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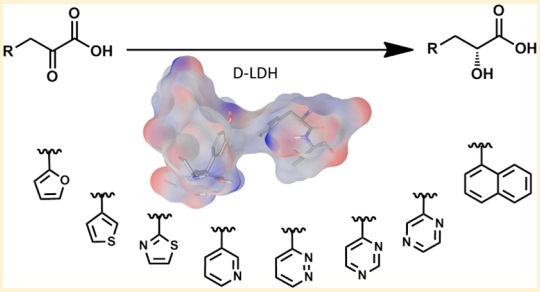
Enantiomerically Pure 3-Aryl- and 3-Hetaryl-2-hydroxypropanoic Acids by Chemoenzymatic Reduction of 2-Oxo Acids

Sivatharushan Sivanathan, Florian Körber, Jannis Aron Tent, Svenja Werner, and Jürgen Scherkenbeck*

Faculty of Mathematics and Natural Sciences, Bergische Universität Wuppertal, Gaußstraße 20, D-42119 Wuppertal, Germany

Supporting Information

ABSTRACT: Phenyllactic acids are found in numerous natural products as well as in active substances used in medicine or plant protection. Enantiomerically pure phenyllactic acids are available by transition-metal-catalyzed hydrogenations or chemoenzymatic reductions of the corresponding 3-aryl-2-oxopropanoic acids. We show here that D-lactate dehydrogenase from *Staphylococcus epidermidis* reduces a broad spectrum of 2-oxo acids, which are difficult substrates for transition-metal-catalyzed reactions, with excellent enantioselectivities in a simple experimental setup.



INTRODUCTION

α-Hydroxy acids are found frequently in natural products.[1] In depsipeptides, α-hydroxy acids constitute essential building blocks, which usually function as mimetics for the corresponding proteinogenic amino acids. As a consequence, a wide range of biological activities has been found for depsipeptides and in particular cyclodepsipeptides.[2−5]

Despite the existence of different literature-known routes to aliphatic and aromatic α-hydroxy acids, no general methods are available that allow the synthesis of enantiomerically pure D-hetaryllactic acids. In particular, the standard-procedure, diazotization of the corresponding α-amino acids in acetic acid, turns out to be cumbersome for many α-hydroxy acids since the α-amino acids have to be synthesized first by Pd-catalyzed couplings of appropriately protected serine derivatives.[6,7] Alternative methods such as asymmetric dihydroxylation of cinnamic acids with subsequent hydrogenolysis or oxynitrilase-catalyzed transcyanations followed by hydrolysis of the cyano group show other shortcomings.[8,9]

The broadest substrate variability is provided by transition-metal-catalyzed, enantioselective hydrogenations of α-oxo acids, which are available from substituted benzaldehydes by various short routes. Commercially available standard catalysts for hydrogenations of α-(acyloxy)acrylates at low (<10 bar) or intermediate (<50 bar) hydrogen pressures include Rh-DiPAMP, Rh-DuPhos, and Ru-BINAP.[10−12] In particular, Rh-DuPhos was found to produce excellent enantiomeric excesses for aryllactic acids. However, pyridine residues act as catalyst poisons and thus are unsuited as substrates for Rh-DuPhos.[13]

During the course of our studies on the anthelmintic cyclooctadepsipeptide PF1022A, we found that enzymatic reductions of 2-oxo acids with a coupled two-enzyme system, consisting of *Staphylococcus epidermidis* lactate dehydrogenase (LDH) and *Candida boidinii* formate dehydrogenase (FDH) for in situ cofactor (NADH) regeneration, represent a straightforward alternative to transition-metal-catalyzed hydrogenations for the synthesis of D-aryllactic acids.[13] The fact that a 3-pyridyl-2-oxo acid, which failed completely in a Rh-DIPAMP-catalyzed hydrogenation, gave an excellent yield and enantioselectivity in the enzymatic reduction, prompted us to further study the scope of D-LDH-catalyzed reductions for the preparation of 3-aryl- and in particular 3-hetaryl-2-hydroxypropanoic acids.

RESULTS AND DISCUSSION

Preparation of 2-Oxo Acids. 3-Aryl- and 3-hetaryl-2-oxo acids can be prepared by various short sequences, usually based on condensation reactions of aromatic aldehydes with different types of CH-acidic compounds. According to a procedure by Horner and Renth,[14] condensation with *N*,*N*-dimethylglycine methyl ester followed by acidic hydrolysis works for most aromatic aldehydes (**1a−h**; Scheme 1a). Except for pyrrole **3c**, α-(dimethylamino)acrylic esters **3** were obtained in good yields as *E*/*Z* mixtures. Subsequent hydrolysis of the enamine moiety with 1 M HCl afforded 2-oxocarboxylic esters **4a−h** (Table 1) in yields between 60 and 85%. NMR studies revealed that 2-oxo esters **4a−h** exist predominantly in the enol form. However, significant equilibrium amounts of the oxo forms were found for compounds **4f** and **4g**.

