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Enantioselective Reduction of 3-Aryl-2-oxo-propanoic Acids: A Comparison of Enzymatic and Transition-Metal-Catalyzed Methods

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Phenyllactic acids are important constituents of depsipeptides, which are a large class of natural products expressing a wide range of biological activities. Despite there being several methods for the enantioselective synthesis of α-hydroxy acids, almost no studies are available addressing the substrate selectivity of transition-metal and enzyme-catalyzed methods for the preparation of substituted phenyllactic or more general aryllactic acids. We report herein comparative results for Rh-DiPAMP (DiPAMP = 1,2-ethandiylbis[(*o*-methoxyphenyl)phenylphosphane]) and lactate dehydrogenase catalyzed enantioselective reductions of several 3-aryl-2-oxopropanoic acids.

Introduction

α-Hydroxy acids are found in numerous natural products, as well as in pharmaceutical and plant-protection agents.[1] In particular, α-hydroxy acids are essential constituents of depsipeptides where they function as mimetics for the corresponding natural amino acids; thus causing a wide range of biological activities.[2–8] During our studies on the solid-phase synthesis of the anthelmintic PF1022A and related biologically active cyclodepsipeptides, we required a set of enantiomerically pure D-aryllactic and D-hetaryllactic acids.[9,10] Despite there being different routes to α-hydroxy acids, no general methods are available that allow the synthesis of a broad variety of structurally diverse aryllactic acids. The basic methods to enantiomerically pure, or at least enantiomerically enriched, phenyllactic acids can be attributed to four basic strategies (Figure 1).

Conventionally, substituted phenylalanines are diazotized in acetic acid to produce acetyl-protected phenyllactic acids with retention of configuration (Figure 1). However, substituted phenylalanines have to be synthesized by Pd-catalyzed couplings of functionalized serine derivatives with a suitable aryl–metal species.[11–13] More recent alternatives utilize enantioselective catalytic methods such as the asymmetric dihydroxylation of cinnamic acids followed by a hydrogenolytic removal of the benzylic hydroxy group (Figure 1).[14] Oxynitrilase-catalyzed transcyanations represent another strategy to phenyllactic acids albeit the enantioselectivities are not excellent.[15] The broadest variability regarding the aryl moieties provide enantioselective hydrogenations of α-oxo acids available in a simple two-step synthesis from benzaldehydes (Figure 1). Enantioselective reductions can be achieved either by equivalent amounts of chiral reductants, such as (–)-*B*-chlorodiisopinocampheylborane (DIP-Cl) and oxazaborolidines, or by organometallic and enzyme catalysts.[5,16–18] In particular, the catalytic methodologies have the potential for producing multigram quantities of aryl- and hetaryllactic acids.

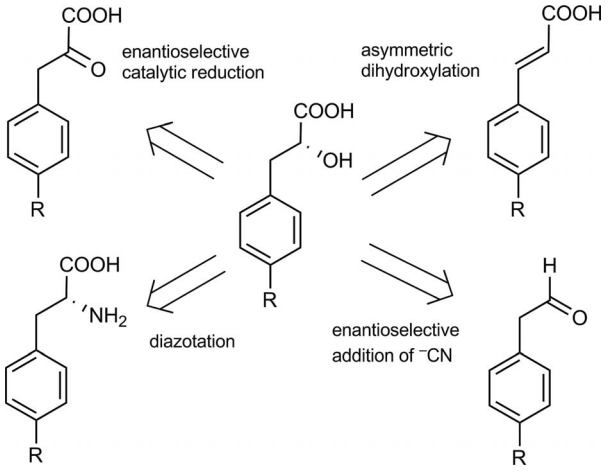

Figure 1. Synthetic routes to phenyllactic acids.

Numerous chiral rhodium catalysts, among those the benchmark ligands TangPhos and ZhangPhos, as well as many others, have been reported to produce excellent enantioselectivities in hydrogenations of α-(acylamino)-acrylic acids, enol acetates, and β-enamino esters.[19–23] However, the number of suitable catalysts for α-(acyloxy)-acrylates performing well at low hydrogen pressures (< 10 bar) in standard laboratory equipment is limited. Ad-

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ditionally, these types of hydrogenations are frequently impaired by reduced yields, mediocre enantioselectivities, or complex ligands.[24–26] With respect to commercial availability and reported enantioselectivities, Rh^{I}-DuPhos, Ru^{II}-BINAP, and Rh^{I}-DiPAMP (DuPhos = 1,2-bis(2,5-diethylphospholano)benzene, BINAP = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, DiPAMP = 1,2-ethandiylbis[(*o*-methoxyphenyl)phenylphosphane]) still remain promising standard catalysts for the hydrogenation of α-(acyloxy)-acrylates (Figure 2).[27,28]

A complementary strategy for the synthesis of α-hydroxy acids is based on the enantioselective enzymatic reduction of 2-oxo acids (Figure 1). Compared with other enzymatic strategies, such as kinetic resolution of racemic α-hydroxy esters with hydrolases or oxynitrilase-catalyzed enantioselective formation of cyanohydrins and subsequent hydrolysis, the stereospecific reduction of a 2-oxo precursor with an alcohol dehydrogenase appears to be the most promising biocatalytic method.[29–32] Moreover, by using a coupled enzyme system consisting of D-lactate dehydrogenase (D-LDH) and formate dehydrogenase (FDH) in a membrane reactor, a continuous multigram production of the respective phenyllactic acid can be accomplished.[33]

