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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 1629–1637

Crystallisation induced asymmetric transformation (CIAT) in the synthesis of furoylalanines and furylcarbinols

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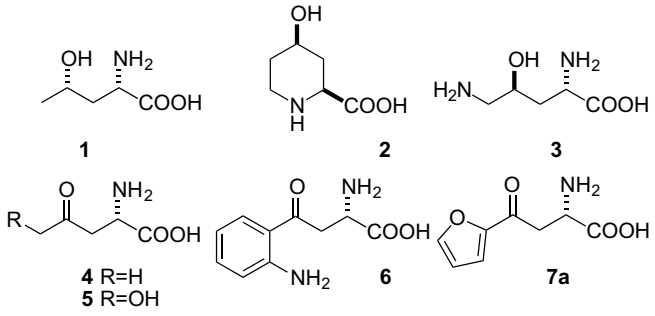
Received 2 March 2006; accepted 24 April 2006
Available online 30 June 2006

Abstract—A new synthesis of enantiomerically highly enriched N-substituted furoylalanines has been developed. This process involves the combination of crystallisation induced asymmetric transformation (CIAT) and a conjugate addition of *N*-nucleophiles to furoylacrylic acids. Further transformations to furoylalanines and substituted furylcarbinols are also described.

1. Introduction

γ-Hydroxy- and γ-oxo-α-aminoacids represent two classes of compounds with frequent occurrence in nature. Many of them are isolated from different sources, for example, γ-hydroxynorvaline **1** was found in the seeds of *Lathyrus odoratus* and in the fungi *Boletus satanus*.[1] Leaves of *Calliandra pittieri* and *Strophantus scandeus*[2] contain 4-hydroxypipecolic acid **2**, the compound representing a basic building block of antibiotic virginiamycin S2.[3] 4-Hydroxyornithine **3** is a structural unit of biphenomycine A, B.[4] γ-Oxo-norleucine **4** was isolated from *Citrobacter freundii*,[5] 5-hydroxy-γ-oxo-norvaline **5** from both *Streptomyces H-8997* and *Streptomyces akiyoshiensis*.[6]



Scheme 1. Some γ-hydroxy- and γ-oxo-α-aminoacids occurring in nature.

Kynurenine **6** is a key intermediate in a trypthophane methabolic pathway[7] (Scheme 1).

In 1973, Hanabusha isolated a new member of γ-oxo-α-aminoacids family, namely L-2-(2′-furoyl)alanine **7a** from *Fagopyrum esculentum*,[8] (Scheme 1). There have also been two reports claiming its occurrence in the roots of *Rumex obtusifolius*[9] and in the seeds of *Fagus silvatica*.[10] In addition, this natural product is considered to be an important degradation product, as revealed by the structure elucidation of ascorbalamic acid.[11] Since the discovery of **7a**, only two of its syntheses have appeared and both represent a similar chiral-pool approach starting from enantiomerically pure aspartic acid.[12,13]

Over the last decade, we[14] and others[15] have discovered a unique stereoselective approach to the synthesis of γ-oxo-derivatives of L-homophenylalanine (L-Hpa) featuring a crystallisation induced asymmetric transformation (CIAT).[16] Thus, we are able to prepare highly enantiomerically enriched derivatives of L-Hpa using inexpensive and readily available aroylacrylic acids and α-methylbenzylamine. The notable advantage of CIAT over previous synthetic methods is the high stereoselectivity, mild reaction conditions (ranging from rt to 40 °C), the use of inexpensive solvents and a simple work-up.

Herein we report a new and highly stereoselective synthesis of furoylalanines **7a–c** using CIAT in the conjugate addition of (*R*)-phenylglycinol and/or (*S*)-phenylethylamine to α,β-unsaturated furoylacrylic acids **10a–c**. The highly enantiomerically enriched, N-substituted furoylalanines

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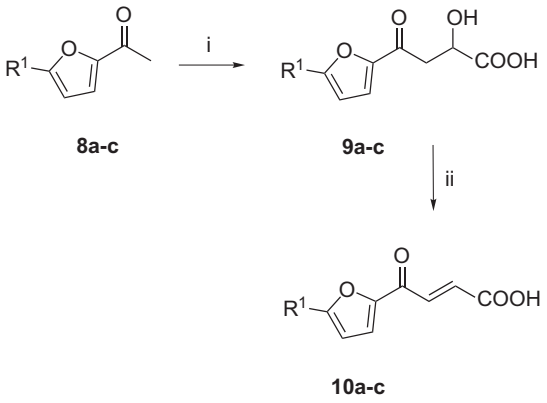
0957-4166/$ - see front matter
doi:10.1016/j.tetasy.2006.04.024

obtained **11a–c**, **12a–c**, which were further transformed to the furylcarbinols **13a–c** and **14a–c**. The latter represent suitable substrates for many useful transformations of the furan ring and are expedient starting materials for the synthesis of natural products using the Achmatowicz reaction.[17]

2. Synthesis

Due to their gastric anti-secretory, anti-ulcer and cytoprotective properties, furoylacrylic acids **10a–c** represent a class of biologically active compounds.[18] There are two methods in the literature describing the preparation of acids **10a** and **b**. However, we found the results reported by Ichihara et al.[8] (KOH, MeOH) as experimentally irreproducible and only complex reaction mixtures were obtained. On the other hand, Bianchi's acid-catalysed condensation[18] (AcOH, concd HCl) worked well for **9a–c**, although, the subsequent elimination failed in our hands. Thus, we have screened different dehydrating agents in order to arrive at the desired products **10a–c**. The best results were obtained using $KHSO_4$ in boiling toluene[19] (Scheme 2).



Scheme 2. Reagents and conditions: (i) glyoxylic acid, 95 °C, 12 h; (ii) $KHSO_4$, toluene, reflux, 2–3 h; crystallisation R^1 = H, Me, Et 22–39% in two steps.

The key step in our synthesis of substituted furoylalanines is represented by the regiospecific and, in tandem with CIAT highly diastereoselective conjugate addition of (*R*)-2-amino-2-phenylethanol and/or (*S*)-1-phenylethylamine to the unsaturated acids **10a–c** (Scheme 3).

The reaction conditions are mild (40 °C, 24–48 h) and the respective adducts **11a–c** and/or **12a–c** can be obtained in moderate to good yields (51–80%) and in excellent de's (92–98%). The reaction medium used plays a crucial role in the success or failure of such CIAT processes. Small alteration of the solvent from more polar MeOH to slightly more lipophilic EtOH was vital to the precipitation of the desired adducts in the case of **10b** and **c** (Table 1).

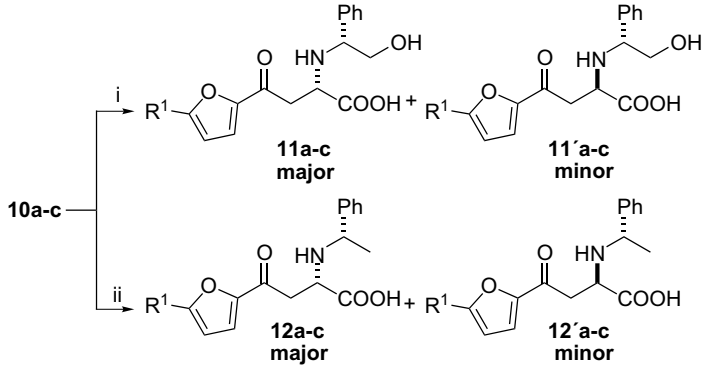
Table 1. CIAT in the conjugate addition of *N*-nucleophiles to **10a–c**

Adduct	R^1	Conditions	dr[a] (%)	Yield[a] (%)
12a	H	MeOH, 24 h	>99:1	74
12b	Me	MeOH, 24 h	—	0
12b	Me	EtOH, 48 h	99:1	56
12c	Et	MeOH, 24h	—	0
12c	Et	EtOH, 48 h	>99:1	55
11a	H	MeOH, 24 h	99:1	80
11b	Me	MeOH, 24 h	—	0
11b	Me	EtOH, 48 h	>99:1	71
11c	Et	MeOH, 48 h	—	0
11c	Et	EtOH, 48 h	96:4	51

[a] Data for solid product isolated by filtration.