Electron-poor pyridine-, pyrazine-, pyridazine-, and pyrimidine-2-oxo esters **4i−l** are available in a short sequence by alkylation of methyl 2,2,2-trimethoxyacetate (**6**) with heteroaromatics **5i−l** according to Scheme 1b (Table 2).[15]

Hydrolysis of esters **4a−l** with LiOH under carefully controlled conditions afforded the lithium 2-oxocarboxylates

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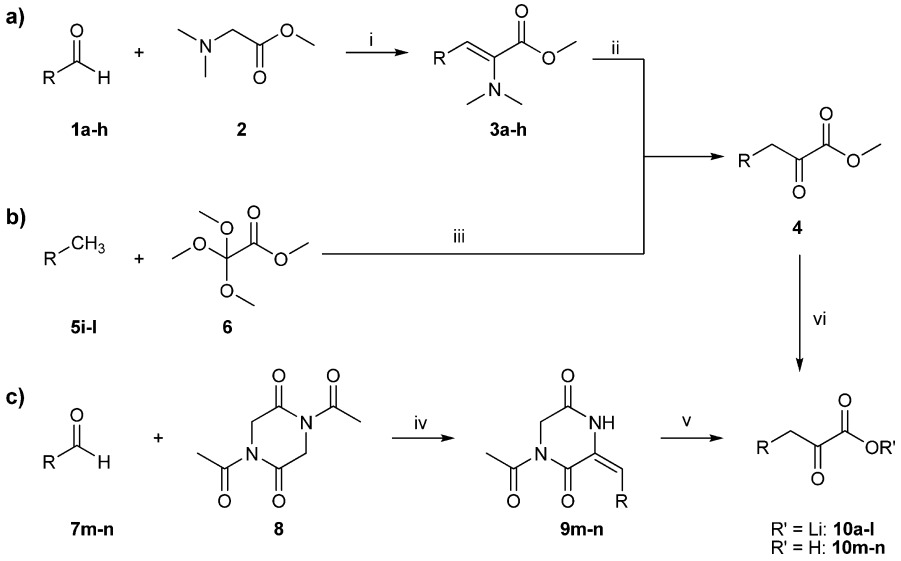
Scheme 1. Preparation of 2-Oxo Acids 10[a]



[a]Reagents and conditions: (i) NaH, MeOH, diethyl ether, 0 °C to rt, 18 h; (ii) 1 M HCl(aq), rt; (iii) LDA, THF, −78 °C to rt, 18 h, then 1 M HCl(aq), 1 h, rt; (iv) NaOtBu, *tert*-butyl alcohol, DCM, 3 h, rt; (v) 6 M HCl(aq), 6 h, reflux; (vi) LiOH, H_2O/THF, 0 °C, 4 h.

Table 1. Yields of Enamines 3 and 2-Oxo Esters 4 by Method (a)

	Residue	3 [%]	4 [%]		Residue	3 [%]	4 [%]
a		85[a]	69[a]	e		53	85
b		80	79	f		43	60
c		8	71	g		68	69
d		97	84	h		65[a]	78[a]

[a]For experimental details, see ref 13.

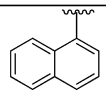
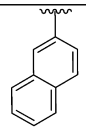
Table 2. Yields of 2-Oxo Esters 4i–l by Method (b)

	Residue	4 [%]		Residue	4 [%]
i		87	k		50
j		92	l		19

10a–l. However, the basic ester cleavages of compounds **4a** and **4c** failed completely because of extensive decomposition of the 2-oxocarboxylates **10a** and **10c**. Unfortunately, enzymatic ester cleavages with *Candida rugosa* lipase as a mild alternative also afforded disappointing yields caused by insufficient solubility and partial decomposition of the 2-oxo esters in water as well as substrate incompatibilities with the enzyme.[16]

A well-suited complementary method, particularly for naphthyl aldehydes, is based on a condensation with 1,4-diacetylpiperazine-2,5-dione (**8**) and subsequent hydrolysis under strongly acidic conditions (Scheme 1c). Following this route, the 2-oxocarboxylic acids **10m** and **10n** were obtained in good to excellent yields (Table 3).[17]

Table 3. Yields of Dioxopiperazines 9m and 9n and 2-Oxo Acids 10m and 10n by Method (c)

	Residue	9 [%]	10 [%]
m		98	97
n		46	91

It should be noted that because of their limited stability in particular under basic conditions, all of the 2-oxo acids were used without further purification for the subsequent enzymatic reductions, as either the free acid or the lithium carboxylate.

Enzymatic Reduction. NAD-dependent L-lactate dehydrogenases have been widely used for the chemoenzymatic syntheses of L-2-hydroxy acids since the pioneering work of Whitesides and others.[18,19] Already in these early studies it was shown that L-lactate dehydrogenases from different sources show a broad and similar substrate acceptance toward aliphatic 2-oxo acids.[18,20,21] Additionally, L-LDH from *Bacillus*

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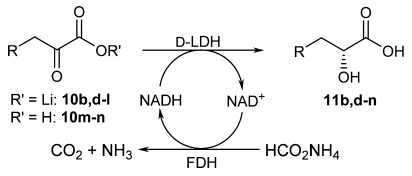
stearothermophilus was genetically engineered to improve the substrate tolerance for bulky aliphatic 2-oxo acids and to invert the stereospecificity of the reduction.[22,23]

The corresponding D-lactate dehydrogenases, however, constitute a heterogeneous class of oxidoreductases and have not been studied as well. The D-lactate dehydrogenases from *Leuconostoc mesenteroides* and *S. epidermidis* were found to tolerate only a narrow spectrum of substrates, including especially aromatic oxo acids.[24,25] This special feature was used to develop a multikilogram synthesis of (*R*)-3-(4-fluorophenyl)-2-hydroxypropanoic acid, an important building block of the rhinovirus protease inhibitor rupintrivir.[26] Because of the high price of NADH, enzymatic reductions with LDH require in situ cofactor regeneration. A coupled two-enzyme redox system consisting of LDH and formate dehydrogenase (FDH) allows the reduction of NAD to NADH in the presence of formate and thus renders the overall process catalytic in NADH (Scheme 2). Best-suited for

Scheme 2. Coupled Two-Enzyme System for Enantioselective Reductions of 2-Oxo Acids



cofactor regeneration with respect to reactivity and price appears to be the FDH from *C. boidinii*. Usually, LDH reductions of 2-oxo acids are performed as either a continuous-flow or a batch process in a membrane reactor.[27] However, we found it more convenient to perform small-scale reactions in simple flasks without repeated use of the enzyme system.