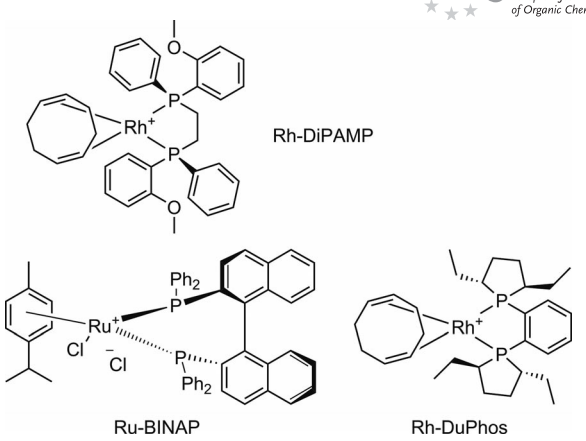
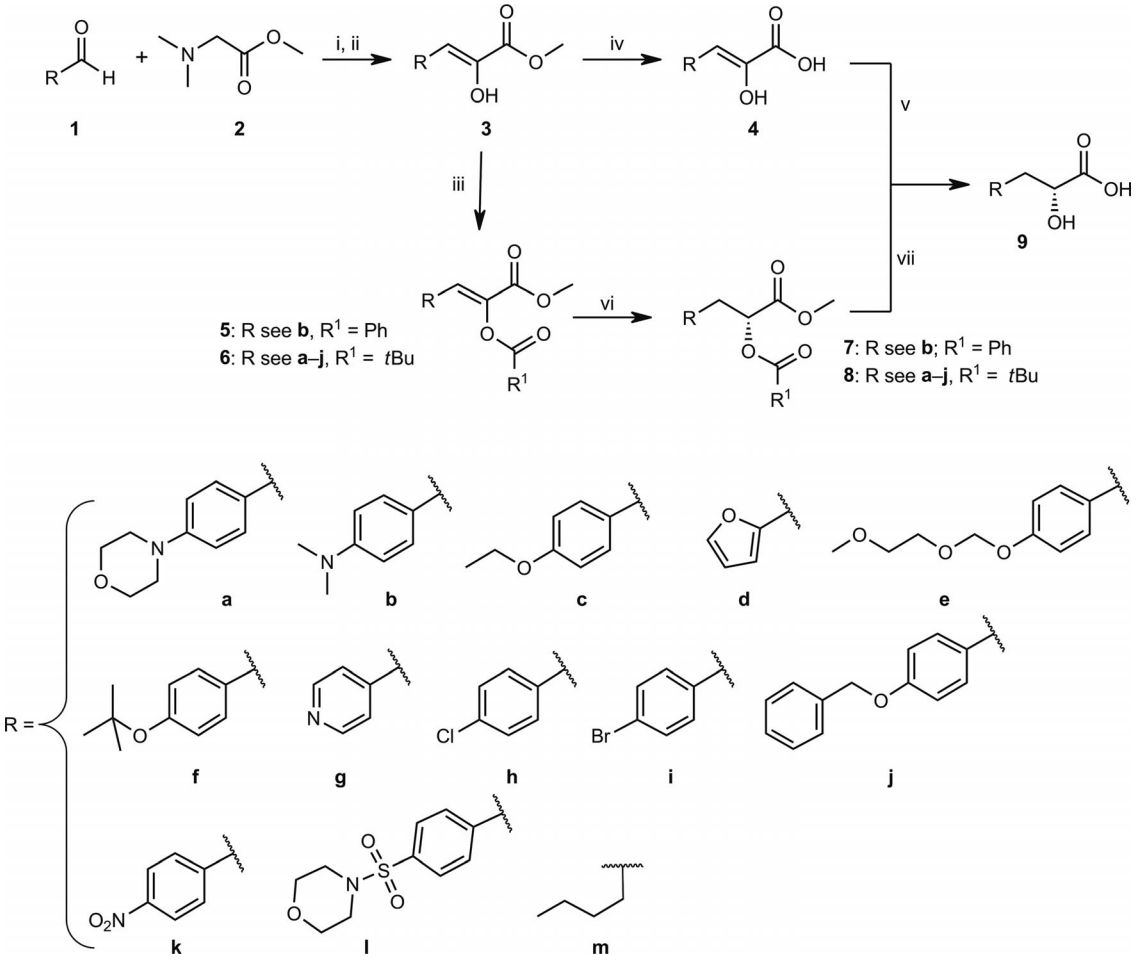


Figure 2. Structures of Rh-DuPhos, Ru-BINAP, and Rh-DiPAMP catalysts.



Scheme 1. Synthesis of starting compounds and enantioselective hydrogenations with a rhodium catalyst and lactate dehydrogenase. Reagents and conditions: (i) NaH, MeOH, ethyl ether, 0 °C → room temp., 18 h; (ii) 1 M HCl_{aq}, room temp.; (iii) **3a**, **3b**: benzoic acid, *N*,*N*′-diisopropylcarbodiimide (DIC), 4-dimethylaminopyridine (DMAP), CH_2Cl_2, room temp., 6 h; **3a**–**j**: pivaloyl chloride, triethylamine (TEA), CH_2Cl_2, 0 °C → room temp., 16 h; (iv) LiOH, H_2O/THF, 0 °C, 4 h; (v) D-LDH, nicotinamide adenine dinucleotide (NADH), FDH, NH_4HCO_2, ethylenediaminetetraacetic acid (EDTA), water, pH = 7, room temp., 15 h; (vi) **5**: 2 mol-% Rh-DuPhos, H_2 (8 bar), CH_2Cl_2, room temp., 24 h; **5**: 1 mol-% Ru-BINAP, H_2 (50 bar), MeOH, 50 °C, 4 d; **6b**: 1 mol-% Ru-BINAP, H_2 (50 bar), MeOH, 50 °C, 4 d; **6a**–**j**: 1 mol-% Rh-DiPAMP, H_2 (5.0 bar), MeOH, room temp., 4 d; (vii) 1 M LiOH (THF/water, 3:5), 0 °C → room temp., 18 h.

Results and Discussion

Preparation of the Starting Materials

2-Oxo acids are common substrates for both rhodium and lactate dehydrogenase catalyzed reductions. They can be easily prepared as *E*/*Z* mixtures by condensation of an aromatic aldehyde (**1**) with an *N*,*N*-dimethylglycine methyl ester (**2**), followed by acidic hydrolysis of the intermediate α-(dimethylamino)acrylic esters, according to a procedure by Horner and Renth (Scheme 1).[34] Hydrolysis of the intermediate enamines with HCl (1 M) afforded the 2-oxocarboxylic esters **3a**–**j** in yields between 54 and 90% (Table 1) after crystallization or distillation (compound **3e**).

Table 1. Yields of starting compounds for rhodium- and enzyme-catalyzed hydrogenations.

Entry	Yield [%] **3**	Yield [%] **4**	Yield [%] **6**
a	79	75	77
b	88	< 1	87
c	73	86	97
d	69	< 1	98
e	72	44	84
f	58	73	74
g	78	91	78
h	90	62	100
i	73	53	94
j	54	72	97

Depending on the type of ligand, specific enol esters are required for high yields and enantioselectivities in Rh- and Ru-catalyzed hydrogenations. Thus, benzoate **5** was prepared as a substrate for Rh-DuPhos and the corresponding pivaloates (**6a**–**j**) for the Rh-DiPAMP and Ru-BINAP catalysts. All acylation products were found to have exclusively the thermodynamic more stable *Z* configuration, as proved by NOESY NMR spectroscopy and X-ray structural analysis of enol esters **6b**, **6d**, and **6i**.[35] However, as already demonstrated by Burk et al., the stereochemical course of Rh-DuPhos-catalyzed hydrogenations is independent of the *E*/*Z* configuration of the enol esters used as substrates.[27] Unfortunately, the synthesis of 2-oxo esters **3k**–**m** failed due to extensive formation of aldol condensation products during hydrolysis.