In order to establish the expected stereochemical development of (*S*)-1-phenylethylamine addition to **10a**, we monitored the reaction by HPLC (Biospher SGX C18 5 μm, 4.6 × 250 mm). As can be gleaned from Figure 1, the ratio of both diastereomeric products **12′a/12a** formed in the reaction mixture was approximately equal at the initial stages (conversion > 90%, dr = 44:56 after 30 min). However, as the CIAT progressed in time, **12a** clearly became a major adduct of the transformation with the concomitant decline of the content of its (2*R*,1′*S*)-configured diastereoisomer **12′a**. Thus, after 24 h of stirring and subsequent filtration of the heterogenous reaction mixture, we obtained **12a** in 74% yield and with 98% de (Fig. 1).

An analogous stereochemical course was also observed for additions of (*S*)-1-phenylethylamine to **10b** and **c** as well as for CIAT process using (*R*)-phenylglycinol and **10a–c**.



Scheme 3. Reagents and conditions: (i) (*R*)-2-amino-2-phenylethanol, 40 °C; (ii) (*S*)-phenylethylamine, 40 °C, other conditions are in Table 1.

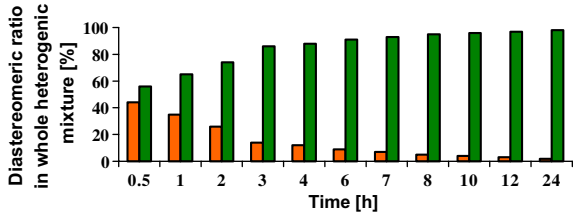
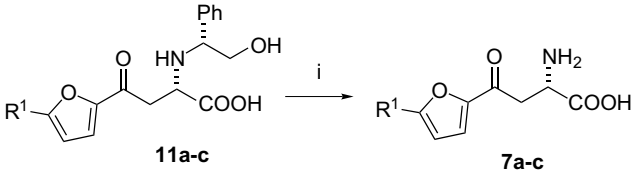


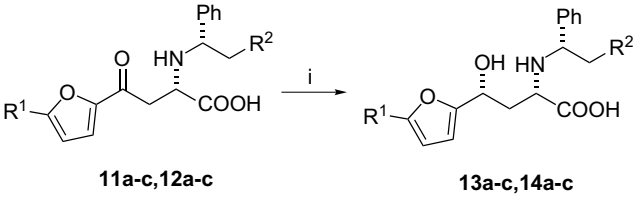
Figure 1. Stereochemical development of (*S*)-1-phenylethylamine addition to **10a**; (■) (2*R*,1′*S*)-diastereomer **12′a**, (■) (2*S*,1′*S*)-diastereomer **12a**.

The final stage of the furoylalanines **7a–c** synthesis required the removal of benzyl substituents on nitrogen. The attempts to deprotect **11a–c** and/or **12a–c** under acidic hydrogenolytic conditions (H_2/Pd, cat. HCl, MeOH) failed. Gratifyingly, the neutral oxidative conditions[20] applied to **11a–c** furnished the desired free amino acids **7a–c** in poor to acceptable yields (20–69%). This was mainly due to the high solubility and instability of the products in aqueous solvent that considerably complicate the work-up and subsequent purification of targets **7a–c**. We assume that N-dealkylation proceeeds via the mechanism analogous to the oxidative cleavage of 1,2-diols with $NaIO_4$. This hypothesis is strongly supported by the fact that we have isolated benzaldehyde from the reaction mixture. Finally, the oxidative N-dealkylation proceeds without any observable racemisation (Scheme 4).



Scheme 4. Reagents and conditions: (i) $NaIO_4$, H_2O, Et_3N, rt, pH = 7, 30 min; R_1 = H 69% (**7a**), R_1 = Me 36% (**7b**), R_1 = Et 35% (**7c**) after crystallisation.

Next, we have turned our attention to the synthesis of substituted furylcarbinols **13a–c** and **14a–c**. In our previous paper,[21] we have described the highly diastereoselective reduction of N-substituted 2-amino-4-aryl-4-oxobutanoic acids to the corresponding N-substituted *syn*-α-amino-γ-hydroxybutanoic acids. In the cases of **11a–c** and **12a–c**, the application of $NaBH_4/MnCl_2{\cdot}4H_2O$ reductive system led to the formation of the desired *syn*-γ-hydroxyamino acids **13a–c** and **14a–c** in good yields (70–90%) and excellent *syn*:*anti* selectivities (de 94–98%) (Scheme 5 and Table 2). Manganese(II) chloride is an indispensable reagent in



Scheme 5. Reagents and conditions: (i) $NaBH_4$, $MnCl_2{\cdot}4H_2O$, MeOH, 0–5 °C, 30 min.

Table 2. Reduction of **11a–c** and **12a–c**

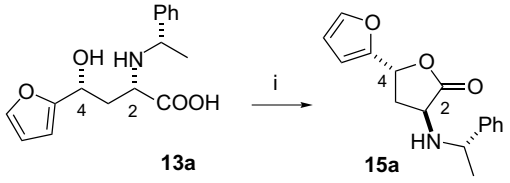
Product	R^1	R^2	*syn*:*anti*		Yield[b] (%)
			a	b	
13a	H	H	95:5	98:2	90
13b	Me	H	96:4	97:3	72
13c	Et	H	96:4	97:3	82
14a	H	OH	95:5	98:2	70
14b	Me	OH	96:4	97:3	70
14c	Et	OH	96:4	99:1	77

[a] Data for crude reaction mixture.
[b] Data for isolated solid product.

this highly diastereoselective reduction, due to the complexation with 2-amino-4-oxo moiety forming a six-membered chelate ring.

2.1. Elucidation of the relative configuration

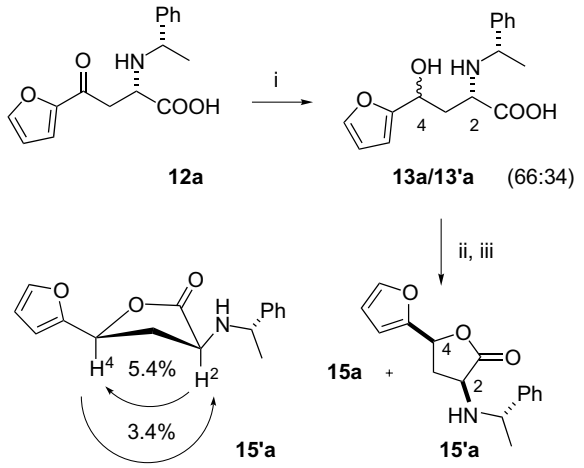
The determination of the relative configurations of furylcarbinols **13a–c** and **14a–c** were based on the results obtained from NOE experiments, which were performed on cyclic derivatives **15a** and **15′a**. Acidic lactonisation of **13a** under various conditions (HCl or PTSA or $SOCl_2$) led, however, to complex reaction mixtures only. Gratifyingly, the employment of DCC allowed us to prepare the desired lactone **15a** under mild conditions (Scheme 6).



Scheme 6. Reagents and conditions: (i) DCC, CH_2Cl_2, 24 h, rt, 51%.

