one hydrochloride 4b

To the well-homogenized presonicated suspension of hydroxy acid **3b** (1.25 g, 4 mmol) in water (40 ml), 5 M HCl (160 ml) was added dropwise under vigorous stirring. The reaction mixture was stirred at 50 °C for 30 h. Fine crystalline raw product (d.r. >95:5) was filtered off and recrystallized. Yield: 0.93 g (70%); m.p.: 217–220 °C (CH_3CN/EtOH; d.r. >99:1); $[\alpha]_D^{20} = +2.8$ (*c* 0.6, MeOH); ^{1}H NMR (DMSO-d_6): δ 10.7 (br s, 2H, NH_2^+), 7.65 (br d, 2H, $J = 6$ Hz, H-2, H-6 Ph), 7.38–7.48 (m, 3H, Ph), 7.36 (d, 2H, $J = 8.1$ Hz, H-2, H-6 Tol.), 7.21 (d, 2H, $J = 8.1$ Hz, H-3, H-5 Tol.), 5.41 (dd, 1H, $J = 5.4$ Hz, $J = 10.6$ Hz, H-4), 4.83 (bq, 1H, $J = 6.6$ Hz, H-1′), 4.29 (dd, 1H, $J = 8.4$ Hz, $J = 11.0$ Hz, H-2), 2.74 (ddd, 1H, $J = 12.3$ Hz, $J = 8.4$ Hz, $J = 5.7$ Hz, H-3_{eq}), 2.54 (bdd, 1H, $J = 12.3$ Hz, $J = 10.6$ Hz, H-3_{ax}), 2.29 (s, 3H, CH_3), 1.64 (d, 3H, $J = 6.9$ Hz, H-2′). ^{13}C NMR (NaOD/D_2O): δ 171.5 (C-1), 138.6 (C- qAr), 136.7 (C- qAr), 134.8 (C- qAr), 129.2 (CH_{Ar}), 129.1 (CH_{Ph}), 129.0 (CH_{Ar}), 128.3, 126.9 (CH_{Ar}), 79.0 (C-4), 55.8, 52.8 (C-1′, C-2), 34.8 (C-3) 20.8 (C-2′), 19.4 (CH_3). Anal. Calcd for $C_{19}H_{22}ClNO_2$: C, 68.77; H, 6.68; N, 4.22. Found: C, 68.92; H, 6.72; N, 4.42.

4.5. One-pot preparation of butanolides 4c and d

To a homogenized suspension (ultrasound) of oxoamino acids **2c** and **d** (4 mmol) in methanol (60 ml), $MnCl_2 \cdot 4H_2O$ (0.16 g; 0.8 mmol) was added in one portion. Sodium borohydride (0.222 g, 6 mmol) was added to a well-stirred reaction mixture at 15 °C in small portions over a period of 20 min. When the reduction was complete (monitored by HPLC), water (60 ml) was added and the methanol evaporated under reduced pressure. The remaining water solution (50 ml) of hydroxyamino acids **3c** and **d** was treated with concentrated HCl (25 ml) and the reaction mixture stirred at room temperature for an additional 5–10 h. The course of CIAT process was monitored by HPLC. The crystalline solid was filtered, washed with cold 1% HCl solution and ether, and thereafter dried in vacuo to give raw product (d.r. >95:5). Recrystallization from appropriate solvent gave the desired *cis*-butanolide hydrochloride **4c** (84%) and **4d** (91%), respectively.