In contrast to the rhodium-catalyzed hydrogenation, lactate dehydrogenase reduces directly the carbonyl group by transferring a hydride anion from NADH. Additionally, it accepts the unprotected 2-oxo acids as available substrates by a carefully controlled basic hydrolysis of the methyl esters (1.1 equiv. LiOH, THF/H_2O, 0 °C, 4 h; Table 1).

Even under these mild conditions, the electron-rich arylpyruvates **4b** and **4d** tended to undergo aldol condensations (Scheme 1 and Table 1). An enzymatic ester cleavage with *Candida rugosa* lipase under strict pH control resulted in similar problems that were probably caused by the extended reaction times of 1–2 days at room temperature.[36]

Enantioselective Reductions

In a preliminary study, benzoate **5** was used as a model substrate for the Rh-DuPhos and Ru-BINAP catalysts.[24] While Rh-DuPhos-catalyzed hydrogenation gave only a low yield (22%) of phenyllactic ester **7**, which was highly enantioselective (*ee* 98%), the Ru-BINAP catalyst was disappointing with respect to both yield (33%) and enantioselectivity (*ee* 34%). A good yield (79%) and an excellent enantiomeric excess (*ee* 98%) was obtained for aryllactic ester **8b** with Rh-DiPAMP and pivaloate ester **6b** as the substrate after a reaction time of 4 d and 5 bar H_2. Consequently, the Rh-DiPAMP/pivaloate system was chosen for all other hydrogenations (Table 2).[25,37] The somewhat reduced yields of 4-benzyloxyphenyllactic ester **8j** and 4-bromophenyllactic ester **8i** can be attributed to incomplete conversion and losses during chromatographic purification. Remarkably, no reaction could be observed for 3-pyridino-2-oxo acrylate **6g**, which presumably acted as a catalyst poison.[38] The *R* configuration of the resulting aryllactic acids was established by X-ray structural analysis of compound **8h**.[35]

Table 2. Rhodium and lactate dehydrogenase catalyzed reductions of arylpyruvates.

	Yield [%] Rh-DIPAMP	*ee*[a] [%]		Yield [%] D-LDH	*ee*[a] [%]
8a	90	99	**9a**	66	> 99
8b	79	95	**9b**[b]	–	–
8c	96	96	**9c**	37	96
8d	81	96	**9d**[b]	–	–
8e	92	96	**9e**	75	82
8f	91	98	**9f**	72	> 99
8g	–	–	**9g**	95	> 99
8h	91	> 99	**9h**	44	> 99
8i	60	96	**9i**	68	98
8j	73	69	**9j**	60	88

[a] The *ee* values were obtained by chiral HPLC with comparison to the racemic material. [b] Starting material decomposed under the reaction conditions.

Finally, the esters were cleaved without loss of enantiomeric purity in one step with an aqueous solution of LiOH (3 equiv.), to obtain the α-hydroxy acids **9a**–**j** in yields ranging from 72 to 95% after a prolonged reaction time (2–3 d) caused by the bulky pivaloyl group.

Enzymatic reductions with D-LDH require NADH as a cofactor, which is oxidized to NAD during the reaction. Due to the high price of NADH, in situ cofactor regeneration is essential for the synthesis of preparative amounts of aryllactic acids. A coupled two-enzyme redox system utilizing FDH as the second biocatalyst allows the reduction of NAD back to NADH in the presence of formate, which is oxidized to CO_2. This experimental setup renders the overall process catalytic in NADH (Figure 3).[31–33,39]

In principle, LDH reductions can be performed under either continuous-flow or batch-process conditions in an ultrafiltration-membrane reactor.[33,40] A fundamental advantage of a continuous-flow reactor is its high degree of flexibility regarding control of reaction time and flow rate as well as recovery of products and enzymes. However, with a continuous reactor we were unable to obtain more than 30% turnover with the reference compound phenylpyruvate (**10**) due to significant enzyme inactivation after 10–15 h reaction time.

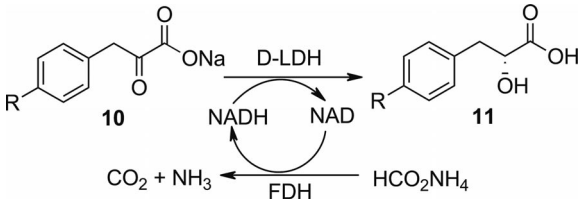


Figure 3. Scheme for LDH-catalyzed reductions with cofactor regeneration.

In a batch run, the reactor was initially charged with a solution of the substrate phenylpyruvate (**10**) or 2-oxo acids **4a**–**j** (10 mM) in water (50 mL), containing EDTA (0.025 mM), mercaptoethanol (0.05 mM), NAD (0.1 mM), and $HCOONH_4$ (40 mM), followed by D-LDH (20 U/mL) and FDH (1 U/mL).[41] After an overall reaction time of around 24 h, the turnover was complete (Table 2). The reactor was flushed with argon or nitrogen (0.1–0.2 bar pressure) and the reaction was filtered slowly (40–80 min) through the membrane (polyethersulfone, cutoff: 10 kDa). Only minor inactivation of the enzyme system was observed under these conditions. A new run with fresh starting material and buffer solution afforded almost complete conversion (95%).

The generally somewhat lower yields of the enzymatic reduction can be attributed to limited stability, in particular, of electron-rich 2-oxo-carboxylic acids (Table 2). Long-chain aryl–alkyl ether **4e** turned out to be a poor substrate for the enzyme-catalyzed reduction. Apparently, the binding pocket of D-LDH is not able to accommodate long-chain *para* substituents in the correct position for a highly enantioselective reduction. This behavior can already be observed to a minor extent for ethyl ether **9c**, which shows slightly reduced enantiomeric purity. Remarkably, 3-pyridino-2-oxopropanoic acid **4g**, which had completely failed in the rhodium-catalyzed hydrogenation, was an excellent substrate for D-LDH (yield 95%, *ee* > 99%, Table 2).

Conclusions

A comparative study on transition-metal (Rh-DiPAMP) and enzyme-catalyzed (D-LDH) reductions of a series of 3-aryl-2-oxopropanoic acids was conducted to provide a straightforward access to enantiomerically enriched aryl- and hetaryllactic acids on a gram scale.