In a typical run, D-LDH and FDH were added at pH 6.2−7.0 to an aqueous solution (50 mL) consisting of one of the Li carboxylates **10b,d−l** or acids **10m,n** (10 mM, unpurified), EDTA (0.025 mM), mercaptoethanol (0.05 mM), ammonium formate (40 mM), and NADH (0.1 mM). The reaction mixture was stirred for 16−24 h at room temperature. After evaporation of water, the corresponding free 2-hydroxy acid **11b,d−n** was obtained by chromatographic purification under acidic conditions. Enantiomeric excesses were determined by chiral HPLC analysis of the corresponding methyl esters prepared from 2-hydroxy acids **11b,d−n** with thionyl chloride in MeOH. Racemic reference compounds were obtained by $NaBH_4$ reduction of 2-oxo esters **4**.

S. epidermidis D-LDH tolerates an amazingly broad diversity of aromatic and heteroaromatic oxo acids (Table 4). All of the substrates were reduced with perfect enantioselectivity, even in the case of furanyloxopropanoic acids, which have been described previously as difficult substrates for L-LDHs from rabbit muscle, bovine heart, chicken liver, and lobster tail.[18] Somewhat reduced enantiomeric excesses in *S. epidermidis* D-LDH-catalyzed reductions have been found only for phenyllactic acids with extended 4-aryloxy and 4-alkoxyalkyl substituents. The moderate yields for some of the hetaryllactic acids **11** can be attributed to partial decomposition of 2-oxo acids **10** during basic ester cleavage. In all examples, 2-oxo acid **10** was consumed completely by the enzyme.

Table 4. Yields and Enantiomeric Excesses of D-LDH-Catalyzed Reductions

compd	yield [%]	*ee* [%][a]	compd	yield [%]	*ee* [%][a]
11b	27[b]	>99	**11i**	99[b]	>99
11d	38[b]	>99	**11j**	70[b]	>99
11e	23[b]	>99	**11k**	29[b]	>99
11f	66[b]	>99	**11l**	57[b]	>99
11g	38[b]	>99	**11m**	75[c]	>99
11h	86[b]	>99	**11n**	75[d]	>99

[a]Enantiomeric excesses were determined by chiral HPLC of the methyl esters prepared from compounds **11b,d−n** and the corresponding racemates as references. [b]Yields were determined over two steps: ester hydrolysis and enzymatic reduction. The yields correspond to the free carboxylic acids, which were obtained from their lithium salts during chromatographic purification by addition of 0.1% HOAc to the solvent. [c]Starting material: **10m**. [d]Starting material: **10n**.

LDHs catalyze the reversible reduction of pyruvate to lactic acid with concomitant oxidation of NADH to NAD^+. While L-LDHs have a wide occurrence in nature, D-LDHs are found only in invertebrates, lower fungi, and prokaryotic organisms.[28] Although D- and L-LDHs catalyze the same reaction and differ only in the stereochemistry of the enantioselective reduction, they belong to different protein classes. Of the two enzymes, L-LDH is by far better understood with respect to the mode of substrate binding and mechanism of catalysis. Only a limited number of NAD-dependent D-lactate dehydrogenase crystal structures have been reported, among those the D-LDHs from *Lactobacillus bulgaricus*, *Lactobacillus helveticus*, *Lactobacillus pentosus*, and the thermophilic bacterium *Aquifex aeolicus*.[29]

The functionally active units of D-lactate dehydrogenases comprise homodimers that show very similar folds consisting of two $\beta\alpha\beta$ domains for each subunit. One domain binds the NADH cofactor and the other the pyruvate substrate, with the active site located at the interdomain cleft. Remarkably, despite decades of research on LDHs, the recently published crystal structure of *A. aeolicus* D-LDH is the first one showing the ternary complex of the enzyme with NADH and D-lactic acid in the catalytically active closed conformation.[29] This structural information provides the basis for a qualitative model that helps in understanding the broad substrate tolerance of *S. epidermidis* D-LDH.

According to the widely accepted binding model, NADH and subsequent pyruvate binding induce a conformational shift from the open to the closed conformation of D-LDHs, forming the active site, which is excluded from water by an arrangement of lipophilic amino acids. The 2-oxo acid is buried deep inside the enzyme in a channel located at the interdomain cleft (Figure 2a). The closed conformation is stabilized by the substrate itself, which is tightly fixed in the binding pocket by a hydrogen-bonding network formed by residues from both the cofactor and the substrate binding domains. In detail, His294 and Arg231 form H-bonds with the OH group of lactic acid and Arg231, Gly74, Val73, and Tyr96 with the carboxylate (Figure 1). The nicotinamide residue of NADH is located proximate to the 2-oxo function in a way that the hydride ion is transferred to the *si*-face of the prochiral 2-oxo acid.[28,30]

The methyl group of lactic acid is directed into a highly lipophilic channel lined with the residues Phe49, Tyr51, Ile227, Leu254, Ile295, Tyr297, and Tyr298. In the closed