4.5.1. *cis*-(3*R*,5*R*)-5-(4-Methoxyphenyl)-3-{[(1*R*)-1-phenylethyl]amino}dihydrofuran-2(3*H*)-one hydrochloride 4c. Yield: 1.17 g (84%; d.r. = 99:1); mp 220–224 °C (CH_3CN/EtOH; d.r. >99:1); $[\alpha]_D^{20} = -5.2$ (*c* 1, MeOH); ^{1}H NMR (CD_3OD/DCl): δ 7.2–7.5 (m, 5H, Ph), 7.19 (d, 2H, *J* = 8.7 Hz, H-2′, H-6′), 6.86 (d, 2H, *J* = 8.7 Hz, H-3′, H-5′), 5.08 (dd, 1H, *J* = 11.4 Hz, *J* = 5.1 Hz, H-4), 4.2 (m, 1H, H-5), 3.79 (s, 3H, H-7), 3.59 (dd, 1H, *J* = 12 Hz, *J* = 7.8 Hz, H-2), 2.25 (m, 1H, H-3), 1.80 (m, 1H, H-3), 1.44 (d, 3H, *J* = 6.6 Hz, H-6). ^{13}C NMR (NaOD/D_2O): δ 176.9 (C-1), 160.0, 144.3, 129.9 (C-q), 129.6, 127.6, 127.2, 114.1 (C_{Ar}), 78.6 (C-4), 58.5, 57.5 (C-2, C-1′), 55.3 (OCH_3), 40.4 (C-3), 24.5 (C-6). Anal. Calcd for $C_{19}H_{22}ClNO_3$: C, 65.61; H, 6.38; N, 4.03. Found: C, 65.47; H, 6.48; N, 4.08.

4.5.2. *cis*-(3*R*,5*R*)-5-(4-Methoxy-3-methylphenyl)-3-{[(1*R*)-1-phenylethyl]amino}dihydrofuran-2(3*H*)-one hydrochloride 4d. Yield: 1.32 g (91%; d.r. 99:1); mp 212–213°C (CH_2Cl_2/MeOH/Et_2O; d.r. >99:1); $[\alpha]_D^{20} = -8.7$ (*c* 0.6, MeOH); ^{1}H NMR (DMSO-d_6): δ 7.62–7.68 (m, 2H, Ph), 7.36–7.50 (m, 3H, Ph), 7.28 (d, 1H, *J* = 9.3 Hz, H-6″), 7.28 (br s, 1H, H-2″), 6.95 (d, 1H, *J* = 9.3 Hz, H-5″), 5.39 (dd, 1H, *J* = 5.4 Hz, *J* = 10.8 Hz, H-4), 4.81 (bq, 1H, *J* = 6.9 Hz, H-1′), 4.35 (dd, 1H, *J* = 8.7 Hz, *J* = 11.7 Hz, H-2), 3.79 (s, 3H, OCH_3), 2.65–2.77 (m, 1H, H-3), 2.40–2.56 (m, 1H, H-3), 2.15 (s, 3H, CH_3), 1.65 (d, 3H, *J* = 6.6 Hz, H-2′) ^{13}C NMR (NaOD/D_2O): δ 171.5 (C-1, C-2), 158.0, 129.0, 126.0 (C- q), 136.8 (C-1″), 129.1, 128.3, 128.2, 110.3 (CH_{Ph}) 126.2 (C-4″), 79.2 (C-4), 56.0, 55.5, 53.1 (C-2, 5.8), 34.7 (C-3), 19.3 (CH_3), 16.1 (C-2′). Anal. Calcd for $C_{20}H_{24}ClNO_3$: C, 66.38; H, 6.69; N, 3.87. C, 66.08; H, 6.87; N, 3.92.

4.6. *anti*-(2*R*,4*R*,1′*R*)-4-(4-Aryl)-4-hydroxy-2-(1′-phenylethylamino)butanoic acids *anti*-3b-*anti*-3d; General procedure

To a solution of the corresponding butanolides **4b–d** (2 mmol) in methanol (20 ml), 1 M NaOH solution (4 ml; 4 mmol) was added under vigorous stirring at room temperature. The reaction mixture was stirred for 30 min and treated with 20 ml of water. Methanol was evaporated under reduced pressure. The pH of the residue was adjusted to 5.5–6.0 with 1 M HCl. Precipitated crude product was filtered off, washed with water (2 × 5 ml) and ether (10 ml), and dried at 50 °C under diminished pressure for 2 h.

