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The first example of a crystallization-induced asymmetric transformation (CIAT) in the Mannich reaction

Pavol Jakubec *, Pavel Petráš, Andrej Ďuriš, Dušan Berkeš *

Department of Organic Chemistry, Institute of Organic Chemistry, Catalysis and Petrochemistry, Slovak University of Technology, Radlinského Street 9, SK-812 37 Bratislava, Slovakia

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ABSTRACT

The novel synthesis of highly enantioenriched N-substituted α-amino-γ-alkyl(aryl)-γ-oxobutanoic acids is described. The process involves the combination of a crystallization-induced asymmetric transformation (CIAT) and the Mannich reaction. The role of *retro*-Mannich and *retro*-Michael reactions in the mechanism of the highly stereoselective transformation is also discussed.

1. Introduction

Despite the rapid improvement of classic protocols and the discovery of new methods in asymmetric synthesis, crystallization-induced asymmetric transformation (CIAT) remains one of the most interesting methods for the stereoselective formation of enantiomerically pure organic compounds. There are numbers of intriguing applications, where CIAT has been used to obtain enantiomerically and diastereoisomerically pure compounds simply by preferential crystallization of one of the equilibrating isomers. Notable advantages of CIAT over other tools of an asymmetric synthesis include mild reaction conditions, the use of inexpensive reagent grade solvents, no need for an inert atmosphere and simple work-up procedures.[1–3]

Over the last decade, as a part of our ongoing research devoted to the synthesis of α-amino-γ-alkyl(aryl)-γ-oxobutanoic acids **1**, we have described the application of crystallization-induced asymmetric transformation (CIAT) in the Michael addition of N-nucleophiles to acylacrylic acids **2** (Scheme 1, path a).[4–10]

The enantiomerically pure aminoacids **1** were further transformed to γ-amino-γ-hydroxy-γ-aryl(alkyl)-butanoic acids, their cyclic lactams or homophenylalanines.[11,12] The synthetic utility of our methodology has been well documented in several syntheses of small target molecules represented by: furoylalanin[7] isolated from *Fagopyrum esculentum*, *Rumex obtusifolius*, *Fagus silvatica*; substituted β-methyl-α-homophenylalanines[9] (terminal aminoacids of the nikkomycins and an aminoacid of depsipeptide kulokekahilide-1) and aliphatic α-aminoacids[8] isolated from *Streptomyces diastaticus* (a subunit of longicatenamycin) and *Claviceps purpurea*. Starting from the suitable Michael acceptor **2**, our reaction sequence provides a straightforward approach to α-amino-γ-alkyl(aryl)-γ-oxobutanoic acids **1**. The synthesis of unsaturated Michael acceptor **2** is very well documented by the Friedel–Crafts acylation of arenes,[13] elimination of bromoketones[14] and other methods.[15] Arguably, the most general methods for the synthesis of aroylacrylic acid **2** is the condensation of ketones **4** with glyoxylic acid **5**.[7–9,16] Thus, aminoacids **1** are available in two steps starting from commercially available compounds (ketone **4**, *ent*-(1-phenylethyl)amine **3** and glyoxylic acid **5**) utilising CIAT in the reversible Michael addition of nucleophiles (Scheme 1, path A). An alternative retrosynthetic analysis of **1** revealed a possibility to prepare enantiomerically pure substituted aminobutanoic acids **1** directly from commercial ketones **4** by employing one of the most powerful synthetic tools for C–C bond formation, the Mannich reaction (Scheme 1, path B).[17] Such a transformation might shorten the reaction pathway and avoid the sometimes complicated synthesis of Michael acceptor **2**. The Mannich reaction, in its original or more sophisticated form, has been known for almost a century and many excellent asymmetric variants have been developed including metal-catalysed, organocatalysed and versions employing stoichiometric chiral reagents.[18] However, to the best of our knowledge, there are no reported examples of the application of CIAT in Mannich reactions. Recently, an example of asymmetric amplification in a heterogeneous mixture was described, where an enantioenriched crystalline product was obtained in a reversible Mannich reaction with the use of racemic or achiral catalyst.[19] The critical point of CIAT is the compatibility of the epimerization in solution with preferential crystallization of one stereoisomer.[1] Knowing the physical-chemical properties and behaviour of aminoacids **1** from our previous research,[4–9] we believed that **1** could undergo simultaneous epimerization (either via *retro*-aza-Michael addition or *retro*-Mannich reaction) with the preferential crystallization of one stereoisomer.

* Corresponding authors. Present address: Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford OX1 3TA, UK (P.J.). Tel./fax: +421 2 52968560 (D.B.).
E-mail addresses: pavol.jakubec@zoznam.sk (P. Jakubec), dusan.berkes@stuba.sk (D. Berkeš).