While the yields of the rhodium-catalyzed hydrogenations were slightly better, enantiomeric excesses were comparable for both the metal- and enzyme-catalyzed procedures. Nevertheless, the enzymatic route is more efficient, since it does not need any protecting-group chemistry. Thus, for multigram syntheses the enzymatic process appears to be advantageous. D-LDH and FDH are reasonably priced and are stable in a batch reactor for at least 48 h. The cofactor NADH is needed only in catalytic amounts (0.01 equiv.), and thus, is not a relevant cost factor. In contrast to rhodium-catalyzed hydrogenation, 2-oxo-3-(4-pyridyl)propanoic acid (**4g**) is an excellent substrate for D-LDH, providing easy access to almost enantiomerically pure pyridinolactic acids.

Experimental Section

General: The starting materials 4-morpholinobenzaldehyde, 4-(dimethylamino)benzaldehyde, 4-ethoxybenzaldehyde, 2-furancarbaldehyde, 4-(methoxyethoxymethoxy)benzaldehyde, 4-(*tert*-butoxy)benzaldehyde, 4-pyridinecarbaldehyde, 4-chlorobenzaldehyde, 4-bromobenzaldehyde, and 4-(benzyloxy)benzaldehyde were either purchased or prepared by standard literature procedures.[42] All reactions, except the saponifications, hydrolysis reactions, and the enzymatic reductions, were performed in dried solvents. Dichloromethane and TEA were heated at reflux for 1 h over calcium hydride and distilled. Ethyl ether was heated at reflux for several hours over $LiAlH_4$ and then distilled. Methanol was heated at reflux over magnesium oxide and distilled. The instrumentation used was as follows: ^{1}H NMR: Bruker Avance 400, Bruker Avance III 600 ^{13}C NMR: Bruker Avance 400, Bruker Avance III 600. FTIR: Nicolet PROTÉGÉ 460 E.S.P. MS: (Bruker microTOF): ESI-MS, (Varian IT 500-MS) Iontrap. LC: Preparative low-pressure chromatography (LPLC) was performed by using silica gel 60 μm (230–400 mesh, Macherey–Nagel), Büchi pump. TLC: silica gel 60 F_{254} (Merck). Enantiomeric excess values were determined by chiral HPLC in comparison to racemic material, which was prepared either by reduction of the 2-oxo esters **3a**–**j** with $NaBH_4$ for the enzymatic route or by hydrogenation of enol esters **6** with $Pd(OH)_2$/C (20%, 8 mol-%) for the rhodium-catalyzed procedure. For better HPLC analysis the methyl esters (MeOH, $SOCl_2$) of the chiral 2-hydroxy acids **9** were used.

General Procedure for the Preparation of the Enamines: Sodium hydride (2 equiv.) was suspended in Et_2O then methanol (0.2 equiv.) and aldehydes **1a**–**c** (1 equiv.) were added under vigorous stirring. The suspensions were cooled to 0 °C and *N*,*N*-dimethylglycine methyl ester (3 equiv.) was added dropwise. After stirring in an ice–water bath, the reactions were warmed to room temperature overnight (18 h). Ice water and CH_2Cl_2 were added at 0 °C. The aqueous layers were extracted three times with CH_2Cl_2; the combined organic phases were dried with Na_2SO_4, evaporated, and dried in vacuo. The crude products were purified by kugelrohr distillation in vacuo.

(*E*/*Z*)-Methyl 2-(Dimethylamino)-3-(4-morpholinophenyl)acrylate: Starting material: *p*-morpholinobenzaldehyde (**1a**; 3.81 g, 19.31 mmol). Yield after distillation (220 °C, 8×10^{-3} mbar): 91% (5.11 g, 17.58 mmol), yellow solid, m.p. 70 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.67, 2.72 (2 s, 6 H, NCH_3), 3.14, 3.23 (2 t, J = 4.9 Hz, 4 H, NCH_2), 3.72, 3.81 (2 s, 3 H, OCH_3), 3.87 (m, J = 4.9 Hz, 4 H, OCH_2), 5.59, 6.93 (2 s, 1 H, olefinic-H), 6.82, 6.88 (2 d, J = 8.9, 9.0 Hz, 2 H, Ar-H), 7.05, 7.71 (2 d, J = 8.8, 9.0 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 40.6, 42.4, 48.4, 49.2, 51.3, 52.1, 66.7, 66.8, 107.0, 129.3, 114.4, 115.4, 126.2, 127.9, 131.6, 137.8, 142.0, 149.2, 151.0, 167.3, 168.5 ppm. IR (KBr): $\tilde{\nu}$ = 1717 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 231 (46), 291 (100). HRMS (ESI): calcd. for $C_{16}H_{23}N_2O_3$ $[M + H]^+$ 291.1703, found 291.1704.

(*E*/*Z*)-Methyl 2-(Dimethylamino)-3-(4-dimethylaminophenyl)acrylate: Starting material: *p*-*N*,*N*-dimethylaminobenzaldehyde (**1b**; 4.50 g, 29.86 mmol). Yield after distillation (195 °C, 2.9×10^{-2} mbar): 87% (6.45 g, 26.03 mmol), yellow solid, m.p. 36–38 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.68, 2.71 (2 s, 6 H, NCH_3-enamine), 2.94, 3.01 (2 s, 6 H, NCH_3), 3.74, 3.81 (2 s, 3 H, OCH_3), 5.64, 7.00 (2 s, 1 H, olefinic-H), 6.66, 6.71 (2 d, J = 9.0, 9.1 Hz, 2 H, Ar-H), 7.03, 7.75 (2 d, J = 8.5, 9.1 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.1, 40.5, 40.7, 42.3, 51.1, 52.2, 108.5, 131.3, 111.5 112.5, 123.0, 128.0, 132.1, 136.2, 150.5, 167.5 ppm. IR (KBr): $\tilde{\nu}$ = 1701 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) =

189 (99), 249 (100). HRMS (ESI): calcd. for $C_{14}H_{20}N_2NaO_2$ [M + Na]$^+$ 271.1417, found 271.1414.