4.6.1. *anti*-(2*R*,4*R*)-4-Hydroxy-4-(4-methylphenyl)-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid *anti*-3b. Yield 0.51 g (81%; d.r. 98:2); mp 180–190 °C; $[\alpha]_D^{20} = +29.6$ (*c* 1, 0.1 M NaOH); ^{1}H NMR (NaOD/D_2O): δ 7.2–7.5 (m, 5H, Ph), 7.23 (d, 2H, *J* 7.8, H_{Tol}), 7.04 (d, 2H, *J* 7.8, H_{Tol}), 4.69 ('t', 1H, *J* ≅ 6.6, H-4), 3.63 (q, 1H, *J* 6.6, H-1′), 2.72 ('t', 1H, *J* ≅ 6.6, H-2), 2.29 (s, 3H, CH_3), 1.95 ('t', 2H, *J* ≅ 6.6, H-3), 1.34 (d, 3H, *J* 6.6, H-2′). ^{13}C NMR (NaOD/D_2O): δ 184.4 (s, C-1), 74.7 (d, C-4), 61.6 (d, C-2), 59.3 (d, C-1′), 43.8 (t, C-3), 25.9 (q, C-2′), 23.0 (CH_3), 146.7 (s, C_{ipso} of Ph), 143.1, 139.8 (s, C_{Tol}), 131.6, 131.2, 129.9, 128.7 (d, CH_{Ar}). Anal. Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.62; H, 7.52; N, 4.29.

4.6.2. *anti*-(2*R*,4*R*)-4-Hydroxy-4-(4-methoxyphenyl)-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid *anti*-3c. Yield 0.38 g (57%; d.r. 97:3); mp 182–185 °C; $[\alpha]_D^{20} = +18.8$ (*c* 1, 0.1 M NaOH); ^{1}H NMR (NaOD/D_2O): δ 7.18–7.40 (m, 5H, Ph), 7.08 (d, 2H, *J* 8.7, H_{An}), 6.84 (d, 2H, *J* 8.7, H_{An}), 4.65 ('t', 1H, *J* ≅ 6.6, H-4), 3.77 (s, 3H, CH_3O), 3.61 (q, 1H, *J* 6.6, H-1′), 2.66 ('t', 1H, *J* ≅ 6.6, H-2), 1.93 (m, 2H, H-3), 1.31 (d, 3H, *J* 6.6, H-2′). ^{13}C NMR (NaOD/D_2O): δ 184.7 (s, C-1), 74.3 (d, C-4), 61.4 (d, C-2), 59.3 (d, C-1′), 58.1 (CH_3O), 44.0 (t, C-3), 26.0 (q, C-2′), 146.6 (s, C_{ipso} of Ph), 130.2 (d, C-4″ of Ph), 160.9, 138.4 (s, C_{An}), 131.5, 130.4, 130.1, 116.7 (d, CH_{Ar}). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25.[‡]

4.6.3. *anti*-(2*R*,4*R*)-4-Hydroxy-4-(4-methoxy-3-methylphenyl)-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid *anti*-3d. Yield 0.55 g (80%; d.r. 99:1); mp 179–181 °C; $[\alpha]_D^{20} = +12.6$ (*c* 1, 0.1 M NaOH); ^{1}H NMR (NaOD/D_2O): δ 7.15–7.40 (m, 5H, Ph), 6.99 (br s, 1H, H-2″Ar), 6.96 (d, 1H, *J* 8.4, H_{Ar}), 6.83 (d, 1H, *J* 8.4, H_{Ar}), 4.62 ('t', 1H, *J* ≅ 6.3, H-4), 3.79 (s, 3H, CH_3O), 3.61 (q, 1H, *J* 6.6, H-1′), 2.66 ('t', 1H, *J* ≅ 6.5, H-2), 2.11 (s, 3H, CH_3), 1.93 (m, 2H, H-3), 1.30 (d, 3H, *J* 6.6, H-2′). ^{13}C NMR (NaOD/D_2O): δ 184.7 (s, C-1), 74.4 (d, C-4), 61.5 (d, C-2), 59.3 (d, C-1′), 58.5 (CH_3O), 44.0 (t, C-3), 26.1 (q, C-2′), 18.3 (CH_3), 146.6 (s, C_{ipso} of Ph), 130.2 (d, C-4″ of Ph), 159.3, 138.1, 129.3 (s, C_{Ar}), 131.4, 131.3, 130.0, 127.9, 113.8 (d, CH_{Ar}). Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.06; H, 7.55; N, 3.96.