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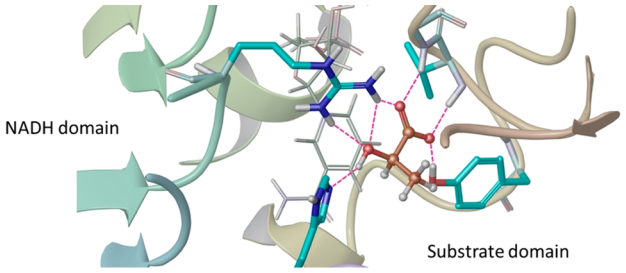

Figure 1. Model for the fixation of lactic acid in the active site of *S. epidermidis* D-LDH.

conformation, this pocket extends throughout the catalytic domain. On reopening of D-LDH after hydride transfer to pyruvate, the residues forming the interdomain cleft are separated from each other and the product is released.

The aromatic rings of Phe49 and Tyr297 are oriented perpendicular to the substrate and have been proposed in related D-lactate dehydrogenases to play a major role in ligand discrimination by hindering the binding of long and/or bulky 2-oxo acids.[30] However, on the basis of our results that clearly demonstrate a broad substrate acceptance even for sterically hindered substituents, Phe49 and Tyr297 cannot be decisive for substrate selection. Rather, an inherent flexibility of the lipophilic channel might provide an explanation for the remarkable tolerance toward aryl- and hetaryl-2-oxo acids as substrates.

Energy minimizations (using the Schrödinger molecular modeling suite) of phenyllactic acid, furyllactic acid **11b**, naphthyllactic acid **11m**, and *p*-(benzyloxy)phenyllactic acid in the pyruvate binding site with fixed positions of the carboxylate and freely moving protein residues 5 Å around the substrate revealed significant flexibility of the aromatic residues in the channel: in particular, Tyr297, Tyr298, Phe49, and Tyr51 shift while Tyr96 is largely unaffected (Figure 2d). As a consequence of those adaptations, the pore at the back side of the interdomain cleft is widened, allowing the bulky naphthyl residue to be accommodated and the long benzyloxy substituent to be placed at the outer rim of the enzyme's pocket (Figure 2b,c).

SUMMARY AND CONCLUSION

We have shown that the D-lactate dehydrogenase of *S. epidermidis* accepts a broad spectrum of 3-(het)aryl-2-oxopropanoic acids, in particular those that have been shown to be critical in transition-metal-catalyzed hydrogenations. The reductions to the corresponding (het)aryllactic acids are highly enantioselective and can be performed in a simple experimental setup. A qualitative model is presented that helps in understanding the broad substrate tolerance of *S. epidermidis* D-LDH. For heteroaromatic substrates, the enzymatic procedure appears to be superior to transition-metal-catalyzed hydrogenations.

EXPERIMENTAL SECTION

General. The starting materials 3-furaldehyde, 2-thenaldehyde, 3-thenaldehyde, pyridine-3-carboxaldehyde, 2-thiazolecarboxaldehyde, *N*-methyl-2-pyrrolecarboxaldehyde, 1-naphthaldehyde, 2-naphthaldehyde, 2-picoline, 2-methylpyrazine, 3-methylpyrazine, methyl 2,2,2-trimethoxyacetate, and glycine anhydride were either purchased or prepared by standard literature procedures. D-LDH and FDH were purchased from Sigma-Aldrich. NADH was purchased as its disodium salt trihydrate from Molekula. All reactions except the saponifications, hydrolysis reactions, and enzymatic reductions were performed in dried solvents. Dichloromethane and triethylamine were refluxed for 1 h over calcium hydride and distilled. Diethyl ether was refluxed for several hours over $LiAlH_4$ and then distilled. Methanol was refluxed over magnesium and distilled. ^1H (^{13}C) NMR spectra were measured on a 400 or 600 MHz (100 or 151 MHz) NMR spectrometer. IR spectra were recorded on an FT-IR instrument. Mass spectra were recorded using ESI or APCI mode. For the preparative low-pressure liquid chromatography (LPLC), silica gel (60 μm) was used. TLC was perfomed on silica gel 60 F_{254}. Enantiomeric excesses were determined by chiral HPLC of the methyl esters prepared from compounds **11b**,**d**−**n** and the corresponding racemates as references. Chiral HPLC columns used for the determination of enantiomeric excesses were Chiralpak IA, Chiralcel OD-H, and Chiralcel OJ-H.

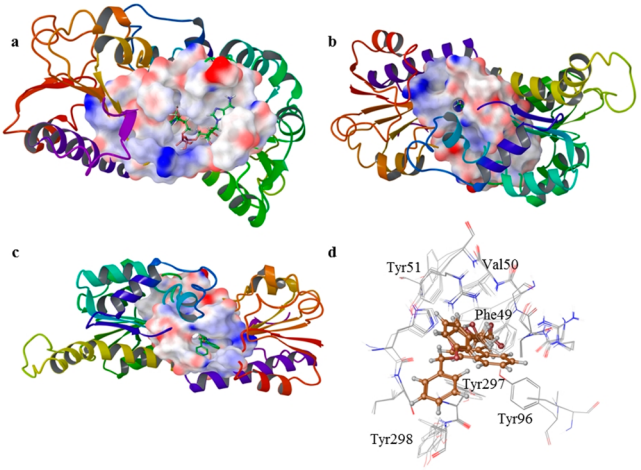

Figure 2. Suggested substrate binding model for *S. epidermidis* D-lactate dehydrogenase: (a) front side of the lipophilic channel with the cofactor binding site; (b) rear side of the lipophilic channel with a small pore; (c) bulky substituents widen the pore and are placed at the exterior of the enzyme; (d) superposition of aryllactic acids and amino acid residues surrounding the binding site. In (a−c) is shown a molecular surface generated around (4 Å) the interdomain cleft with the electrostatic potential projected onto the surface.