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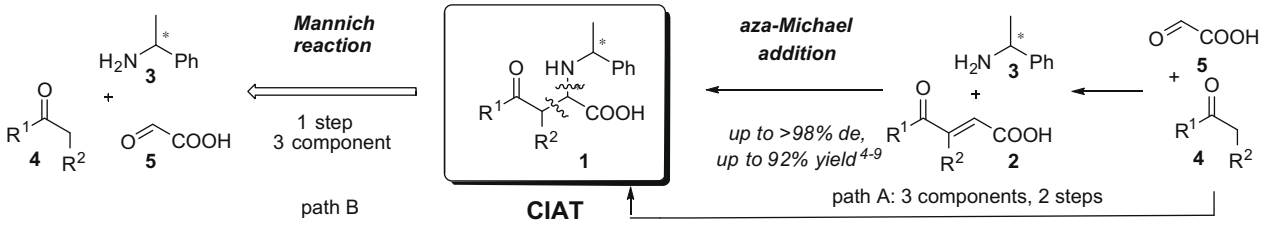


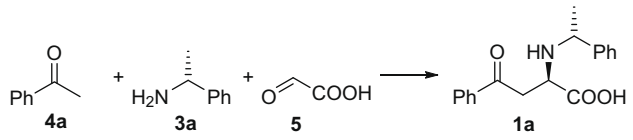
Scheme 1. CIAT for the construction of aminobutanoic acids.

Without the need for an expensive catalyst, strictly anhydrous conditions or other limiting factors, compound **1** could be filtered off as a single stereoisomer directly from the reaction mixture in a three component, one pot Mannich reaction.

Attracted by the simplicity and elegance of our idea, we started our investigation.

2. Results and discussion

Initially, feasibility studies were performed on a representative ketone, acetophenone **4a**, and the in situ formed enantiomerically pure imine derived from glyoxylic acid **5** and (*R*)-phenylethylamine (PEA) **3a** (Scheme 2). The starting materials were reacted in solvents ranging from aprotic to protic polar and completion of the reaction was judged by HPLC analysis. The results are presented in Table 1. The desired product **1a** crystallized out from a range of solvents at room temperature (at 40 °C in EtOH, entry 10) and was isolated by simple filtration in good yields as a single diastereoisomer. The attempts to carry out the reaction at a higher temperature (>40 °C, entries 11 and 12) led to faster decomposition of the starting materials and resulted in lower yields.



Scheme 2. The feasibility study on the model substrate **4a**.

Table 1
The feasibility study on the model substrate

Entry	Solvent	*T*	Time	Yield[a] (%)	Dr[a]
1	—	rt	20 h	44	99:1
2	CH_2Cl_2	rt	5 days	52	98:2
3	$CHCl_3$	rt	6 days	50	98:2
4	THF	rt	5 days	59	99:1
5	Et_2O	rt	4 days	66	99:1
6	Dioxane	rt	6 days	47	98:2
7	BuOH	rt	4 days	44	99:1
8	PrOH	rt	6 days	49	96:4
9	EtOH	rt	5 days	53	98:2
10	EtOH	40 °C	3 days	50	98:2
11	EtOH	50 °C	4 days	27	98:2
12	EtOH	Reflux	1 day	—[b]	—[b]
13	H_2O	rt	1 day	46	99:1

[a] Isolated by filtration of a reaction mixture.
[b] Complex mixture obtained.

With the preferred conditions identified (in Et_2O at rt or in EtOH at 40 °C), the reaction scope and limitation were investigated. A range of aromatic ketones with electron-donating or halogen substituents on the aromatic ring were reacted with glyoxylic acid **5** and (*R*)-PEA **3a**. The results are shown in Scheme 3. Employing the optimal reaction conditions (reaction performed at elevated temperature in EtOH for some ketones) for substituted acetophenones **4a**–**d**, products **1a**–**d** were isolated in moderate to good yields (29–66%), but excellent diastereoselectivities were observed in all cases (dr 98:2 to >99:1).

The introduction of a substituent to the α-position of the ketone (ketones **4e**,**f**) did not decrease the high level of stereoselectivity; from propiophenone the aminoacid **1e** was isolated with impressive dr (dr 98:1:0:1, 48% isolated yield). Tetralone **4f** was found to be an excellent substrate for the transformation and a derivative of constrained homophenylalanine **1f** with two newly created stereogenic centres was obtained as a single diastereoisomer in good yield (53% yield, dr >99:<1:0:0). With the Mannich reaction optimized on arylalkyl ketones **4a**–**f**, we turned our attention to alkylmethyl ketones. From a range of possible aliphatic ketones, we tested pinacolone **4g** and cyclohexylmethylketon **4h** as substrates for the CIAT process in the Mannich reaction. The treatment of ketones **4g**,**h** with glyoxylic acid **5** and (*R*)-PEA **3a** afforded **1g**,**h** in good yields and with excellent diastereoisomeric purity (66%, dr 99:1 for **1g** and 58% yield, dr 98:2 for **1h**, Scheme 4).