(*E*/*Z*)-Methyl 2-(Dimethylamino)-3-(4-ethoxyphenyl)acrylate: Starting material: *p*-ethoxybenzaldehyde (**1c**; 3.49 g, 23.00 mmol). Yield after distillation (175 °C, 8.0×10^{-2} mbar): 96% (5.52 g, 22.15 mmol), yellow liquid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.45 (t, J = 7.0 Hz, 3 H, CH_3-ethoxy), 2.68, 2.73 (2 s, 6 H, NCH_3), 3.71, 3.82 (2 s, 3 H, OCH_3), 4.08 (q, J = 7.0 Hz, 2 H, OCH_2), 5.64, 6.92 (2 s, 1 H, olefinic-H), 6.90 (d, J = 8.6 Hz, 2 H, Ar-H), 7.71 (d, J = 8.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.6, 14.8, 40.6, 42.4, 51.4, 52.1, 63.3, 63.9, 114.1, 114.5, 131.8, 131.9, 127.6, 128.6, 138.3, 142.4, 157.1, 167.3 ppm. IR (film): $\tilde{\nu}$ = 1708 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 190 (92), 250 (100), 272 (2). HRMS (ESI): calcd. for $C_{14}H_{20}NO_3$ [M + H]$^+$ 250.1438, found 250.1442.

General Procedure for Hydrolysis of the Enamines: Enamines were dissolved in aqueous HCl (ca. 100 mL, 1 M). The mixtures were stirred at room temperature (30 min) and then washed twice with CH_2Cl_2. The pH was adjusted to 8 with $NaHCO_3$. The resulting slurries were filtered off and washed with water. The crude products were dried in vacuo and purified by recrystallization.

Methyl 2-Hydroxy-3-(4-morpholinophenyl)acrylate (3a): Starting material: methyl 2-(dimethylamino)-3-(4-morpholinophenyl)acrylate (6.00 g, 20.66 mmol). Solvent for recrystallization: acetone, yield 79% (4.30 g, 16.32 mmol), yellow solid, m.p. 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.23 (t, J = 4.8 Hz, 4 H, NCH_2), 3.88 (t, J = 4.7 Hz, 4 H, OCH_2), 3.92 (s, 3 H, OCH_3), 6.51 (s, 1 H, olefinic-H), 6.91 (d, J = 9.0 Hz, 2 H, Ar-H), 7.72 (d, J = 9.0 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.0, 53.3, 66.9, 111.9, 115.3, 125.5, 131.7, 137.5, 150.7, 166.9 ppm. IR (KBr): $\tilde{\nu}$ = 3403 (O–H), 1685 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 204 (9), 264 (100), 286 (15). HRMS (ESI): calcd. for $C_{14}H_{18}NO_4$ [M + H]$^+$ 264.1230, found 264.1232.

Methyl 3-(4-Dimethylaminophenyl)-2-hydroxyacrylate (3b): Starting material: methyl 2-(dimethylamino)-3-(4-dimethylaminophenyl)-acrylate (1.02 g, 2.64 mmol). Solvent for recrystallization: acetone, yield 88% (0.51 g, 2.31 mmol), yellow solid, m.p. 124–126 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.02 (s, 6 H, NCH_3), 3.91 (s, 3 H, OCH_3), 5.94 (s, 1 H, OH), 6.53 (s, 1 H, olefinic-H), 6.74 (d, J = 8.2 Hz, 2 H, Ar-H), 7.72 (d, J = 8.2 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 40.4, 52.7, 112.0, 112.4, 122.3, 131.3, 136.3, 150.1, 167.1 ppm. IR (KBr): $\tilde{\nu}$ = 3440 (O–H), 1676 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 147 (10), 162 (20), 222 (100), 244 (9). HRMS (ESI): calcd. for $C_{12}H_{16}NO_3$ [M + H]$^+$ 222.1125, found 222.1126.

Methyl 3-(4-Ethoxyphenyl)-2-hydroxyacrylate (3c): Starting material: methyl 2-(dimethylamino)-3-(4-ethoxyphenyl)acrylate (5.48 g, 19.01 mmol). The crude product was recrystallized with Et_2O, yield 73% (4.58 g, 13.81 mmol), yellow solid, m.p. 102–105 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 (t, J = 7.0 Hz, 6 H, CH_3-ethoxy), 3.80, 3.85, 3.92 (3 s, 6 H, OCH_3), 4.05 (m, 4 H, OCH_2), 4.07 (m, 2 H, CH_2-keto form), 5.94 (br. s, 1 H, OH), 6.53 (s, 1 H, olefinic-H), 6.90 (m, 4 H, Ar-H), 7.16 (d, J = 8.0 Hz, 1 H, Ar-H), 7.74 (d, J = 8.0 Hz, 3 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.7, 44.9, 52.9, 53.0, 53.3, 63.2, 63.4, 63.5, 111.3, 113.9, 114.0, 114.5, 114.8, 123.2, 126.7, 129.1, 130.8, 131.4, 132.7, 137.5, 158.4, 158.8, 166.8 ppm. IR (KBr): $\tilde{\nu}$ = 3414 (O–H), 1687 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 163 (100), 223 (92), 245 (19). HRMS (ESI): calcd. for $C_{12}H_{14}NaO_4$ [M + Na]$^+$ 245.0784, found 245.0780.

General Procedure for the Preparation of Pivaloates 6: Enol esters **3** were dissolved in CH_2Cl_2 and stirred for 5 min at 0 °C under an argon atmosphere. Pivaloyl chloride (4 equiv.) and TEA (2 equiv.) were added dropwise. The mixtures were warmed up to ambient temperature and stirring was continued for 16 h. Water was then added, the layers were separated, and the aqueous phases were extracted twice with CH_2Cl_2. The combined organic layers were dried with Na_2SO_4, filtered, and the solvents evaporated. The crude product was dried in vacuo and purified by column chromatography.

(*Z*)-Methyl 3-(4-Morpholinophenyl)-2-(pivaloyloxy)acrylate (6a): Starting material: enol ester **3a** (1.30 g, 4.79 mmol). Solvent for chromatographic purification: cyclohexane/ethyl acetate (9:1), yield 77% (1.29 g, 3.70 mmol), green–yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, CH_3-*t*Bu), 3.25 (t, J = 4.9 Hz, 4 H, NCH_2), 3.82 (s, 3 H, OCH_3), 3.86 (t, J = 4.9 Hz, 4 H, OCH_2), 6.87 (d, J = 8.9 Hz, 2 H, Ar-H), 7.28 (s, 1 H, olefinic-H), 7.53 (d, J = 8.9 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3, 39.0, 48.1, 52.2, 66.7, 114.4, 123.2, 127.3, 131.7, 134.4, 151.9, 163.5 176.3 ppm. IR (film): $\tilde{\nu}$ = 1754 (C=O), 1722 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 348 (100), 695 (20). HRMS (ESI): calcd. for $C_{19}H_{26}NO_5$ [M + H]$^+$ 348.1805, found 348.1806.