General Procedure for the Synthesis of Enamines 3a−h. To a suspension of sodium hydride (2.0 equiv) in dry Et_2O, aldehyde **1a−h** (1.0 equiv) and methanol (0.2 equiv) were added. At 0 °C, *N*,*N*-dimethylglycine methyl ester (3.0 equiv) was added dropwise to the vigorously stirred mixture. The reaction mixture was warmed to room temperature and stirred for 16 h, and then ice water and CH_2Cl_2 were added at 0 °C. The aqueous layers were extracted with CH_2Cl_2 three times. The combined organic phases were dried with Na_2SO_4. After removal of the solvent, the crude product was purified by either kugelrohr distillation in vacuo or column chromatography to obtain the corresponding enamine **3**.

*(E/Z)-Methyl 2-(Dimethylamino)-3-(furan-3-yl)acrylate (**3b**).* Starting material: 3-furaldehyde (**1b**) (4.0 g, 41.6 mmol). Yield of enamine **3b** after distillation at 220 °C, 2 × 10^{-1} mbar: 80% (6.5 g, 33.2 mmol), yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.63 (2s, 6H), 3.75 (2s, 3H), 6.74 (s, 1H), 6.92 (s, 1H), 7.37 (m, 1H), 7.81 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 42.1, 50.9, 110.8, 120.5, 122.7, 139.3, 142.7, 144.4, 166.1 ppm. IR (neat): 1708 (C=O) cm^{-1}. MS (ESI): *m*/*z* (%) = 196 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_{10}H_{14}NO_3$ $[M + H]^+$ 196.0968; found 196.0966.

*(E/Z)-Methyl 2-(Dimethylamino)-3-(1-methyl-1H-pyrrol-2-yl)-acrylate (**3c**).* Starting material: 1-methyl-2-pyrrolecarboxaldehyde (**1c**) (500.0 mg, 4.6 mmol). Yield of enamine **3c** after chromatographic purification (cylohexane/ethyl acetate, 9:1): 8% (80.0 mg, 0.4 mmol), brown solid. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.69 (s, 6H), 3.69 (s, 3H), 3.82 (s, 3H), 6.24 (m, 1H), 6.73 (m, 1H), 7.00 (m, 1H), 7.03 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 34.0,

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42.0, 51.3, 108.9, 114.6, 118.3, 124.9, 128.2, 135.4, 167.2 ppm. IR (neat): 1734 (C═O) cm^{-1}. MS (ESI): m/z (%) = 209 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_{11}H_{17}N_2O_2$ $[M + H]^+$ 209.1285; found 209.1285.

*(E/Z)-Methyl 2-(Dimethylamino)-3-(thiophen-2-yl)acrylate (**3d**).* Starting material: 2-thenaldehyde (**1d**) (1.0 g, 8.7 mmol). Yield of enamine **3d** after distillation at 220 °C, 2×10^{-1} mbar: 97% (1.8 g, 8.5 mmol), yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.66 (s, 6H), 3.81 (s, 3H), 7.05 (dd, ^3J = 5.2 Hz, ^4J = 1.6 Hz, 1H), 7.27 (d, ^3J = 3.6 Hz, 1H), 7.45 (d, ^3J = 5.2 Hz, 1H), 7.55 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 41.9, 51.2, 125.9, 129.2, 131.2, 131.3, 136.7, 137.4, 165.9 ppm. IR (neat): 1703 (C═O) cm^{-1}. MS (ESI): m/z (%) = 212 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_{10}H_{14}NO_2S$ $[M + H]^+$ 212.0740; found 212.0739.

*(E/Z)-Methyl 2-(Dimethylamino)-3-(thiophen-3-yl)acrylate (**3e**).* Starting material: 3-thenaldehyde (**1e**) (300.0 mg, 2.6 mmol). Yield of enamine **3e** after distillation at 220 °C, 2×10^{-1} mbar: 53% (289.3 mg, 1.4 mmol), yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.68 (s, 6H), 3.82 (s, 3H), 7.06 (s, 1H), 7.30 (m, 1H), 7.51 (m, 1H), 7.74 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 42.3, 51.4, 124.4, 124.8, 175.5, 129.1, 136.3, 139.0, 166.7 ppm. IR (neat): 1728 (C═O) cm^{-1}. MS (ESI): m/z (%) = 212 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_{10}H_{14}NO_2S$ $[M + H]^+$ 212.0740; found 212.0740.

*(E/Z)-Methyl 2-(Dimethylamino)-3-(thiazol-2-yl)acrylate (**3f**).* Starting material: 2-thiazolecarboxaldehyde (**1f**) (300.0 mg, 2.7 mmol). Yield of enamine **3f** after distillation at 140 °C, 5×10^{-2} mbar: 43% (240.6 mg, 1.1 mmol), yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 2.69 (s, 6H), 3.83 (s, 3H), 7.42 (d, ^3J = 3.2 Hz, 1H), 7.58 (s, 1H), 7.90 (d, ^3J = 3.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 41.8, 51.7, 122.8, 127.8, 142.5, 161.7, 165.1 ppm. IR (neat): 1734 (C═O) cm^{-1}. MS (ESI): m/z (%) = 213 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_9H_{13}N_2O_2S_1$ $[M + H]^+$ 213.0692; found 213.0694.