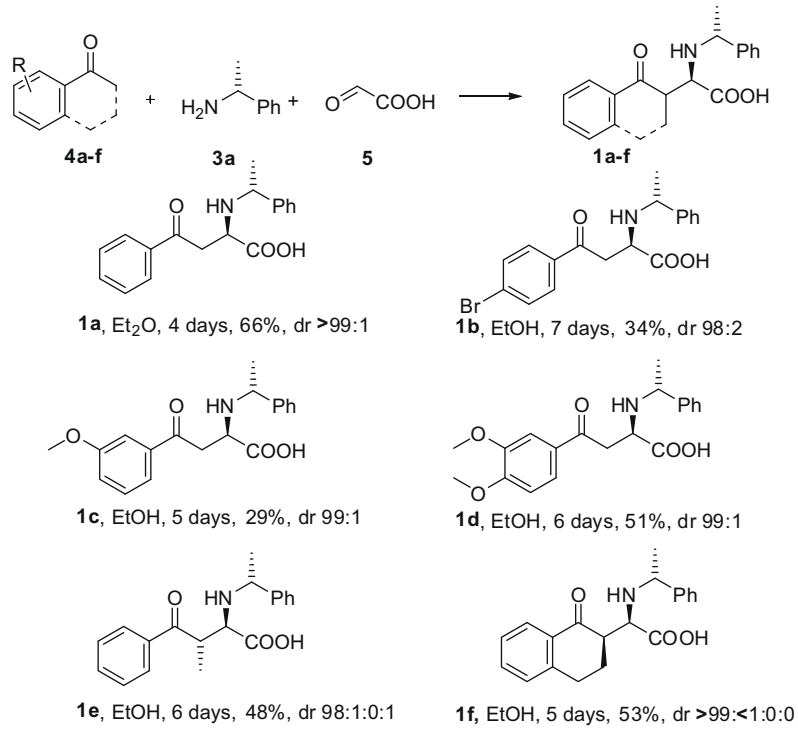
Having investigated the possibility of ketones **4a**–**h** undergoing a highly diastereoselective Mannich reaction, we next investigated the origin of the diastereoselectivity.

The stereochemical development in the Mannich reaction of tetralone **4f** with the (*R*)-PEA **3a** and glyoxylic acid **5** was monitored by HPLC analysis (Fig. 1). As can be seen from Figure 1, at an early stage of the reaction, poor diastereoselectivity was observed, originating from low asymmetric induction in the Mannich reaction (dr 18:28:26:28 after 4 h). However, as the reaction progressed, (2*R*,2′*R*,1″*R*)-diastereoisomer **1f** became the major diastereoisomer in the reaction with simultaneous decline of its other three diastereoisomers. Simultaneously, a significant change in the appearance of the reaction mixture took place. The solution became saturated and **1f** began to crystallize out, resulting in a dramatic change in the ratio of diastereoisomers. The simultaneous epimerization of the other diastereoisomers in the solution shifted the equilibrium to the side of the preferentially crystallizing (2*R*,2′*R*,1″*R*)-diastereoisomer. After 79 h (dr in the heterogeneous mixture 87:3:2:8), (2*R*,2′*R*,1″*R*)-**1f** was isolated by simple filtration as a virtually single diastereoisomer (dr 99:1:0:0) in 53% yield.

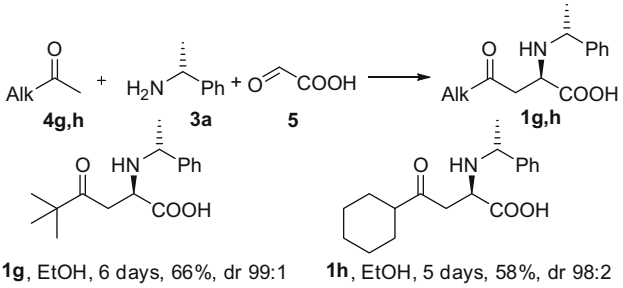
A similar stereochemical course was observed in all the substrates tested, thus providing strong support for our explanation of the high stereoselectivities observed (Fig. 2 represents the stereochemical development of the reaction with propiophenone **4e**, the (*R*)-PEA **3a** and glyoxylic acid **5**).