As expected, there were no NOE's observed between protons at C-2 and C-4 suggesting the relative 2,4-*anti*-configuration of **15a**. This, in turn, would indicate the 2,4-*syn*-configuration of **13a**. On the other hand, the reduction of **12a** with the exclusion of $MnCl_2$ produced a diastereomeric mixture of 2,4-*syn*-**13a** and 2,4-*anti*-**13′a** furylcarbinols in a 66:34 ratio. Subsequent lactonisation of this mixture furnished the corresponding lactones **15a** and **15′a** in a diastereomeric ratio of 66:34 suggesting that no epimerisation occurred during the cyclisation. The desired **15′a** was isolated from the mixture by means of FLC and its NOE data clearly showed the expected 2,4-*cis* relative configuration (Scheme 7).

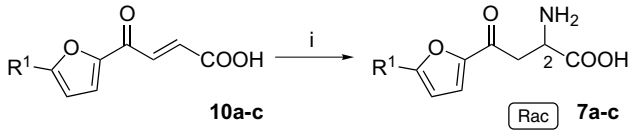
Furthermore, the basic hydrolysis of 2,4-*cis* lactone **15′a** furnished its parent 2,4-*anti*-hydroxyacid **13′a**, thus confirming its stereochemistry. Finally, the hydroxyacid **13′a** is a minor product obtained by stereoselective reduction of **12a** in the $NaBH_4$–$MnCl_2$ system (Scheme 5). This naturally implies that the major product of the reduction has to be 2,4-*syn*-hydroxyacid **13a**. The relative configurations of all other furylcarbinols **13b–c** and **14a–c** were tentatively assigned on the basis of these results.



Scheme 7. Reagents and conditions: (i) $NaBH_4$, MeOH, rt, 30 min, 79%, dr 66:34; (ii) DCC, rt, CH_2Cl_2, 24 h; (iii) FLC; **15a** 36%, **15′a** 19%.

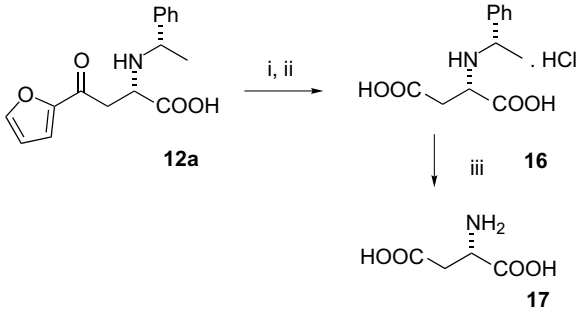
2.2. Elucidation of the absolute configuration

At first, we have prepared racemic mixtures of **7a–c** by the conjugate addition of aqueous ammonia to furoylacrylic acids **10a–c** (Scheme 8).



Scheme 8. Reagents and conditions: (i) 26% aq NH_3, 1 h, $R^1 = H$ 40%, $R^1 = Me$ 43%, $R^1 = Et$ 43%, yields refer to the pure material after crystallisation.

This material was used next as HPLC standard for the determination of enantiomeric excesses. On the basis of the claim that (*S*)-α-amino acids always elute first under the respective analytical conditions (CROWNPAK CR (+), Daicel, Japan, eluent $HClO_4$, pH = 2.0), we were able to tentatively assign the absolute configuration of the newly created stereogenic centre at C-2 of **7a–c**. In addition, the comparison of the measured value of specific rotation of **7a** {$[\alpha]_D^{20} = +43.2$ (*c* 0.5, 1 M HCl)/with known literature data for **7a**/$[\alpha]_D^{20} = +43.0$ (*c* 1, 2 M HCl)}[12] confirmed the absolute (*S*)-configuration. In order to establish the absolute configuration of the newly created stereogenic centre at C-2 of **12a**, we transformed **12a** into a known compound (Scheme 9). As expected, the $NaIO_4/RuCl_3$ mediated oxidation of the furan ring[22] afforded the N-substituted diacid **16**. Its final transformation to (*S*)-aspartic acid **17** was accomplished by catalytic reduction. Finally, the absolute configuration of **17** was determined by HPLC on a chiral stationary phase.



Scheme 9. Reagents and conditions: (i) $RuCl_3$, $NaIO_4$, H_2O, CCl_4, CH_3CN, rt, 30 min; (ii) HCl, 25% after two steps; (iii) H_2, Pd/C, ~100%.

3. Conclusion

We have successfully broadened the scope of CIAT in the conjugate addition of *N*-nucleophiles to furoylacrylic acids **10**. We have subsequently utilised this stereoselective process in the novel synthesis of highly diastereo- and/or enantiomerically enriched furoylalanines **7**, **11**, **12**. The main advantage of our synthetic approach over the previous methods lies in the simple experimental setup including work-up and purification. The furoylalanines prepared were employed as suitable substrates for the synthesis of furylcarbinols **13** and **14**. These compounds represent an appropriate starting material for many synthetically useful transformations of furan rings. The determination of the relative and/or absolute configurations was carried out by comparison of the known literature data with results obtained from polarimetric and NOE experiments, as well as those of chiral HPLC analyses.

4. Experimental

4.1. General

All reagents were used as received without further purification unless otherwise specified. (*S*)-Phenylethylamine (99+%, 99% ee) was obtained from ACROS and (*R*)-2-amino-2-phenylethanol was prepared from (*R*)-phenylglycine.[23] Melting points were obtained using a Kofler hot plate and are uncorrected. Optical rotations were measured with POLAR L-μP polarimeter (IBZ Messtechnik) with a water-jacked 10.000 cm cell at a wavelength of sodium line D ($\lambda = 589$ nm). Specific rotations are given in units of 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 ml. ^{1}H NMR spectra were recorded on a Varian VXR-300 (299.94 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million and are referenced to the tetramethylsilane (TMS) as internal standard ($\delta_{Me} = 0.00$ for 299.94 MHz). Coupling constants (*J*) are recorded in hertz. The following abbreviations were used throughout to characterise signal multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet), b (broad). Abbreviations with quotation marks mean that the appearance of the signal is different from that theoretically predicted. ^{13}C NMR spectra were recorded on a Varian VXR-300 (75.43 MHz) spectrometer. The multiplicities of the carbons were assigned from a broadband decoupled analysis used in a conjunction with either APT or DEPT programmes. Chemical shifts are quoted in parts per million and are referenced to the tetramethylsilane (TMS) as internal standard ($\delta = 0.00$ ppm for 75.43 MHz).

HPLC experiments were performed on PYE UNICAM chromatographic system (PU 4015 pump working in izocratic mode). Multichannel detector PU 4021 was performed in SUM ABS mode at wavelengths ranging from 210 to 310 nm. The following columns and eluents were used for HPLC experiments: Biospher SGX C_{18} 5 μm, 4.6 × 250 mm; Nova-Pak C_{18} 5 μm; 4.6 × 250 mm, CROWNPAK CR (+); $HClO_4$, pH = 2.0, water/CH_3CN 6:1, 1.5% of Et_3N; water/CH_3CN 2:3, 1.5% of Et_3N. Injection volume was 20 μl.

4.2. Synthesis

4.2.1. (2*E*)-4-(Furan-2-yl)-4-oxobut-2-enoic acid 10a. A mixture of ketone **8a** (181.6 mmol, 20 g) and glyoxylic acid monohydrate (1.5 equiv, 272.5 mmol, 25.069 g) was stirred for 12 h at 95 °C. Toluene (500 ml) and $KHSO_4$ (2 equiv, 363.2 mmol, 49.453 g) were added and the resulting suspension vigorously stirred at reflux for 2.5 h. Activated charcoal was added and insoluble material was removed by filtration. The crystalline compound obtained by filtrate cooling was filtered off, washed with heptane and dried to furnish an acid **10a** (11.891 g, 39%) as a yellow solid. Mp = 160–162 °C (H_2O), lit.[18] mp = 158–160 °C (propane-2-ol); ^{1}H NMR (d_6-DMSO): 8.12 (d, 1H, J = 1.5, H–Ar); 7.82 (d, 1H, J = 3.7, H–Ar); 7.70 (d, 1H, J = 15.4, H-3); 6.80 (dd, 1H, J = 3.7, J = 1.5, H–Ar); 6.74 (d, 1H, J = 15.4, H-2); ^{13}C NMR (d_6-DMSO): 175.8 (C-4); 166.1 (C-1); 152.0, 149.5, 135.4, 132.4, 121.4, 113.2 (C–Ar, C-2, C-3).