*(E/Z) Methyl-2-(dimethylamino)-3-(pyridin-3-yl)acrylate (**3g**).* Starting material: pyridine-3-carboxaldehyde (**1g**) (3.3 g, 30.0 mmol). Yield of enamine **3g** without purification: 68% (4.8 g, 20.4 mmol), yellow oil. ^1H NMR (600 MHz, $CDCl_3$): δ = 2.63 (s, 6H), 3.80 (s, 3H), 6.66 (s, 1H), 7.24 (m, 1H), 7.90 (m, 1H), 8.41 (m, 1H), 8.66 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 42.6, 51.8, 120.7, 123.1, 131.2, 136.0, 142.1, 148.4, 150.9, 166.4 ppm. IR (neat): 1714 (C═O) cm^{-1}. MS (ESI): m/z (%) = 207 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_{11}H_{15}N_2O_2$ $[M + H]^+$ 207.1128; found 207.1125.

General Procedure for the Hydrolysis of Enamines 3a–h. A suspension of enamine **3** in aqueous HCl (ca. 100 mL, 1 M) was stirred for 1 h at room temperature. The aqueous phase was then washed with Et_2O three times. The combined organic phases were dried over Na_2SO_4, and the solvent was removed in vacuo. Where possible, the crude product was purified by recrystallization to obtain the corresponding 2-oxo ester **4**.

*Methyl 3-(Furan-3-yl)-2-hydroxyacrylate (**4b**).* Starting material: (*E*/*Z*)-methyl 2-(dimethylamino)-3-(furan-3-yl)acrylate (**3b**) (6.3 g, 32.1 mmol). The crude product **4b** was recrystallized from diethyl ether. Yield: 79% (4.3 g, 25.4 mmol), orange solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3H), 6.21 (s-br, 1H), 6.45 (s, 1H), 6.72 (d, ^4J = 1.9 Hz, 1H), 7.44 (m, 1H), 7.86 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.9, 102.6, 110.6, 119.2, 138.6, 142.9, 143.6, 166.1 ppm. IR (neat): 3412 (O–H), 1689 (C═O) cm^{-1}. MS (ESI): m/z (%) = 167 (100) $[M - H]^-$. HRMS (ESI): calcd for $C_8H_7O_4$ $[M - H]^-$ 167.0350; found 167.0335.

*Methyl 2-Hydroxy-3-(1-methyl-1H-pyrrol-2-yl)acrylate (**4c**).* Starting material: (*E*/*Z*)-methyl 2-(dimethylamino)-3-(1-methyl-1*H*-pyrrol-2-yl)acrylate (**3c**) (66.0 mg, 0.3 mmol). Yield of 2-oxo ester **4c**: 71% (41.0 mg, 0.2 mmol), yellow solid. ^1H NMR (600 MHz, $CDCl_3$): δ = 3.70 (s, 3H), 3.92 (s, 3H), 6.23 (s-br, 1H), 6.27 (m, 1H), 6.56 (s, 1H), 6.72 (m, 1H), 6.98 (s, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 33.9, 52.8, 100.6, 109.1, 114.4, 124.6, 127.2, 135.8, 166.4 ppm. IR (neat): 3397 (O–H), 1651 (C═O) cm^{-1}. MS (ESI): m/z (%) = 182 (100) $[M + H]^+$. HRMS (APCI): calcd for $C_9H_{12}NO_3$ $[M + H]^+$ 182.0812; found 182.0812.

*Methyl 2-Hydroxy-3-(thiophen-2-yl)acrylate (**4d**).* Starting material: (*E*/*Z*)-methyl 2-(dimethylamino)-3-(thiophen-2-yl) acrylate (**3d**) (512.4 mg, 2.4 mmol). The crude product **4d** was recrystallized from diethyl ether. Yield: 84% (374.0 mg, 203.0 mmol), yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3H), 6.48 (s-br, 1H), 6.87 (s, 1H), 7.09 (dd, ^3J = 5.2 Hz, ^4J = 1.5 Hz, 1H), 7.32 (m, 1H), 7.44 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.9, 106.01, 127.0, 128.2, 128.9, 136.7, 137.1, 166.0 ppm. IR (neat): 3403 (O–H), 1656 (C═O) cm^{-1}. MS (ESI): m/z (%) = 185 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_8H_8NaO_3S$ $[M + Na]^+$ 207.0086; found 207.0082.

*Methyl 2-Hydroxy-3-(thiophen-3-yl)acrylate (**4e**).* Starting material: (*E*/*Z*)-methyl 2-(dimethylamino)-3-(thiophen-3-yl)acrylate (**3e**) (1.0 g, 4.8 mmol). Yield of 2-oxo ester **4e**: 85% (757.9 mg, 4.1 mmol), brown solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.92 (s, 3H), 6.35 (s-br, 1H), 6.64 (s, 1H), 7.32 (m, 1H), 7.44 (dd, ^3J = 5.1 Hz, ^4J = 1.2 Hz, 1H), 7.75 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.9, 105.7, 125.1, 126.3, 128.9, 135.0, 138.2, 166.0 ppm. IR (neat): 3450 (O–H), 1742 (C═O) cm^{-1}. MS (ESI): m/z (%) = 185 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_8H_8NaO_3S$ $[M + Na]^+$ 207.0086; found 207.0082.