One of the critical points of CIAT process is the reversibility of the chemical reaction involved.[1] In the reaction of ketones with imines the most likely transformations, which should be considered, are *retro*-Mannich and *retro*-Michael reactions. To investigate the role of both reactions, we performed a cross experiment between enantiomerically pure Mannich adduct **1c**, (*R*)-PEA **3a** and acetophenone **4a** (Scheme 5, Fig. 3).

The starting materials were reacted under standard Mannich conditions (EtOH, 40 °C, Scheme 5) and monitored by HPLC (Fig. 3). After 1 h, significant amounts of unsaturated aroylacrylic acid **2c** were detected, providing evidence for a fast *retro*-Michael



Scheme 3. The scope and limitation of the Mannich reaction on aryl-alkylketones.



Scheme 4. The Mannich reaction with dialkylketones.

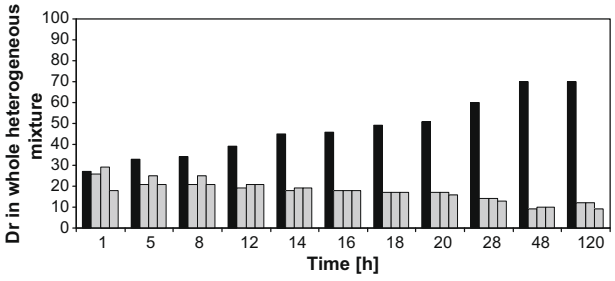


Figure 2. Stereochemical development of the Mannich reaction of **4e** with **3a** and **5**; ■ (2*R*,3*S*,1′*R*)-diastereoisomer **1e**, ▒ other 3 diastereoisomers of **1e**.

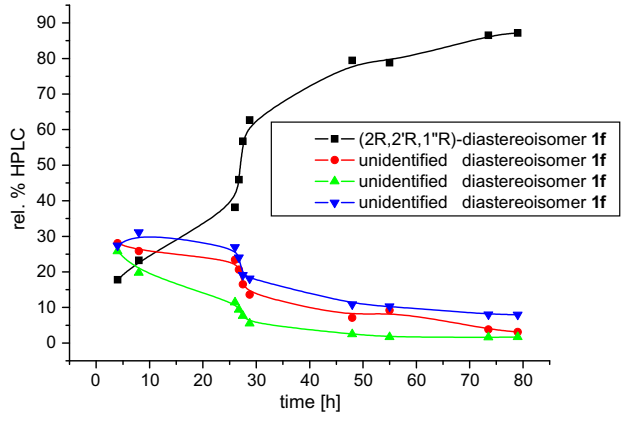
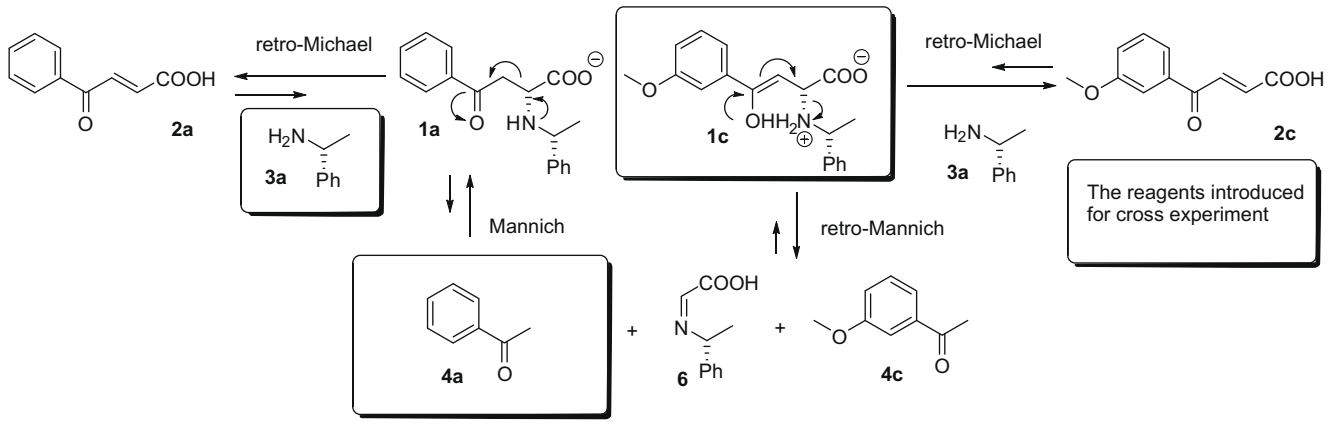