4.2.2. (2*E*)-4-(5-Methylfuran-2-yl)-4-oxobut-2-enoic acid (10b). According to the procedure above (for 3.0 g of **8b** used 3.336 g of glyoxylic acid, 6.591 g of $KHSO_4$, 50 ml of toluene) **10b** (1.250 g, 29%) was obtained as a yellow solid. Mp = 164–166 °C (H_2O), lit.[18] mp = 159–162 °C (AcOEt); ^{1}H NMR ($CDCl_3$): 7.80 (d, 1H, J = 15.4, H-3); 7.34 (d, 1H, J = 3.4, H–Ar); 6.97 (d, J = 15.4, H-2); 6.28 (d, 1H, J = 3.4, H–Ar); 2.46 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): 175.1 (C-4); 170.2 (C-1); 160.2, 151.6, 137.7, 130.5, 122.2, 110.1 (C–Ar, C-2, C-3); 14.2 (*C*H_3).

4.2.3. (2*E*)-4-(5-Ethylfuran-2-yl)-4-oxobut-2-enoic acid (10c). A mixture of ketone **8c** (112.5 mmol, 15.5 g) and glyoxylic acid monohydrate (1.5 equiv, 168.8 mmol, 15.535 g) was stirred for 12 h at 95 °C. The viscous liquid was partitioned to six equal parts in toluene (6 × 40 ml), $KHSO_4$ (6 × 5.11 g, overall 225 mmol) was added and resulting mixtures were vigorusly stirred at reflux for 3 h. Activated charcoal was added and the insoluble solid removed by filtration. The combined filtrates were cooled to −20 °C and left to stand for 24 h. The crystalline material was filtered, washed with heptane and dried to obtain acid **10c** (4.832 g, 22%) as a yellow solid. Mp = 112–113 °C (H_2O); ^{1}H NMR ($CDCl_3$): 7.81 (d, 1H, J = 15.8, H-3); 7.37 (d, 1H, J = 3.4, H–Ar); 6.98 (d, 1H, J = 15.8, H-2); 6.29 (d, 1H, J = 3.4, H–Ar); 2.80 (q, 2H, J = 7.3, CH_2CH$_3$); 1.32 (t, 3H, J = 7.3, CH$_2$CH_3); ^{13}C NMR ($CDCl_3$): 175.2 (C-4); 170.4 (C-1); 165.6, 151.4, 137.7, 130.5, 122.2, 108.5 (C–Ar, C-2, C-3); 21.9 (*C*H$_2$CH$_3$); 11.6 (CH$_2$*C*H$_3$). Calcd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.19. Found C, 61.62; H, 5.17.

4.3. General procedure for the conjugate addition of *N*-nucleophiles to unsaturated acids (10a–c)

Acid **10a** (12.0 mmol, 2.0 g) was dissolved in methanol (30 ml). (*S*)-1-Phenylethylamine (1.1 equiv, 13.2 mmol, 1.69 ml) was then added and the resulting solution vigorously stirred at 40 °C for 24 h. The suspension was cooled to rt, at which point the solid was filtered off, washed with Et_2O (20 ml) and dried to obtain amino acid **12a** (2.551 g, 74%, dr 99:1) as a white solid.

4.3.1. (2*S*,1′*S*)-4-(Furan-2-yl)-4-oxo-2-[(1′-phenylethyl)amino]-butanoic acid 12a. After recrystallisation from H_2O: dr >99:1. Mp = 172–173 °C (decomposition); $[\alpha]_D^{25}$ = +37.2 (*c* 0.9, MeOH/1 M HCl 3:1); ^{1}H NMR (CD_3OD/DCl): 7.86 (d, 1H, J = 1.5, H–Ar); 7.51–7.56 (m, 5H, H–Ph); 7.45 (d, 1H, J = 3.5, H–Ar); 6.71 (dd, 1H, J = 3.5, J = 1.5, H–Ar); 4.73 (q, 1H, J = 6.9, H-1′); 4.15 (dd, 1H, J = 4.5, J = 5.9, H-2); 3.61 (dd, 1H, J = 18.8, J = 5.9, H-3B); 3.54 (dd, 1H, J = 18.8, J = 4.5, H-3A); 1.78 (d, 3H, J = 6.9, H-2′); ^{13}C NMR (CD_3O/DCl): 185.0 (C-4); 170.4 (C-1); 152.5, 149.5, 136.6, 131.1, 130.7, 129.2, 120.6, 114.0 (C–Ar); 60.3, 54.1 (C-1′, C-2); 39.3 (C-3); 20.4 (C-2′). Calcd for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.88. Found: C, 67.06; H, 6.01; N, 4.85.

4.3.2. (2*S*,1′*S*)-4-(5-Methylfuran-2-yl)-4-oxo-2-[(1′-phenylethyl)amino]-butanoic acid 12b. According to the general procedure (for 3.0 g of **10b** used 2.33 ml of (*S*)-phenylethylamine, 90 ml of EtOH at 40 °C, 48 h), **12b** (2.83 g, 56%, dr 99:1) was obtained as a white solid. After recrystallisation from EtOH: dr 99:1. Mp = 172–173 °C (decomposition), $[\alpha]_D^{25}$ = +50.3 (*c* 1.0, MeOH/1 M HCl 3:1); ^{1}H NMR (CD_3OD/DCl): 7.49–7.58 (m, 5H, H–Ph); 7.37 (d, 1H, J = 3.5, H–Ar); 6.35 (d, 1H, J = 3.5, H–Ar); 4.73 (q, 1H, J = 6.9, H-1′); 4.10 ('t', 1H, J = 4.5, J = 5.4, H-2); 3.58 (dd, 1H, J = 18.8, J = 5.4, H-3B); 3.50 (dd, 1H, J = 18.8, J = 4.5, H-3A); 2.40 (s, 3H, CH_3); 1.79 (d, 3H, J = 6.9, H-2′); ^{13}C NMR (CD_3OD/DCl): 184.2 (C-4); 170.4 (C-1); 160.8, 151.2, 136.7, 131.0, 130.6, 129.2, 122.6, 110.8 (C–Ar), 60.2 (C-2); 54.3 (C-1′); 38.9 (C-3); 20.4 (C-2′); 13.9 (*C*H$_3$). Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found C, 67.69; H, 6.33; N, 4.64.

4.3.3. (2*S*,1′*S*)-4-(5-Ethylfuran-2-yl)-4-oxo-2-[(1′-phenylethyl)-amino]-butanoic acid 12c. According to the general procedure (for 3.0 g of **10c** used 2.16 ml of (*S*)-phenylethylamine, 90 ml of EtOH at 40 °C, 48 h), **12c** (2.66 g, 55%, dr >99:1) was obtained as a white solid. After recrystallisation from H_2O: dr >99:1. Mp = 173–175 °C (decomposition), $[\alpha]_D^{25}$ = +50.7 (*c* 0.3, MeOH/1 M HCl 3:1); ^{1}H NMR (CD_3OD/DCl): 7.50–7.57 (m, 5H, H–Ph); 7.38 (d, 1H, J = 3.5, H–Ar); 6.37 (d, 1H, J = 3.5, H–Ar); 4.73 (q, 1H, J = 6.9, H-1′); 4.12 (dd, 1H, J = 5.0, J = 6.4, H-2); 3.56 (dd, 1H, J = 18.6, J = 6.4, H-3B); 3.49 (d, 1H, J = 18.6, J = 5.0, H-3A); 2.77 (q, 2H, J = 7.4, CH_2CH$_3$); 1.78 (d, 3H, J = 6.9, H-2′); 1.30 (t, 3H, J = 7.4, CH$_2$CH_3); ^{13}C NMR (CD_3OD/DCl): 184.2 (C-2); 170.4 (C-1); 165.9, 151.2, 136.7, 131.0, 130.7, 129.1, 122.3, 109.3 (C–Ar); 60.3 (C-2); 54.4 (C-1′); 38.9 (C-3); 22.6 (*C*H$_2$CH$_3$); 20.2 (C-2′); 12.2 (CH$_2$*C*H$_3$). Calcd for $C_{18}H_{21}NO_4$:

C, 68.55; H, 6.71; N, 4.44. Found: C, 68.25; H, 6.73; N, 4.42.