*Methyl 2-Hydroxy-3-(thiazol-2-yl)acrylate (**4f**).* Starting material: (*E*/*Z*)-methyl 2-(dimethylamino)-3-(thiazol-2-yl)acrylate (**3f**) (228.0 mg, 1.1 mmol). Yield of 2-oxo ester **4f**: 60% (119.0 mg, 0.6 mmol), yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.93 (s, 3H), 6.83 (s, 1H), 7.31 (d, ^3J = 3.2 Hz, 1H), 7.84 (d, ^3J = 3.2 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.8, 100.3, 117.9, 141.4, 149.3, 163.7, 165.6 ppm. IR (KBr): 2949 (O–H), 1725 (C═O) cm^{-1}. MS (ESI): m/z (%) = 186 (100) $[M + H]^+$, 108 (19) $[M + Na]^+$. HRMS (ESI): calcd for $C_7H_6NO_3S$ $[M - H]^-$ 184.0074; found 184.0073.

*Methyl 2-Oxo-3-(pyridin-3-yl)propanoate and Methyl 2-Hydroxy-3-(pyridin-3-yl)acrylate (**4g**).* Starting material: (*E*/*Z*)-methyl 2-(dimethylamino)-3-(pyridin-3-yl)acrylate (**3g**) (4.8 g, 20.6 mmol). The crude product **4g** was recrystallized from acetone. Yield: 69% (2.55 g, 14.2 mol), yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.90, 3.96 (2s, 6H), 4.18 (s, 2H), 6.51 (s, 1H), 7.33, 7.60, 8.26, 8.51, 8.58, 8.84 (6m, 8H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 42.8, 53.3, 53.4, 107.3, 123.6, 136.7, 137.4, 141.1, 148.3, 148.9, 150.5, 150.6, 166.0, 190.1 ppm. IR (neat): 1720 (C═O) cm^{-1}. MS (ESI): m/z (%) = 180 (100) $[M + H]^+$. HRMS (ESI): calcd for $C_7H_6NO_3S$ $[M - H]^-$ 184.0074; found 184.0073.

General Procedure for the Preparation of 2-Oxo Esters 4i–l. *N*-Butyllithium was added dropwise at −78 °C to a solution of diisopropylamine (2.0 equiv) in dry THF. After 20 min of stirring at 0 °C, 2-picoline (**5i**), 2-methylpyrazine (**5j**), 3-methylpyridazine (**5k**), or 4-methylpyrimidine (**5l**) (1.0 equiv) was added at −78 °C. The mixture was stirred for 15 min, and then methyl 2,2,2-trimethoxyacetate (**6**) (1.1 equiv) was added. The solution was warmed to room temperature, stirred overnight, poured into 1 M HCl, and stirred at room temperature again for 1 h. The reaction mixture was neutralized with saturated $NaHCO_3$ solution and extracted with Et_2O (3×). The combined organic phases were washed with brine and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was purified by flash chromatography to obtain the corresponding methyl acrylate **4i–l**.

*Methyl 2-Hydroxy-3-(pyridin-2-yl)acrylate (**4i**).* Starting material: 2-picoline (**5i**) (50.0 mg, 0.5 mmol). The crude material was purified by column chromatography with cylohexane/ethyl acetate, 1:1. Yield of 2-oxo ester **4i**: 87% (84.0 mg, 0.4 mmol), yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3H), 6.55 (s, 1H), 7.18 (m, 2H), 7.73 (m, 1H), 8.40 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.4, 103.3, 120.9, 123.3, 137.6, 145.1, 152.7, 156.5, 164.3 ppm. IR (neat): 1715 (C═O) cm^{-1}. MS (ESI): m/z (%) = 180 (100) $[M + H]^+$, 202 (65) $[M + Na]^+$. HRMS (ESI): calcd for $C_9H_9NNaO_3$ $[M + Na]^+$ 202.0475; found 202.0475.

*Methyl 2-Hydroxy-3-(pyrazin-2-yl)acrylate (**4j**).* Starting material: 2-methylpyrazine (**5j**) (50.0 mg, 0.5 mmol). The crude material **4j**

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was purified by column chromatography with cylohexane/ethyl acetate, 1:1. Yield: 92% (88.5 mg, 0.5 mmol), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.91 (s, 3H), 6.63 (s, 1H), 8.41 (m, 1H), 8.47 (m, 1H), 8.56 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.8, 101.5, 140.4, 142.1, 145.1, 151.8, 152.3, 163.3 ppm. IR (neat): 1721 (C=O) cm^{-1}. MS (ESI): m/z (%) = 181 (100) [M + H]$^+$, 203 (85) [M + Na]$^+$. HRMS (ESI): calcd for $C_8H_8N_2NaO_3$ [M + Na]$^+$ 203.0427; found 203.0427.

*Methyl 2-Hydroxy-3-(pyridazin-3-yl)acrylate (**4k**).* Starting material: 3-methylpyridazine (**5k**) (50.0 mg, 0.5 mmol). The crude material **4k** was purified by column chromatography with cylohexane/ethyl acetate, 1:1. Yield: 50% (48.2 mg, 0.3 mmol), yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.93 (s, 3H), 6.34 (s, 1H), 7.39 (m, 2H), 8.61 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 52.7, 94.6, 128.3, 129.0, 145.8, 157.4, 163.8, 164.1 ppm. IR (neat): 3400 (O−H), 1719 (C=O) cm^{-1}. MS (ESI): m/z (%) = 181 (100) [M + H]$^+$, 203 (37) [M + Na]$^+$. HRMS (ESI): calcd for $C_8H_8N_2NaO_3$ [M + Na]$^+$ 203.0427; found 203.0427.