Figure 1. Stereochemical development of the Mannich reaction of **4f** with **3a** and **5**.

addition. Only trace amounts of other new compounds were detected at an early stage of the reaction (HPLC trace after 1 h and 6 h). However, after 24 h several products of *retro*-Mannich reaction and consequent transformation were observed. The primary product of the *retro*-Mannich reaction of **1c**, ketone **4c**, was detected. The presence of a second degradative product of the *retro*-Mannich reaction, imine **6** derived from glyoxylic acid and (*R*)-PEA **3a**, was confirmed indirectly. Imine **6** reacted in a competitive Mannich reaction with the present ketone **4a** providing aminoacid **1a**. This underwent a subsequent *retro*-Michael reaction providing the product of elimination, unsaturated acid **2a**, which was identified in the reaction mixture as well. Although, the amount of the acids **2a**,**c** in the reaction mixture remained at constant concentration (a comparison of the trace after 24 h and 120 h), the amount of acetophenones **1a**,**c** varied until it become approximately equal (after 120 h). This simplified model with fast *retro*-Michael reaction and relatively slow *retro*-Mannich reaction (we did not consider the further possible transformation of imine **6** or degradative reaction of glyoxylic acid) provides a plausible explanation for epimerization in such type of transformations and is supported by several related examples in the literature.[20] *retro*-Michael addition, as a competitive undesired side-reaction, was described in aminomethylation of aldehydes by Gellman.[21] A subsequent example of *retro*-Michael addition explains the *syn*–*anti* epimerization in a three component phenolic Mannich reaction.[22] Based on both, literature precedence and our experimental findings, we believe that *retro*-Michael and



Scheme 5. A plausible explanation of epimerization in the cross experiment.

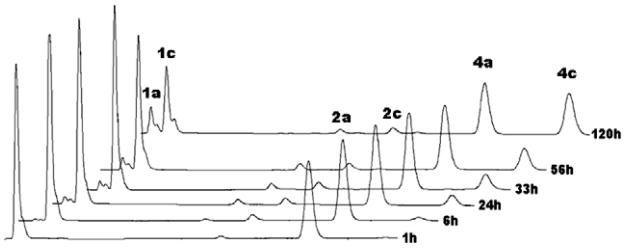


Figure 3. HPLC traces of reaction mixture of a cross experiment between **1c**, amine **3a** and ketone **4a**. Retention times: t_R 6.6 min **1a**, t_R 7.2 min **1c**, t_R 13.2 min **2a**, t_R 15.0 min **2c**, t_R 18.5 min **4a**, t_R 21.4 min **4c**.; trace ordered according to reaction time from 1 h to 120 h.

retro-Mannich reactions take place simultaneously in the Mannich condensation between ketones **4** and imines **6**. Both transformations ensure reversibility of the process, a necessary point for CIAT process. On the other hand, we assume that the degradation of some reactive intermediates causes lower chemical yields in several examples (transformation of **4b**,**c** to **1b**,**c**).

The absolute stereochemistry of derivatives **1a**, **e**, **f** and **1g** was assigned by comparison of those with authentic samples obtained previously (NMR data and chirooptical properties).[4–9] Assuming the same stereochemical outcome of the CIAT process, stereochemistry of new compounds **1b**–**d**, **1h** was assigned by analogy.

3. Conclusion

In conclusion, an efficient Mannich reaction of ketones with an in situ formed imine derived from phenylethylamine and glyoxylic acid has been developed. Using mild conditions, substituted aminobutanoic acids were isolated in excellent stereochemical purity. Further development to this work and its application in the synthesis of complex biologically active compounds is ongoing in our laboratory, and the work will be disclosed in due course.

4. Experimental

4.1. General

Reagents were used as received without further purification, unless otherwise stated. (*R*)-Phenylethylamine (99+%, 99% ee) was obtained from ACROS. 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-jacket 10,000 cm cell at a 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. IR spectra were measured on Nicolet 5700 FTIR spectrometer in KBr disks. ^{1}H NMR spectra were recorded on a Varian VXR-300 (299.94 MHz) spectrometer. Chemical shift (δ) is quoted in parts per million and is referenced to the tetramethylsilane (TMS) as an internal standard (δ_{Me} = 0.00 for 299.94 MHz). Coupling constant (J) is recorded in Hertz. The following abbreviations were used through to characterize signal multiplicities: s (singlet), d (doublet), t (triplet), m (multiplet) and br (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 VRX-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. Chemical shifts are quoted in parts per million and are referenced to the tetramethylsilane (TMS) as the internal standard (δ = 0.00 for 75.43 MHz). HPLC experiments were performed on PYE UNICAM chromatographic system (PU 4015 pump working in isocratic 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: C18 5 μm reverse phase column Phenomenex Luna C18 250 × 4.6 mm or Phenomenex Luna Phenyl–Hexyl 250 × 4.6 mm or Waters Symmetry 5 μm C18 250 × 4.6 mm. Eluent was a mixture of acetonitrile/water/Et_3N 400:600:10 or 250:750:15, pH adjusted to 2.9–3.5 by H_3PO_4. The mobile phase was pumped through the system at 0.5–1.5 mL/min at room temperature.