4.3.4. (2*S*,1′*R*)-4-(Furan-2-yl)-2-[(2′-hydroxy-1′-phenylethyl)-amino]-4-oxobutanoic acid 11a. According to the general procedure (for 6.6 mmol, 1.1 g of **10a** used 1.1 equiv, 7.3 mmol, 0.999 g of (*R*)-2-amino-2-phenylethanol, 20 ml of MeOH at 40 °C, 24 h), **11a** (1.16 g, 80%, dr 99:1) was obtained as a white solid. After recrystallisation from EtOH: dr >99:1. Mp = 165–167 °C (decomposition), $[\alpha]_D^{25} = +23.2$ (*c* 0.5, MeOH/1 M HCl 3:1); ^{1}H NMR (CD_3OD/DCl): 7.86 (d, 1H, *J* = 1.5, H–Ar); 7.52–7.60 (m, 5H, H–Ph); 7.48 (d, 1H, *J* = 3.5, H–Ar); 6.71 (dd, 1H, *J* = 3.5, *J* = 1.5, H–Ar); 4.75 (dd, 1H, *J* = 5.0, *J* = 8.9, H-1′); 4.26 (dd, 1H, *J* = 4.5, *J* = 6.4, H-2); 4.07 (dd, 1H, *J* = 11.9, *J* = 8.9, H-2′B); 3.98 (dd, 1H, *J* = 11.9, *J* = 5.0, H-2′A); 3.69 (dd, 1H, *J* = 18.8, *J* = 6.4, H-3B); 3.58 (dd, 1H, *J* = 18.8, *J* = 4.5, H-3A); ^{13}C NMR (d_6-acetone/DCl): 186.0 (C-4); 170.5 (C-1); 153.1, 149.2, 133.2, 131.6, 131.3, 131.0, 120.9, 114.4 (C–Ar); 67.0 (C-2′); 64.3, 54.3 (C-1′, C-2); 40.0 (C-3). Calcd for $C_{16}H_{17}NO_5$: C, 63.36; H, 5.65; N, 4.62. Found: C, 63.09; H, 5.66; N, 4.64.

4.3.5. (2*S*,1′*R*)-2-[(2′-Hydroxy-1′-phenylethyl)amino]-4-(5-methylfuran-2-yl)-4-oxobutanoic acid 11b. According to the general procedure (for 1.0 g of **10b** used 0.840 g of (*R*)-2-amino-2-phenylethanol, 25 ml of EtOH at 40 °C, 48 h), **11b** (1.259 g, 71%, dr >99:1) was obtained as a white solid. After recrystallisation from EtOH–CH_3CN: dr >99:1. Mp = 164–165 °C (decomposition), $[\alpha]_D^{25} = +36.7$ (*c* 0.6, MeOH/1 M HCl 3:1). ^{1}H NMR (CD_3OD/DCl): 7.51–7.59 (m, 5H, H–Ph); 7.36 (d, 1H, *J* = 3.5, H–Ar); 6.35 (d, 1H, *J* = 3.5, H–Ar); 4.74 (dd, 1H, *J* = 5.0, *J* = 8.9, H-1′); 4.24 (dd, 1H, *J* = 4.0, *J* = 6.4, H-2); 4.05 (dd, 1H, *J* = 11.9, *J* = 8.9, H-2′B); 3.98 (dd, 1H, *J* = 11.9, *J* = 5.0, H-2′A); 3.62 (dd, 1H, *J* = 18.8, *J* = 6.4, H-3B); 3.51 (dd, 1H, *J* = 18.8, *J* = 4.0, H-3A); 2.41 (s, 3H, C*H*$_3$); ^{13}C NMR (CD_3OD/DCl): 184.7 (C-4); 170.4 (C-1); 160.9, 151.3, 132.6, 131.4, 130.7, 129.9, 122.6, 110.8 (C–Ar); 66.1 (C-2′); 63.6, 54.3 (C-2, C-1′); 38.7 (C-3); 13.9 (*C*H$_3$). Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 63.91; H, 6.09; N, 4.44.

4.3.6. (2*S*,1′*R*)-4-(5-Ethylfuran-2-yl)-2-[(2′-hydroxy-1′-phenylethyl)amino]-4-oxobutanoic acid 11c. According to the general procedure (for 2.0 g of **10c** used 1.549 g of (*R*)-2-amino-2-phenylethanol, 40 ml of EtOH at 40 °C, 48 h), **11c** (1.719 g, 51%, dr 96:4) was obtained as a white solid. After recrystallisation from EtOH: dr 98:2. Mp = 172–173 °C (decomposition); $[\alpha]_D^{25} = +31.3$ (*c* 0.5, MeOH/1 M HCl 3:1); ^{1}H NMR (CD_3OD/DCl): 7.50–7.62 (m, 5H, H–Ph); 7.40 (d, 1H, *J* = 3.5, H–Ar); 6.38 (d, 1H, *J* = 3.5, H–Ar); 4.73 (dd, 1H, *J* = 4.5, *J* = 8.9, H-1′); 4.35–4.39 (m, 1H, H-2); 4.08 (dd, 1H, *J* = 11.4, *J* = 8.9, H-2′B); 3.99 (dd, 1H, *J* = 11.4, *J* = 4.5, H-2′A); 3.54–3.68 (m, 2H, H-3); 2.77 (q, 2H, *J* = 7.4, C*H*$_2$CH$_3$); 1.30 (t, 3H, *J* = 7.4, CH$_2$C*H*$_3$); ^{13}C NMR (CD_3OD/DCl): 184.5 (C-4); 169.6 (C-1); 166.2, 151.0, 132.5, 131.4, 130.0, 130.7, 122.7, 109.4 (C–Ar); 66.0 (C-2′); 63.6, 54.4 (C-2, C-1′); 38.7 (C-3); 22.6 (*C*H$_2$CH$_3$); 12.2 (CH$_2$*C*H$_3$). Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 65.51; H, 6.40; N, 4.24.

4.4. General procedure for the preparation of hydroxyacids 13 and 14

Acid **12a** (10.4 mmol, 3.0 g) was suspended in MeOH (90 ml) and $MnCl_2{\cdot}4H_2O$ (0.2 equiv, 2.1 mmol, 0.41 g), was dissolved in the mixture. The resulting suspension was cooled to 0–5 °C, $NaBH_4$ (2 equiv, 20.9 mmol, 0.773 g) was then added over 10 min and the reaction mixture stirred for 30 min. The solvent was evaporated in vacuo and 5% aq soln of $NaHCO_3$ (150 ml) was added to the residue and the mixture stirred at rt for 15 min. The brown solid was filtered off and the pH of the filtrate adjusted to 6.0–6.5. The precipitated solid was filtered, washed with H_2O (100 ml), Et_2O (50 ml) and dried to obtain the hydroxyacid **13a** (2.70 g, 90%, dr 98:2) as a white solid.