(*Z*)-Methyl 3-(4-Dimethylaminophenyl)-2-(pivaloyloxy)acrylate (6b): Starting material: enol ester **3b** (1.07 g, 4.82 mmol). Solvent for chromatographic purification: cyclohexane/ethyl acetate (9:1), yield 87% (1.28 g, 4.18 mmol), yellow crystalline solid, m.p. 88–89 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.45 (s, 9 H, CH_3-*t*Bu), 3.03 (s, 6 H, NCH_3), 3.83 (s, 3 H, OCH_3), 6.68 (d, J = 9.1 Hz, 2 H, Ar-H), 7.29 (s, 1 H, olefinic-H), 7.52 (d, J = 9.1 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.4, 39.1, 40.2, 52.2, 111.7, 120.0, 128.1, 132.0, 133.7, 151.3, 163.9, 176.4 ppm. IR (KBr): $\tilde{\nu}$ = 1751 (C=O), 1713 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 306 (100), 328 (5), 611 (16), 633 (6). HRMS (ESI): calcd. for $C_{17}H_{24}NO_4$ [M + H]$^+$ 306.1700, found 306.1700.

(*Z*)-Methyl 3-(4-Ethoxyphenyl)-2-(pivaloyloxy)acrylate (6c): Starting material: enol ester **3c** (2.20 g, 7.85 mmol). Solvent for chromatographic purification: cyclohexane/ethyl acetate (20:1), yield 97% (2.38 g, 7.65 mmol), white crystalline solid, m.p. 55–56 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.41 (s, 9 H, CH_3-*t*Bu), 1.44 (t, J = 6.9 Hz, 3 H, CH_3-ethoxy), 3.84 (s, 3 H, OCH_3), 4.08 (q, J = 6.9 Hz, 2 H, OCH_2), 6.90 (d, J = 8.8 Hz, 2 H, Ar-H), 7.31 (s, 1 H, olefinic-H), 7.55 (d, J = 8.8 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (150 MHz, $CDCl_3$): δ = 14.7, 27.1, 39.0, 52.3, 63.5, 114.5, 124.6, 127.0, 131.8, 135.5, 160.1, 163.3, 176.1 ppm. IR (KBr): $\tilde{\nu}$ = 1755 (C=O), 1715 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 307 (100), 324 (31), 329 (6). HRMS (ESI): calcd. for $C_{17}H_{22}NaO_5$ [M + Na]$^+$ 329.1359, found 329.1359.

General Procedure for Asymmetric Rh-Catalyzed Hydrogenations: Acrylic esters **6** and Rh-DiPAMP (1 mol-%) were dissolved under a nitrogen atmosphere in dry methanol (60 mL) and hydrogenated at room temperature under a hydrogen pressure of 5 bar. After stirring for 4 d, the solvent was evaporated and the crude products were purified by column chromatography.

(*R*)-Methyl 3-(4-Morpholinophenyl)-2-(pivaloyloxy)propanoate (8a): Starting material: methyl acrylate **6a** (0.55 g, 1.59 mmol). Solvent for chromatographic purification: cyclohexane/ethyl acetate (9:1), yield 90% (0.50 g, 1.43 mmol, 99% *ee*), colorless oil. $[\alpha]_D^{25}$ = +3.4 (c = 0.35 in MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 9 H, CH_3-*t*Bu), 3.05 (dd, J = 8.3, 14.4 Hz, 1 H, $C_\beta H_2$), 3.13 (m, 1 H, $C_\beta H_2$), 3.15 (t, J = 4.6 Hz, 2 H, NCH_2), 3.73 (s, 3 H, OCH_3), 3.87 (t, J = 4.7 Hz, 2 H, OCH_2), 5.16 (m, 1 H, $C_\alpha H$), 6.87 (d, J = 8.4 Hz, 2 H, Ar-H), 7.15 (d, J = 8.7 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.1, 36.6, 38.6, 49.4, 52.1, 66.9, 72.8, 115.6, 127.5, 130.1, 150.2, 170.3, 177.8 ppm. IR (Film): $\tilde{\nu}$ =

1767 (C=O), 1735 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 350 (100), 372 (23). HRMS (ESI): calcd. for $C_{19}H_{28}NO_5$ $[M + H]^+$ 350.1962, found 350.1963.

(*R*)-Methyl 3-(4-Dimethylaminophenyl)-2-(pivaloyloxy)propanoate (8b): Starting material: methyl acrylate **6b** (0.18 g, 0.57 mmol). Solvent for chromatographic purification: cyclohexane/ethyl acetate (9:1), yield 79% (0.14 g, 0.45 mmol, 95% *ee*), colorless oil. $[\alpha]_D^{25}$ = +2.4 (*c* = 0.17 in MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.22 (s, 9 H, CH_3-*t*Bu), 2.94 (s, 6 H, NCH_3), 3.04 (dd, *J* = 8.6, 14.4 Hz, 1 H, $C_\beta H_2$), 3.12 (dd, *J* = 4.3, 14.3 Hz, 1 H, $C_\beta H_2$), 3.73 (s, 3 H, OCH_3), 5.14 (m, 1 H, $C_\alpha H$), 6.70 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.12 (d, *J* = 8.8 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.0, 38.5, 40.9, 36.4, 52.0, 73.1, 112.7, 123.9, 130.0, 149.6, 170.4, 177.8 ppm. IR (KBr): $\tilde{\nu}$ = 1765 (C=O), 1725 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 308 (100), 330 (14). HRMS (ESI): calcd. for $C_{17}H_{26}NO_4$ $[M + H]^+$ 308.1856, found 308.1856.

(*R*)-Methyl 3-(4-Ethoxyphenyl)-2-(pivaloyloxy)propanoate (8c): Starting material: methyl acrylate **6c** (1.50 g, 4.90 mmol). Solvent for chromatographic purification: cyclohexane/ethyl acetate (9:1), yield 96% (1.44 g, 4.68 mmol, 96% *ee*), colorless oil. $[\alpha]_D^{20}$ = +8.1 (*c* = 1.56 in MeOH). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 9 H, CH_3-*t*Bu), 1.42 (t, *J* = 7.0 Hz, 3 H, CH_3-ethoxy), 3.06, 3.14 (2 dd, *J* = 4.3, 9.1 Hz, 2 H, $C_\beta H_2$), 3.73 (s, 3 H, OCH_3), 4.03 (q, *J* = 7.0 Hz, 2 H, OCH_2), 5.16 (dd, *J* = 4.3, 9.1 Hz, 1 H, $C_\alpha H$), 6.83 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.14 (d, *J* = 8.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 26.9, 36.5, 38.6, 52.1, 63.4, 72.8, 114.3, 127.9, 130.3, 157.9, 170.2, 177.8 ppm. IR (film): $\tilde{\nu}$ = 1760 (C=O), 1737 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 207 (100), 309 (2), 326 (20), 331 (3). HRMS (ESI): calcd. for $C_{17}H_{24}NaO_5$ $[M + Na]^+$ 331.1517, found 331.1516.