4.2. General procedure for the Mannich reaction

To a solution of (*R*)-phenylethylamine **3a** (20.0 mmol, 2.424 g) in EtOH (or Et_2O) was added slowly glyoxylic acid **5** (10.0 mmol, 0.921 g). After being stirred for 10 min, ketone **4** (10.0 mmol) was added and the resulting solution was stirred at 40 °C (at rt where Et_2O used) until HPLC analysis had shown complete consumption of starting materials (typical 4–6 days). The suspension was cooled to rt, at which point, the solid was filtered off, washed (EtOH, Et_2O) and dried to obtain aminoacid **1** as a white solid.

4.2.1. (2*R*)-4-Oxo-4-phenyl-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid 1a

According to the general procedure (for 10.0 mmol, 1.202 g of **4a** was used 20.0 mmol, 2.424 g of (*R*)-PEA **3a**, 10.0 mmol, 0.920 g of glyoxylic acid monohydrate **5** and 10 mL of Et_2O; 4 days, RT, washed with Et_2O) **1a** (1.952 g, 66%, dr >99:1) was obtained as a white solid. Mp = 192–195 °C (EtOH–H_2O, lit.[11] 194–196 °C (CH_3CN–H_2O); $[\alpha]_D^{20} = -23.0$ (*c* 0.6, THF/1 M HCl 4:1), lit.[11] $[\alpha]_D^{20} = -36.5$ (*c* 0.5, MeOH/1 M H_2SO_4 3:1); IR (KBr disk) 3047, 3008, 2987, 2862,

1697, 1628, 1607, 1568, 1458, 1449, 1385, 1355, 1301, 1277, 1244, 1076, 1054, 1001, 986, 772, 750, 703, 689. NMR data and elemental analysis are in agreement with those published.[11]

4.2.2. (2*R*)-4-(4-Bromophenyl)-4-oxo-2-{[(1*R*)-1-phenylethyl]-amino}butanoic acid 1b

According to the general procedure (for 2.5 mmol, 0.498 g of **4b** was used 5.0 mmol, 0.606 g of (*S*)-PEA **3a**, 2.5 mmol, 0.230 g of glyoxylic acid **5**, 0.5 mL of EtOH; 7 days, washed with Et_2O) **1b** (0.320 g, 34%, dr 98:2) was obtained as a white solid. Mp = 187–189 °C (EtOH–H_2O); $[\alpha]_D^{20} = -43.0$ (*c* 0.9, MeOH/1 M HCl 3:1); IR (KBr disk) 3027, 2983, 2851, 1697, 1631, 1606, 1587, 1566, 1478, 1458, 1383, 1354, 1275, 1248, 1207, 1072, 1053, 1012, 988, 810, 771, 760, 700; ^{1}H NMR (300 MHz, acetone-d_6/DCl): 1.80 (d, 3H, *J* = 6.9), 3.89 (ddd, 2H, *J* = 18.8, 5.5, 5.0), 4.10 ('t', 1H, *J* = 5.5, 5.1), 4.83 (q, 1H, *J* = 6.9), 7.35–7.48 (m, 3H), 7.61–7.70 (m, 4H), 7.82–7.89 (m, 2H); ^{13}C NMR (acetone-d_6/DCl): 21.5, 40.3, 54.4, 60.4, 129.8, 129.9, 130.9, 131.1, 131.7, 133.4, 136.0, 137.1, 170.3, 196.3.

4.2.3. (2*R*)-4-(3-Methoxyphenyl)-4-oxo-2-{[(1*R*)-1-phenylethyl]-amino}butanoic acid 1c