4.4.1. (2*S*,4*R*,1′*S*)-4-(Furan-2-yl)-4-hydroxy-2-[(1′-phenylethyl)amino]-butanoic acid 13a. After recrystallisation from EtOH: dr >99:1. Mp = 216–217 °C (decomposition); $[\alpha]_D^{25} = -37.2$ (*c* 1.0, 0.1 M NaOH); ^{1}H NMR (CD_3OD/DCl): 7.45–7.60 (m, 6H, H–Ar); 6.35–6.39 (m, 1H, H–Ar); 6.29 (d, 1H, *J* = 3.0, H–Ar); 4.83 (dd, 1H, *J* = 4.0, *J* = 9.4, H-4); 4.61 (q, 1H, *J* = 6.9, H-1′); 3.78 (t, 1H, *J* = 6.4, H-2); 2.27–2.44 (m, 2H, H-3); 1.79 (d, 3H, *J* = 6.9, H-2′); ^{13}C NMR (d_6-DMSO/DCl): 169.3 (C-1); 156.2, 142.1, 136.1, 129.2, 129.1, 128.1, 110.2, 105.9 (C–Ar); 62.0 (C-4); 56.7, 54.2 (C-2, C-1′), 35.5 (C-3); 20.1 (C-2′). Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.64; H, 6.44; N, 4.80.

4.4.2. (2*S*,4*R*,1′*S*)-4-Hydroxy-4-(5-methylfuran-2-yl)-2-[(1′-phenylethyl)amino]-butanoic acid 13b. According to the general procedure (from 1.0 g of **12b**), **13b** (0.723 g, 72%, dr 97:3) was obtained as a white solid. Compound **13b** creates only stable gel in EtOH, analytical sample obtained after drying of gel, dr >99:1. Mp = 182–184 °C (EtOH); $[\alpha]_D^{25} = -44.0$ (*c* 0.1, 0.1 M NaOH); ^{1}H NMR (CD_3OD): 7.35–7.55 (m, 5H, H–Ph); 6.08 (d, 1H, *J* = 3.5, H–Ar); 5.91 (d, 1H, *J* = 3.5, H–Ar); 4.68 (dd, 1H, *J* = 8.8, *J* = 3.5, H-4); 4.32 (q, 1H, *J* = 6.4, H-1′); 3.28–3.31 (m, 1H, H-2); 2.02–2.33 (m, 5H, H-3, C*H*$_3$); 1.64 (d, 3H, *J* = 6.4, H-2′); ^{13}C NMR (CD_3OD): 174.6 (C-1); 155.3, 152.8, 139.9, 130.3, 130.2, 128.7, 107.9, 107.0 (C–Ar); 67.9 (C-4); 61.6, 59.1 (C-1′, C-2); 37.7 (C-3); 22.0 (C-2′); 13.4 (*C*H$_3$). Calcd for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.62. Found: C, 66.97; H, 6.95; N, 4.65.

4.4.3. (2*S*,4*R*,1′*S*)-4-(5-Ethylfuran-2-yl)-4-hydroxy-2-[(1′-phenylethyl)amino]-butanoic acid 13c. According to the general procedure (from 1.50 g of **12c**), **13c** (1.273 g, 82%, dr 97:3) was obtained as a white solid. After recrystallisation from EtOH–CH_3CN: dr 99:1. Mp = 193–195 °C; $[\alpha]_D^{25} = -35.1$ (*c* 1.0, 0.1 M NaOH); ^{1}H NMR (CD_3OD): 7.47–7.59 (m, 5H, H–Ph); 6.15 (d, 1H, *J* = 2.7, H–Ar); 5.96 (d, 1H, *J* = 2.7, H–Ar); 4.76 ('t', 1H, *J* = 5.2, *J* = 8.2, H-4); 4.60 (q, 1H, *J* = 6.4, H-1′); 2.62 (q, 2H, *J* = 7.7, C*H*$_2$CH$_3$); 2.23–2.39 (m, 1H, H-3); 1.78 (d, 3H, *J* = 6.4, H-2′); 1.22 (t, 3H, *J* = 7.7, CH$_2$C*H*$_3$); ^{13}C NMR (CD_3OD): 174.5 (C-1); 158.9, 154.4, 136.7, 131.1, 130.8, 128.9, 108.2, 105.6 (C–Ar); 66.1 (C-4); 61.5, 59.5 (C-1′, C-2); 36.3 (C-3); 22.2 (*C*H$_2$CH$_3$); 20.4 (C-2′); 12.6 (CH$_2$*C*H$_3$). Calcd for $C_{18}H_{23}NO_4$: C, 68.12; H, 7.30; N, 4.41. Found: C, 68.29; H, 7.33; N, 4.43.

4.4.4. (2*S*,4*R*,1′*R*)-4-(Furan-2-yl)-4-hydroxy-2-[(2′-hydroxy-1′-phenylethyl)amino]-butanoic acid 14a. According to the general procedure (from 2.6 g of **11a**), **14a** (1.843 g, 70%, dr 98:2) was obtained as a white solid. After recrystallisation from EtOH–CH_3CN–H_2O: dr 99:1. Mp = 169–171 °C (decomposition); $[\alpha]_D^{25} = -43.9$ (*c* 1.0, 0.1 M NaOH); ^{1}H NMR (d_6-DMSO): 7.47 (d, 1H, *J* = 1.8, H–Ar); 7.20–7.32 (m, 5H, H–Ph); 6.28 (dd, 1H, *J* = 3.5, *J* = 1.8, H–Ar); 6.06 (d, 1H, *J* = 3.5, H–Ar); 4.70 ('t', 1H, *J* = 6.4, *J* = 7.0, H-4); 3.72 (dd, 1H, *J* = 4.1, *J* = 8.2, H-1′); 3.33–3.46 (m, 2H, H-2′); 2.88 (dd, 1H, *J* = 5.2, *J* = 7.6, H-2); 1.82–2.04 (m, 2H, H-3); ^{13}C NMR (d_6-DMSO): 174.7 (C-1); 156.8, 141.4, 139.8, 128.0, 127.5, 127.1, 109.8, 105.4 (C–Ar); 66.1 (C-2′); 63.7, 62.8, 55.8 (C-1′, C-2, C-4); 39.1 (C-3). Calcd for $C_{16}H_{19}NO_5 \cdot 1/2H_2O$: C, 61.14; H, 6.41; N, 4.46. Found: C, 61.37; H, 6.44; N, 4.40.

4.4.5. (2*S*,4*R*,1′*R*)-4-Hydroxy-2-[(2′-hydroxy-1′-phenylethyl)-amino]-4-(5-methylfuran-2-yl)-butanoic acid 14b. According to the general procedure (from 1.0 g of **11b**), **14b** (0.72 g, 70%, dr 97:3) was obtained as a white solid. After recrystallisation from H_2O: dr >99:1. Mp = 172–173 °C (decomposition); $[\alpha]_D^{25} = -43.1$ (*c* 1.0, 0.1 M NaOH); ^{1}H NMR (NaOD/D_2O): 7.30–7.45 (m, 5H, H–Ph); 6.06 (d, 1H, *J* = 2.7, H–Ar); 5.93 (d, 1H, *J* = 2.7, H–Ar); 4.69 (t, 1H, *J* = 6.9, H-4); 3.69–3.73 (m, 3H, H-2′, H-1′); 2.85 (dd, 1H, *J* = 4.8, *J* = 8.9, H-2); 2.23 (s, 3H, C*H*$_3$), 1.90–2.10 (m, 2H, H-3); ^{13}C NMR (NaOD/D_2O): 184.2 (C-1); 155.6, 155.5, 141.9, 131.6, 130.0, 130.9, 110.8, 108.7 (C–Ar); 68.6 (C-2′); 68.5, 65.8, 62.1 (C-2, C-1′, C-4); 40.8 (C-3); 15.4 (*C*H$_3$). Calcd for $C_{17}H_{21}NO_5 \cdot H_2O$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.57; H, 6.88; N, 4.13.