General Procedure for Ester Cleavage to 2-Hydroxy Acids 9: 2-Hydroxy esters **8** were dissolved in THF (5 mL) at room temperature and solutions of LiOH (3 equiv.) in water (30 mL) were added. After stirring for 4 d at ambient temperature, the solutions were extracted twice with CH_2Cl_2. The aqueous phases were evaporated and the crude products were purified by column chromatography.

(*R*)-2-Hydroxy-3-(4-morpholinophenyl)propanoic Acid (9a): Starting material: ester **8a** (1.07 g, 3.06 mmol). Solvent for chromatographic purification: $CHCl_3$/MeOH (7:3), yield 84% (0.65 g, 2.57 mmol), bright red solid, m.p. 115–117 °C. $[\alpha]_D^{22}$ = +2.9 (*c* = 0.21 in MeOH). ^1H NMR (400 MHz, [D$_4$]methanol): δ = 2.81 (dd, *J* = 8.2, 14.0 Hz, 1 H, $C_\beta H_2$), 3.07 (dd, *J* = 3.2, 14.0 Hz, 1 H, $C_\beta H_2$), 3.10 (t, *J* = 4.8 Hz, 4 H, NCH_2), 3.84 (t, *J* = 4.8 Hz, 4 H, OCH_2), 4.19 (m, 1 H, $C_\alpha H$), 6.90 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.21 (d, *J* = 8.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 40.9, 51.2, 68.2, 73.0, 117.2, 130.6, 131.4, 151.5, 177.4 ppm. IR (KBr): $\tilde{\nu}$ = 3427 (O–H), 1586 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 250 (100). HRMS (ESI): calcd. for $C_{13}H_{18}NO_4$ $[M + H]^+$ 252.1230, found 252.1235.

(*R*)-3-(4-Dimethylaminophenyl)-2-hydroxypropanoic Acid (9b): Starting material: ester **8b** (0.77 g, 2.49 mmol). Solvent for chromatographic purification: ethyl acetate/MeOH (9:1) + 0.1% HOAc, yield 100% (0.52 g, 2.49 mmol), bright yellow foam. $[\alpha]_D^{25}$ = +11.9 (*c* = 0.32 in MeOH). ^1H NMR (400 MHz, [D$_4$]methanol): δ = 2.76 (dd, *J* = 8.0, 14.0 Hz, 1 H, $C_\beta H_2$), 2.88 (s, 6 H, NCH_3), 3.03 (dd, *J* = 3.5, 14.0 Hz, 1 H, $C_\beta H_2$), 4.14 (m, 1 H, $C_\alpha H$), 6.74 (d, *J* = 8.8 Hz, 2 H, Ar-H), 7.16 (d, *J* = 8.8 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 40.9, 41.6, 75.1, 114.7, 129.2, 131.3, 151.0, 181.3 ppm. IR (KBr): $\tilde{\nu}$ = 3431 (O–H), 1562 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 208 (100). HRMS (ESI): calcd. for $C_{11}H_{16}NO_3$ $[M + H]^+$ 210.1125, found 210.1129.

(*R*)-3-(4-Ethoxyphenyl)-2-hydroxypropanoic Acid (9c): Starting material: ester **8c** (1.26 g, 4.10 mmol). Solvent for chromatographic purification: ethyl acetate/MeOH (9:1 + 0.05% HOAc), yield 86% (0.74 g, 3.52 mmol), white solid, m.p. 156–160 °C. $[\alpha]_D^{25}$ = +28.3 (*c* = 0.23 in MeOH). ^1H NMR (400 MHz, [D$_4$]methanol): δ = 1.37 (t, *J* = 6.9 Hz, 3 H, CH_3-ethoxy), 2.84 (m, 1 H, $C_\beta H_2$), 3.07 (m, 1 H, $C_\beta H_2$), 4.00 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.27 (m, 1 H, $C_\alpha H$), 6.82 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.18 (d, *J* = 8.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 15.1, 40.8, 64.3, 73.5, 115.1, 131.0, 131.4, 135.9, 158.8, 178.5 ppm. IR (KBr): $\tilde{\nu}$ = 3466 (O–H), 3187 (O–H), 1739 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 209 (100). HRMS (ESI): calcd. for $C_{11}H_{13}O_4$ $[M - H]^-$ 209.0819, found 209.0813.

General Procedure for the Hydrolysis of Enol Esters 3 and Enantioselective Enzymatic Reduction: Enol esters **3** were suspended at 0 °C in an aqueous solution of LiOH (1.1 equiv.). After stirring for 5 h at room temperature, the reaction mixtures were extracted twice with CH_2Cl_2. The organic layers were combined and the solvents evaporated. The dried raw materials were used without further purification for the enzymatic reductions. Solutions of EDTA (0.025 mM), mercaptoethanol (0.05 mM), ammonium formate (40 mM), 2-oxo acids **4** (10 mM), and NAD (0.1 mM) were dissolved in water (50 mL) in an ultrafiltration cell (polyethersulfone membrane, cutoff = 10 kDa). The pH was adjusted to 7.0 by using 1 M HCl. Then the enzymes D-LDH (200 U, *Staphylococcus epidermis*, activity: 97 U/mg solid) and FDH (5 U, *Candida boidinii*, activity: 0.45 U /mg solid) were added. The solutions were stirred between 15 h and 24 h at room temperature. After that time the solutions were filtered through the membrane by using a low argon pressure (0.1–0.3 bar). The crude products were purified by column chromatography (ethyl acetate/MeOH, 7:3 + 0.1% AcOH) after evaporation of water.