According to the general procedure (for 2.5 mmol, 0.375 g of **4c** was used 5.0 mmol, 0.606 g of (*R*)-PEA **3a**, 2.5 mmol, 0.230 g of glyoxylic acid **5**, 1.0 mL of EtOH; 5 days, washed with Et_2O) **1c** (0.240 g, 29%, dr 99:1) was obtained as a white solid. Mp = 165–170 °C (EtOH–H_2O); $[\alpha]_D^{20} = -46.4$ (*c* 1.0, MeOH/1 M HCl 3:1); IR (KBr disk) 3028, 2982, 2939, 2841, 1696, 1631, 1608, 1583, 1566, 1483, 1458, 1451, 1432, 1382, 1354, 1319, 1302, 1288, 1276, 1262, 1229, 1193, 1076, 1041, 993, 856, 788, 769, 701, 685; ^{1}H NMR (300 MHz, acetone-d_6/DCl): 1.81 (d, 3H, *J* = 6.9), 3.80 (s, 3H), 3.89 (ddd, 2H, *J* = 18.7, 5.3, 5.2), 4.09 ('t', 1H, *J* = 5.5, 5.2), 4.82 (q, 1H, *J* = 6.9), 7.12–7.19 (m, 1H, *J* = 8.2, 2.6), 7.35–7.60 (m, 6H), 7.67 (m, 2H); ^{13}C NMR (acetone-d_6/DCl): 21.5, 40.5, 54.7, 60.4, 56.7, 114.0, 121.7, 122.5, 130.0, 131.0, 131.2, 131.6, 137.3, 138.5, 161.4, 170.6, 197.1; Calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 68.05; H, 6.23; N, 4.20.

4.2.4. (2*R*)-4-(3,4-Dimethoxyphenyl)-4-oxo-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid 1d

According to the general procedure (for 25.0 mmol, 4.500 g of **4d** was used 50.0 mmol, 6.060 g of (*R*)-PEA **3a**, 25.0 mmol, 2.300 g of glyoxylic acid **5**, 4.0 mL of EtOH; 6 days, washed with EtOH, Et_2O) **1d** (4.600 g, 51%, dr 99:1) was obtained as a white solid. Mp = 173–176 °C (EtOH–H_2O); $[\alpha]_D^{20} = -65.9$ (*c* 1.0, MeOH/1 M HCl 3:1); IR (KBr disk) 3132, 2980, 2960, 2934, 2837, 1690, 1623, 1595, 1587, 1581, 1517, 1468, 1458, 1449, 1439, 1413, 1381, 1355, 1332, 1268, 1230, 1214, 1196, 1169, 1125, 1021, 997, 903, 842, 824, 767, 703; ^{1}H NMR (300 MHz, acetone-d_6/DCl): 1.82 (d, 3H, *J* = 6.9), 3.84 (s, 3H), 3.88 (s, 3H), 3.84–3.96 (dd, 2H, *J* = 18.5, *J* = 5.4), 4.06 ('t', 1H, *J* = 5.5, 5.2), 4.82 (q, 1H, *J* = 6.8), 7.03 (d, 1H, *J* = 8.5), 7.36–7.51 (m, 4H); 7.61–7.72 (m, 3H); ^{13}C NMR (acetone-d_6/DCl): 21.6, 40.0, 54.0, 60.4, 57.0, 57.2, 111.9, 112.4, 125.1, 130.0, 130.1, 131.0, 131.2, 137.4, 150.6, 155.7, 170.8, 195.8; Calcd for $C_{20}H_{23}NO_5$: C, 67.21; H, 6.49; N, 3.92. Found: C, 63.65; H, 6.50; N, 3.73.

4.2.5. (2*R*,3*S*)-3-Methyl-4-oxo-4-phenyl-2-{[(1*R*)-1-phenylethyl]amino}butanoic acid 1e

According to the general procedure (for 5.0 mmol, 0.670 g of **4e** was used 10.0 mmol, 1.212 g of (*R*)-PEA **3a**, 5.0 mmol, 0.460 g of glyoxylic acid **5**, 1.0 mL of EtOH; 6 days, washed with Et_2O) **1b** (0.750 g, 48%, dr 98:1:0:1) was obtained as a white solid. Mp = 197–198 °C (EtOH–H_2O), lit.[9] *ent*-**1e** mp = 197–198 °C (H_2O); $[\alpha]_D^{20} = -17.4$ (*c* 1.0, MeOH/1 M HCl 3:1), lit.[9] *ent*-**1e** $[\alpha]_D^{25} = +17.4$ (*c* 1.0, MeOH/1 M HCl 3:1); IR (KBr film) 3041, 2998, 2879, 1694, 1644, 1631, 1576, 1465, 1447, 1426, 1388, 1378, 1348, 1287, 1269, 1218, 1075, 1051, 983, 968, 920, 872, 808, 784, 764, 755, 698; NMR data and elemental analysis are in agreement with those published.[9]

4.2.6. (2*R*)-[(2*R*)-1-Oxo-1,2,3,4-tetrahydronaphthalen-2-yl]-{[(1*R*)-1-phenylethyl]amino}ethanoic acid 1f