4.4.6. (2*S*,4*R*,1′*R*)-4-(5-Ethylfuran-2-yl)-4-hydroxy-2-[(2′-hydroxy-1′-phenylethyl)amino]-butanoic acid 14c. According to the general procedure (from 1.0 g of **12c**), **14c** (0.77 g, 77%, dr 99:1) was obtained as a white solid. After recrystallisation from EtOH: dr 99:1. Mp = 175–177 °C; $[\alpha]_D^{25} = -40.5$ (*c* 1.0, 0.1 M NaOH); ^{1}H NMR (CD_3OD): 7.47–7.54 (m, 5H, H–Ph); 6.13 (d, 1H, *J* = 3.5, H–Ar); 5.94 (d, 1H, *J* = 3.5, H–Ar); 4.73 (dd, 1H, *J* = 4.1, *J* = 8.8, H-4); 4.46 ('t', 1H, *J* = 5.3, *J* = 5.3, H-1′); 4.03 (dd, 1H, *J* = 11.7, *J* = 4.1, H-2′B); 3.94 (dd, 1H, *J* = 11.7, *J* = 5.3, H-2′A); 3.47 (dd, 1H, *J* = 5.3, *J* = 8.2, H-2); 2.65 (q, 2H, *J* = 7.6, C*H*$_2$CH$_3$); 2.18–2.34 (m, 2H, H-3); 1.22 (t, 3H, *J* = 7.6, CH$_2$C*H*$_3$); ^{13}C NMR (CD_3OD): 172.4 (C-1); 158.7, 155.1, 134.6, 130.7, 130.4, 129.8, 107.8, 105.6 (C–Ar); 68.8 (C-4); 64.8, 64.1, 61.2 (C-2, C-1′, C-2′); 36.9 (C-3); 22.2 (*C*H$_2$CH$_3$); 12.6 (CH$_2$*C*H$_3$). Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 65.19; H, 7.01; N, 4.18.

4.4.7. (2*S*)-2-Amino-4-(furan-2-yl)-4-oxobutanoic acid 7a. The adduct **11a** (4.3 mmol, 1.3 g) was suspended in 4% aq soln of $NaIO_4$ (1.5 equiv, 6.4 mmol, 34.4 g), Et_3N (0.13 ml) was added and the resulting mixture stirred at rt for 30 min. The solid was filtered off, the filtrate washed with Et_2O (2 × 20 ml) and the water layer evaporated to dryness in vacuo (*t* < 45 °C). The obtained yellow solid was washed with MeOH (30 ml); the insoluble material was filtered and the filtrate evaporated to dryness in vacuo. The crude product was suspended in THF (25 ml) and water (2 ml) added while refluxing. The resulting emulsion was cooled to −20 °C and kept for 1 h. After warming to room temperature, the solid was filtered off, washed with THF (20 ml), Et_2O (20 ml) and dried to obtain the aminoacid **7a** (0.585 g, 67%, ee >98%) as a white solid. Mp = 153–155 °C (H_2O), lit.[8] mp = 148–149 °C, lit.[10] mp > 150 °C (H_2O) lit.[12] mp = 150 °C, lit.[13] mp = 156 °C, $[\alpha]_D^{25} = +43.2$ (*c* 0.5, 1 M HCl), lit.[13] $[\alpha]_D^{25} = +39.0$ (*c* 1.0, 1 M HCl), lit.[12] $[\alpha]_D^{22} = +43.0$ (*c* 1.0, 2 M HCl), lit.[10] $[\alpha]_D^{22} = +46.5$ (*c* 1.1, 2 M HCl); ^{1}H NMR (D_2O): 7.83 (d, 1H, *J* = 1.4, H–Ar); 7.53 (d, 1H, *J* = 3.4, H–Ar); 6.70 (dd, 1H, *J* = 3.4, *J* = 1.4, H–Ar); 4.21 (dd, 1H, *J* = 6.2, *J* = 4.1, H-2); 3.62 (dd, 1H, *J* = 18.6, *J* = 4.1, H-3B); 3.54 (dd, 1H, *J* = 18.6, *J* = 6.2, H-3A); ^{13}C NMR (D_2O): 190.4 (C-4); 176.2 (C-1); 153.7, 152.1, 124.3, 116.0 (C–Ar); 53.2 (C-2); 40.8 (C-3). Calcd for $C_8H_9NO_4 \cdot H_2O$: C, 47.76; H, 5.51; N, 6.96. Found: C, 47.66; H, 5.53; N, 6.95.

4.4.8. (2*S*)-2-Amino-4-(5-methylfuran-2-yl)-4-oxo-butanoic acid 7b. According to the preparation of **7a** (from 1.0 g of **11b**), **7b** (0.25 g, 36%, er >99:1) was obtained as a white solid. Mp = 153–156 °C (THF–H_2O); $[\alpha]_D^{25} = +49.1$ (*c* 1.0, 1 M HCl); ^{1}H NMR (D_2O): 7.45 (d, 1H, *J* = 3.4, H–Ar); 6.35 (d, 1H, *J* = 3.4, H–Ar); 4.15 (dd, 1H, *J* = 6.2, *J* = 4.8, H-2); 3.54 (dd, 1H, *J* = 18.6, *J* = 4.8, H-3B); 3.47 (dd, 1H, *J* = 18.6, *J* = 6.2, H-3A); 2.39 (s, 3H, C*H*$_3$); ^{13}C NMR (D_2O): 189.4 (C-4); 176.3 (C-1); 164.0, 152.5, 126.5, 112.9 (C–Ar); 53.5 (C-2); 40.3 (C-3); 16.1 (*C*H$_3$). Calcd for $C_9H_{11}NO_4 \cdot H_2O$: C, 50.23; H, 6.09; N, 6.51. Found: C, 50.29; H, 6.06; N, 6.54.

4.4.9. (2*S*)-2-Amino-4-(5-ethylfuran-2-yl)-4-oxo-butanoic acid 7c. According to the preparation of **7a** (from 1.0 g of **11c**), **7c** (0.21 g, 35%, er 96:4) was obtained as a white solid. Mp = 154–155 °C (THF–H_2O); $[\alpha]_D^{25} = +40.4$ (*c* 0.5, 1 M HCl); ^{1}H NMR (D_2O): 7.48 (d, 1H, *J* = 3.4, H–Ar); 6.39 (d, 1H, *J* = 3.4, H–Ar); 4.15 (dd, 1H, *J* = 6.9, *J* = 4.8, H-2); 3.55 (dd, 1H, *J* = 17.9, *J* = 4.8, H-3B); 3.48 (dd, 1H, *J* = 17.9, *J* = 6.9, H-3A); 2.75 (q, 2H, *J* = 7.6, C*H*$_2$CH$_3$); 1.26 (t, 3H, *J* = 7.6, CH$_2$C*H*$_3$); ^{13}C NMR (D_2O): 189.4 (C-4); 176.3 (C-1); 169.2, 152.3, 126.4, 111.3 (C–Ar); 53.4 (C-2); 40.2 (C-3); 24.2 (*C*H$_2$CH$_3$); 13.8 (CH$_2$*C*H$_3$). Calcd for $C_{10}H_{13}NO_4 \cdot H_2O$: C, 52.40; H, 6.60, N, 6.11. Found C, 52.14; H, 5.95; N, 6.15.

4.4.10. *rac*-2-Amino-4-(furan-2-yl)-4-oxobutanoic acid 7a. Acid **10a** (60.2 mmol, 10.000 g) was dissolved in ammonia (26% aq soln, 250 ml) and stirred at rt. After 1 h, the solution was evaporated to dryness (brown solid, 12.521 g). The crude product was dissolved in boiling MeOH (280 ml), activated charcoal was added and the mixture filtered. The filtrate was cooled to rt, precipitated solid was filtered off, washed with MeOH and dried to obtain acid *rac*-**7a** (4.391 g, 40%) as a white solid. Mp = 156–158 °C (H_2O), lit.[8] mp = 149–150 °C.