3-(4-Morpholinophenyl)-2-oxopropanoic Acid (4a): Starting material: 2-oxo ester **3a** (1.73 g, 6.58 mmol), yield 75% (1.24 g, 4.95 mmol), yellow solid. ^1H NMR (400 MHz, [D$_4$]methanol): δ = 3.19 (t, *J* = 4.7 Hz, 1 H, NCH_2), 3.21, 3.40 (2 m, 1 H, NCH_2), 3.79 (t, *J* = 4.9 Hz, 1 H, OCH_2), 3.84, 3.87 (2 t, *J* = 4.8 Hz, 1 H, OCH_2), 6.75, 7.12, 7.79 (3 d, *J* = 9.1 Hz, 2 H, Ar-H), 7.02, 7.05, 7.08 (3 m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 46.2, 50.5, 51.0, 51.4, 67.6, 67.7, 68.0, 114.6, 115.2, 116.9, 130.9, 131.9, 133.7, 153.5, 165.0, 192.6 ppm. IR (KBr): $\tilde{\nu}$ = 3439 (O–H), 1602 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 248 (100). HRMS (ESI): calcd. for $C_{13}H_{16}NO_4$ $[M + H]^+$ 250.1074, found 250.1074.

(*R*)-2-Hydroxy-3-(4-morpholinophenyl)propanoic Acid (9a): Starting material: 2-oxo acid **4a** (248.3 mg, 1.0 mmol), yield 66% (166.4 mg, 0.66 mmol), orange solid, m.p. 115–117 °C. $[\alpha]_D^{22}$ = +2.9 (*c* = 0.21 in MeOH). ^1H NMR (400 MHz, [D$_4$]methanol): δ = 2.81 (dd, *J* = 8.2, 14.0 Hz, 1 H, $C_\beta H_2$), 3.07 (dd, *J* = 3.2, 14.0 Hz, 1 H, $C_\beta H_2$), 3.10 (t, *J* = 4.8 Hz, 4 H, NCH_2), 3.84 (t, *J* = 4.8 Hz, 4 H, OCH_2), 4.19 (m, 1 H, $C_\alpha H$), 6.90 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.21 (d, *J* = 8.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 40.9, 51.2, 68.2, 73.0, 117.2, 130.6, 131.4, 151.5, 177.4 ppm. IR (KBr): $\tilde{\nu}$ = 3427 (O–H), 1586 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 250 (100). HRMS (ESI): calcd. for $C_{13}H_{18}NO_4$ $[M + H]^+$ 252.1230, found 252.1230.

3-(4-Ethoxyphenyl)-2-oxopropanoic Acid (4c): Starting material: 2-oxo ester **3c** (0.97 g, 4.34 mmol), yield 86% (0.78 g, 3.75 mmol), white solid. ^1H NMR (400 MHz, [D$_4$]methanol): δ = 1.38 (m, 3 H, CH_3-ethoxy), 3.40, 3.49 (2 m, 2 H, CH_2), 3.99, 4.13 (2 m, 2 H, OCH_2), 6.67–7.86 (m, 4 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]-methanol): δ = 12.7, 37.9, 42.6, 62.9, 112.5, 112.8, 113.0, 113.3, 113.9, 126.3, 126.9, 129.1, 129.9 ppm. IR (KBr): $\tilde{\nu}$ = 3426 (O–H),

1607 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 207 (100). HRMS (ESI): calcd. for $C_{11}H_{11}O_4$ $[M - H]^-$ 207.0663, found 207.0665.

(*R*)-3-(4-Ethoxyphenyl)-2-hydroxypropanoic Acid (9c): 2-Oxo acid **4c** (424.7 mg, 2.04 mmol) was reduced by using the procedure described above, yield 37% (159 mg, 0.75 mmol), white solid, m.p. 156–160 °C. $[\alpha]_D^{25}$ = +28.3 (*c* = 0.23 in MeOH). ^1H NMR (400 MHz, [D$_4$]methanol): δ = 1.37 (t, *J* = 6.9 Hz, 3 H, CH_3-ethoxy), 2.84 (m, 1 H, $C_\beta H_2$), 3.07 (m, 1 H, $C_\beta H_2$), 4.00 (q, *J* = 7.0 Hz, 2 H, OCH_2), 4.27 (m, 1 H, $C_\alpha H$), 6.82 (d, *J* = 8.6 Hz, 2 H, Ar-H), 7.18 (d, *J* = 8.6 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 15.1, 40.8, 64.3, 73.5, 115.1, 131.0, 131.4, 135.9, 158.8, 178.5 ppm. IR (KBr): $\tilde{\nu}$ = 3466 (O–H), 3187 (O–H), 1739 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 209 (100). HRMS (ESI): calcd. for $C_{11}H_{13}O_4$ $[M - H]^-$ 209.0819, found 209.0813.

2-Oxo-3-(pyridin-4-yl)propanoic Acid (4g): Starting material: 2-oxo ester **3g** (0.32 g, 1.77 mmol), yield 91% (0.28 g, 1.61 mmol), yellow foam. ^1H NMR (400 MHz, [D$_4$]methanol): δ = 4.70 (s, 2 H, CH_2), 7.44 (d, *J* = 6.1 Hz, 2 H, Ar-H), 8.49 (d, *J* = 6.1 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 63.3, 122.8, 127.6, 146.0, 149.9, 160.5, 173.0 ppm. IR (KBr): $\tilde{\nu}$ = 3431 (O–H), 1735 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 164 (100). HRMS (ESI): calcd. for $C_8H_6NO_3$ $[M - H]^-$ 164.0353, found 164.0354.

(*R*)-2-Hydroxy-3-(pyridin-4-yl)propanoic Acid (9g): Starting material: 2-oxo acid **4g** (116.3 mg, 0.71 mmol), yield 95% (112 mg, 0.67 mmol), red foam. $[\alpha]_D^{25}$ = +1.7 (*c* = 0.94 in MeOH). ^1H NMR (400 MHz, [D$_4$]methanol): δ = 2.94 (dd, *J* = 8.0, 13.9 Hz, 1 H, $C_\beta H_2$), 3.17 (dd, *J* = 3.7, 13.9 Hz, 1 H, $C_\beta H_2$), 4.24 (m, 1 H, $C_\alpha H$), 7.40 (d, *J* = 6.1 Hz, 2 H, Ar-H), 8.41 (d, *J* = 6.1 Hz, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, [D$_4$]methanol): δ = 41.5, 72.1, 126.9, 149.5, 151.1, 179.9 ppm. IR (KBr): $\tilde{\nu}$ = 3427 (O–H), 1736 (C=O) cm^{-1}. MS (ESI): *m/z* (%) = 166 (100). HRMS (ESI): calcd. for $C_8H_{10}NO_3$ $[M + H]^+$ 168.0655, found 168.0659.

Supporting Information (see footnote on the first page of this article): Characterization data and NMR spectra of all compounds.

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