According to the general procedure (for 6.8 mmol, 1.000 g of **4f** was used 13.7 mmol, 1.658 g of (*R*)-PEA **3a**, 6.8 mmol, 0.630 g of glyoxylic acid **5**, 8.0 mL of EtOH; 5 days, washed with Et_2O) **1f** (1.170 g, 53%, dr >99:<1:0:0) was obtained as a white solid. Mp = 161–164 °C (EtOH–H_2O). lit.[6] mp = 163–164 °C; $[\alpha]_D^{20} = -88.0$ (*c* 0.8, THF/1 M HCl 4:1); lit.[6] $[\alpha]_D^{20} = -88.0$ (*c* 0.8, THF/1 M HCl 4:1); IR (KBr disk) 3075, 3029, 2979, 2938, 2881, 2842, 1693, 1618, 1591, 1581, 1470, 1456, 1438, 1430, 1377, 1346, 1324, 1284, 1236, 1223, 1082, 1066, 1001, 926, 770, 748, 700; NMR data are in agreement with those published.[6]

4.2.7. (2*R*)-5,5-Dimethyl-4-oxo-2-{[(1*R*)-1-phenylethyl]amino}-hexanoic acid 1g

According to the general procedure (for 25.0 mmol, 2.500 g of **4g** was used 50.0 mmol, 6.06 g of (*R*)-PEA **3a**, 25.0 mmol, 2.300 g of glyoxylic acid **5**, 4.0 mL of EtOH; 6 days, washed with EtOH, Et_2O) **1g** (0.320 g, 66%, dr 99:1) was obtained as a white solid. Mp = 213–216 °C (EtOH–H_2O), lit.[8] *ent*-**1g** mp = 213–214 °C; $[\alpha]_D^{20} = +14.4$ (*c* 0.1, MeOH/1 M HCl 3:1), lit.[8] *ent*-**1g** $[\alpha]_D^{25} = -14.7$ (*c* 1.0, MeOH/1 M HCl 3:1); IR (KBr disk) 2976, 2960, 2870, 1720, 1705, 1637, 1608, 1571, 1515, 1478, 1382, 1366, 1319, 1302, 1279, 1205, 1089, 1076, 1061, 1000, 860, 770, 759, 701; NMR data and elemental analysis are in agreement with those published.[8]

4.2.8. (2*R*)-4-Cyclohexyl-4-oxo-2-{[(1*R*)-1-phenylethyl]amino}-butanoic acid 1h

According to the general procedure (for 24.0 mmol, 3.029 g of **4h** was used 48 mmol, 5.792 g of (*R*)-PEA **3a**, 24.0 mmol, 2.2 g of glyoxylic acid **5**, 10.0 mL of EtOH; 5 days, washed with Et_2O) **1h** (3.928 g, 58%, dr 98:2) was obtained as a white solid. Mp = 169–172 °C (EtOH–H_2O), $[\alpha]_D^{20} = +0.5$ (*c* 0.8, MeOH/1 M HCl 3:1); IR (KBr disk) 3030, 2984, 2934, 2850, 1725, 1639, 1609, 1558, 1499, 1481, 1455, 1382, 1355, 1318, 1275, 1211, 1145, 1084, 1073, 1012, 993, 893, 841, 769, 700; ^{1}H NMR (300 MHz, acetone-d_6/DCl): 1.80 (d, 3H, *J* = 6.9), 3.89 (ddd, 2H, *J* = 18.8, 5.5, 5.0), 4.10 (t, 1H, *J* = 5.1), 4.83 (q, 1H, *J* = 6.9), 7.40–7.95 (m, 9H); ^{13}C NMR (acetone-d_6/DCl): 20.8, 26.0, 26.4, 28.6, 40.9, 50.3, 53.3, 59.5, 129.2, 129.9, 130.1, 138.6, 169.7, 209.6.

4.3. The cross experiment

A mixture of (*R*)-phenylethylamine **3a** (20.0 mmol, 2.440 g), ketone **4a** and amino acid **1c** in EtOH (1.5 mL) was stirred at 40 °C. From a heterogenous mixture an analytical sample was taken after 1 h, 6 h, 24 h, 33 h, 56 h and 120 h and analyzed by HLPC on the Phenomenex Luna Phenyl–Hexyl column 250 × 4.6 mm with a mixture of acetonitrile/water/Et_3N 400:600:10 pH adjusted to 3.3 by H_3PO_4, flow 0.5 mL/min, inject 20 μL. Retention times: t_R 6.6 min **1a**, t_R 7.2 min **1c**, t_R 13.2 min **2a**, t_R 15.0 min **2c**, t_R 18.5 min **4a**, t_R 21.4 min **4c**.

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