4.4.11. *rac*-2-Amino-4-(5-methylfuran-2-yl)-4-oxobutanoic acid 7b. According to the preparation of *rac*-**7a** (from 2.6 g of **10b**, 65 ml of 26% aq soln of ammonia) *rac*-**7b** (1.21 g, 43%) was obtained as a white solid. Mp = 156–158 °C (MeOH).

4.4.12. *rac*-2-Amino-4-(5-ethylfuran-2-yl)-4-oxobutanoic acid 7c. According to the preparation of *rac*-**7a** (from 3.0 g of **10c**, 75 ml of 26% aq soln of ammonia) *rac*-**7c** (1.403 g, 43%, crystallisation from H_2O) was obtained as a white solid, mp = 154–156 °C (H_2O).

4.4.13. (2*R*,4*S*,1″*S*)-4-[(1″-Phenylethyl)amino]-3,4-dihydro-2,2′-bifuran-5(2*H*)-one 15a. Acid **13a** (1.7 mmol, 0.5 g) was suspended in CH_2Cl_2 (12 ml), DCC (1.05 equiv, 1.8 mmol, 0.374 g) was added and the resulting suspension stirred at rt for 24 h. The mixture was evaporated to *ca.* 5 ml volume and the insoluble solids filtered off. The filtrate was evaporated to dryness. The crude product (brown oil, 0.552 g) was purified by column chromatography (AcOEt/heptane 1:3) to obtain *trans*-lactone **15a** (0.239 g, 51%, dr 99:1) as a yellowish oil. $R_f = 0.22$ (AcOEt/heptane 1:3), $[\alpha]_D^{25} = -189.6$ (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$): 7.22–7.40 (m, 6H, H–Ar); 6.29 (dd, 1H, $J = 3.5$, $J = 1.8$, H–Ar); 6.24 (d, 1H, $J = 3.5$, H–Ar); 5.40 (dd, 1H, $J = 2.9$, $J = 8.2$, H-2); 4.10 (q, 1H, $J = 6.4$, C*H*CH_3); 3.76 (dd, 1H, $J = 8.2$, $J = 9.4$, H-4); 2.05–2.23 (m, 2H, H-3); 1.41 (d, 3H, $J = 6.4$, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$): 177.2 (C-5); 150.9, 144.7, 143.2, 128.4, 127.2, 126.9, 110.3, 109.0 (C–Ar); 71.8 (C-2); 58.0, 55.1 (C-4, *C*HCH$_3$); 35.3 (C-3); 24.5 (CH*C*H$_3$). Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found C, 70.68; H, 6.33; N, 5.19.

4.4.14. (2*S*,4*S*,1″*S*)-4-[(1-Phenylethyl)amino]-3,4-dihydro-2,2′-bifuran-5(2*H*)-one 15′a. Aminoacid **12a** (7.0 mmol, 2.0 g) was suspended in MeOH (30 ml), $NaBH_4$ (4 equiv, 28.0 mmol, 1.031 g) was then added in one portion and the resulting mixture stirred at rt for 10 min. The solvent was evaporated, and H_2O (40 ml) was added and the pH of a solution adjusted to 6.5. The precipitated solid was filtered off, washed with water (20 ml), Et_2O (20 ml) and dried to obtain a mixture of acids **13a**/**13′a** (1.607 g, 79%, dr 66:34) as a white solid. This material was suspended in CH_2Cl_2 (60 ml), DCC (1.1 equiv, 6.1 mmol, 1.256 g) was added and the resulting suspension was stirred at rt for 24 h. The insoluble solid was filtered off and a filtrate was evaporated to dryness (brown oil, 1.71 g). The crude oil was purified by column chromatography (AcOEt/heptane 1:6) to obtain *trans*-lactone **15** (0.680 g, 36%, dr 99:1, $R_f = 0.22$ AcOEt/heptane 1:3) as a yellowish oil and *cis*-lactone **15′a** (0.360 g, 19%, dr 98:2, $R_f = 0.31$ AcOEt/heptane 1:3) as a white solid. Mp = 74–76 °C (AcOEt/heptane); $[\alpha]_D^{25} = +50.7$ (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$): 7.23–7.41 (m, 6H, H–Ar); 6.38 (d, 1H, $J = 3.5$, H–Ar); 6.34 (dd, 1H, $J = 3.5$, $J = 1.8$, H–Ar); 5.14 ('t', 1H, $J = 8.2$, $J = 8.2$, H-2); 4.18 (q, 1H, $J = 6.4$, C*H*CH_3); 3.54 ('t', 1H, $J = 10.6$, $J = 9.4$, H-4); 2.04–2.21 (m, 2H, H-3); 1.42 (d, 3H, $J = 6.4$, CHC*H*$_3$); ^{13}C NMR ($CDCl_3$): 176.7 (C-5); 149.6, 144.7, 143.7, 128.5, 127.4, 127.1, 110.5, 110.3 (C–Ar); 71.4 (C-2); 58.3, 57.0 (C-4, *C*HCH$_3$); 36.0 (C-3); 24.7 (CH*C*H$_3$). Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.03; H, 6.35; N, 5.17.

4.4.15. (2*S*,1′*S*)-2-[(1-Phenylethyl)amino]-butanedioic acid hydrochloride 16. $RuCl_3{\cdot}xH_2O$ (~0.05 equiv, 0.7 mmol, 0.144 g) was dissolved in H_2O (130 ml) after which CH_3CN (160 ml), CCl_4 (130 ml) and $NaIO_4$ (10 equiv, 139.2 mmol, 29.778 g) were gradually added. The resulting suspension was vigorously stirred at rt for 5 min, then aminoacid **12a** (13.9 mmol, 4.0 g) was added in one portion and the mixture stirred at rt for 30 min. The organic solvents were evaporated and the residue filtered. The filtrate was applied on to the top of column of DOWEX (50 W × 8). The column was washed with water until neutral reaction (400 ml) and with ammonia (4% aq soln, 500 ml). A fraction containing aminoacid was evaporated to dryness. The solid (2.015 g, 61%) was dissolved in H_2O (8 ml), after which activated charcoal was added and the mixture filtered. The pH of the filtrate was adjusted to 3.5 with concd HCl. The precipitated solid was filtered off, washed with Et_2O (20 ml) and dried to obtain HCl salt of acid **16** (0.951 g, 25%, dr >95:5) as a white solid. Mp = 204–206 °C lit.[24] mp = 179–181 °C (free aminoacid); $[\alpha]_D^{25} = -46.2$ (*c* 0.5, MeOH), lit.[24] $[\alpha]_D^{25} = -13.4$ (free aminoacid); ^1H NMR (free aminoacid, CD_3OD): 7.48–7.57 (m, 5H, H–Ph); 4.72 (q, 1H, $J = 7.0$, H-1′); 3.95 ('t', 1H, $J = 5.3$, $J = 5.9$, H-2); 3.04 (dd, 1H, $J = 18.2$, $J = 5.9$, H-3B); 2.96 (dd, 1H, $J = 18.2$, $J = 5.3$, H-3A); 1.79 (d, 3H, $J = 7.0$, H-2′); ^{13}C NMR (CD_3OD): 172.2, 170.0 (C-1, C-4); 136.6, 131.0, 130.7, 129.1 (C–Ar); 60.2, 55.4 (C-2, C-1′); 35.2 (C-3); 20.2 (C-2′).

By hydrogenolysis of **16** (1.8 mmol, 0.5 g), aspartic acid **17** (0.26 g, ~100%) was prepared. A sample of **17** was analysed by HPLC with chiral stationary phase (CROWNPAK CR (+), eluent $HClO_4$, pH = 2.0, $t_R = 1.33$ min, er 96:4). NMR data are in good agreement to those published.

Acknowledgements

Financial support by the Slovak Grant Agency No. 1/2469/05 is gratefully acknowledged. We are grateful to Dr. Peter Szolcsányi for his help with the manuscript preparation.

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