4.7. Hydrogenation of *cis*-(3*R*,5*R*)-5-(4-methoxyphenyl)-3-{[(1*R*)-1-phenylethyl]amino}dihydrofuran-2(3*H*)-one hydrochloride 4c

Palladium on charcoal (10%) (0.4 g) was added to a suspension of the lactone **4c** (2 g; 5.7 mmol) in ethanol (30 ml)—0.5 M H_2SO_4 (90 ml). The resulting mixture was stirred under hydrogen at 1.1 bar for 68 h, after

which HPLC analysis showed that no starting material remained. The reaction mixture was then filtered through a Celite pad and ethanol evaporated under reduced pressure. The pH of the remaining water solution was adjusted to 5.5–6.0 at which point, raw product was filtered off and recrystallized from 70% ethanol to give (*R*)-2-amino-4-(4-methoxyphenyl)butanoic acid **5c** (0.97 g, 81%); mp 261–263 °C; ee 99% (HPLC column CROWNPAK CR(+), 150 × 4 mm, mob. phase aqueous solution of $HClO_4$ pH = 1.0, 1.2 ml/min, t_R(*S*)-**5c** = 53 min, t_R(*R*)-**5c** = 115 min); $[\alpha]_D^{20} = -50$ (*c* 0.4, THF/1 M HCl = 4:1){lit.[15] for (*S*)-**5c** $[\alpha]_D^{20} = +42$ (*c* 0.1, 5M HCl)}.

4.8. *cis*-(3*S*,5*S*)-3-Amino-5-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one hydrochloride 6c

To a suspension of oxoamino acid **2c** (2 mmol) in a mixture of methanol/water (150 ml/30 ml), 46% HBr (0.352 g, 2 mmol) was added. The resulting solution was hydrogenated (1.1 bar H_2) over 10% Pd/C (200 mg) at room temperature. The course of the reduction was monitored by HPLC. After consumption of the starting material (3.5–4 h), the catalyst was filtered off. The pH of the solution was adjusted to about 7.0 with 1 M NaOH. Methanol was evaporated in vacuo. The precipitated mixture of hydroxyamino acids (3:7, HPLC) (540 mg) was filtered off, treated with 4 M HCl (8 ml) and vigorously stirred for 4 h at 25 °C. Thereafter, the solid product was isolated by filtration, washed with Et_2O, and dried. Yield 0.40 g (82%; d.r. 95:5); mp 215–216 °C dec. (EtOH/Et_2O; d.r. = 98:2); $[\alpha]_D^{20} = -9$ (*c* 0.6, DMSO) {lit.[30] mp 202–203 °C dec.; $[\alpha]_D^{20} = -3.1$ (*c* 1, H_2O)}. ^{1}H NMR (DMSO-d_6): 7.44 (d, 2H, *J* = 8.7, H-Ar), 6.99 (d, 2H, *J* = 8.7, H-Ar), 5.50 (dd, 1H, $J_{4A,5}$ = 5.3, $J_{4B,5}$ = 10.4, H-5), 4.53 ('t', 1H, $J_{3,4A}$ = 8.7, $J_{3,4B}$ = 10.8, H-3), 2.92–2.82 (m, 1H, H-4A); H-4B overlapped with solvent. ^{13}C NMR (DMSO-d_6): 172.5 (C-2); 159.9, 129.5, 128.6, 114.1 (C-Ar); 79.0 (C-5); 55.3, 49.4 (C-3, CH_3); 35.0 (C-4). Anal. Calcd for $C_{19}H_{22}ClNO_3$: C, 54.22; H, 5.79; N, 5.75. Found: C, 54.17; H, 5.93; N, 5.71.

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