*Methyl 2-Hydroxy-3-(pyrimidin-4-yl)acrylate (**4l**).* Starting material: 3-methylpyrimidine (**5l**) (50.0 mg, 0.5 mmol). The crude material **4l** was purified by column chromatography using cylohexane/ethyl acetate, 1:1. Yield: 19% (18.2 mg, 0.1 mmol), yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.94 (s, 3H), 6.50 (s, 1H), 7.13 (m, ^3J = 5.4 Hz, 1H), 8.66 (d, ^3J = 5.4 Hz, 1H), 9.04 (s, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 52.9, 101.1, 118.9, 155.1, 157.0, 157.2, 162.0, 163.3 ppm. IR (neat): 1737 (C=O) cm^{-1}. MS (ESI): m/z (%) = 181 (100) [M + H]$^+$, 203 (52) [M + Na]$^+$. HRMS (ESI): calcd for $C_8H_9N_2O_3$ [M + H]$^+$ 181.0608; found 181.0607.

1,4-Diacetylpiperazine-2,5-dione (8). Glycine anhydride (5.0 g, 43.8 mmol) was dissolved in acetic anhydride, and the solution was stirred under reflux for 7 h. The solvent was then removed under reduced pressure. The crude product was recrystallized from ethyl acetate/diethyl ether to yield the desired product (8.7 g, 43.9 mmol, 99%) as a brown solid. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.60 (s, 6H), 4.61 (s, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 26.7, 47.2, 165.9, 170.7 ppm. IR (neat): 1698 (C=O) cm^{-1}. MS (ESI): m/z (%) = 221 (100) [M + Na]$^+$. HRMS (ESI): calcd for $C_8H_9N_2O_4$ [M − H]$^-$ 197.0568; found 197.0568.

General Procedure for the Synthesis of Piperazine-2,5-Diones 9m and 9n. 1,4-Diacetyl-piperazine-2,5-dione (**8**) (1.0 equiv) was dissolved in dry DCM. Aldehyde **7m** or **7n** and KO*t*Bu (1.0 equiv) were dissolved in a minimum amount of *tert*-butanol and added to the solution. The reaction mixture was stirred for 3 h, and then the reaction was quenched with a saturated NH_4Cl aqueous solution. The mixture was extracted with ethyl acetate, and the combined organic phases were dried over anhydrous sodium sulfate. After removal of the solvent, the corresponding product **9** was obtained as a solid and used without further purification.

*(Z)-1-Acetyl-3-(naphthalene-1-ylmethylene)piperazine-2,5-dione (**9m**).* Starting material: 1-naphthaldehyde (**7m**) (500.0 mg, 2.5 mmol). Product **9m** was obtained as a brown solid (730.0 mg, 2.5 mmol, 98%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.56 (s, 3H), 4.39 (s, 2H), 7.45 (s, 1H), 7.55−7.69, 7.93−8.02 (2m, 7H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 27.0, 46.1, 115.6, 124.2, 125.7, 126.1, 126.6, 127.1, 128.6, 128.7, 128.8, 130.0, 131.1, 133.3, 160.8, 163.6, 172.0 ppm. IR (neat): 1692 (C=O), 1663 (C=O), 1627 (C=O) cm^{-1}. MS (ESI): m/z (%) = 295 (100) [M + H]$^+$, 317 (22) [M + Na]$^+$. HRMS (ESI): calcd for $C_{17}H_{13}N_2O_3$ [M − H]$^-$ 293.0932; found 293.0933.

*(Z)-1-Acetyl-3-(naphthalene-2-ylmethylene)piperazine-2,5-dione (**9n**).* Starting material: 2-naphthaldehyde (**7n**) (500.0 mg, 2.5 mmol). The product **9n** was obtained as a brown solid (340.0 mg, 1.2 mmol, 46%). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.53 (s, 3H), 4.41 (s, 2H), 7.12 (s, 1H), 7.53−7.59 (m, 2H), 7.69 (m, 1H), 7.90−7.98 (m, 3H), 8.16 (m, 1H) ppm. ^{13}C NMR (101 MHz, DMSO-d_6): δ = 26.6, 45.7, 118.8, 126.5, 126.9, 127.1, 127.5, 128.0, 128.3, 129.2, 130.6, 132.7, 132.8, 161.7, 164.2, 171.9 ppm. IR (neat): 1678 (C=O), 1614 (C=O) cm^{-1}. MS (ESI): m/z (%) = 295 (100) [M + H]$^+$, 317 (92) [M + Na]$^+$. HRMS (ESI): calcd for $C_{17}H_{13}N_2O_3$ [M − H]$^-$ 293.0932; found 293.0933.

General Procedure for the Synthesis of 2-Oxo Acids 10m and 10n. Piperazine-2,5-dione **9m** or **9n** was dissolved in 6 N aqueous HCl. The solution was heated to reflux for 4 h and then cooled to room temperature and extracted with DCM. The combined organic phases were dried over anhydrous sodium sulfate. After concentration in vacuo, the corresponding free carboxylic acid **10m** or **10n** was obtained as a brown solid and used without further purification for subsequent reactions.

*3-(Naphthalene-1-yl)-2-oxopropanoic Acid (**10m**).* Starting material: piperazine-2,5-dione **9m** (103.0 mg, 0.4 mmol). 2-Oxo acid **10m** was obtained in a yield of 97% (72.8 mg, 0.3 mmol) as an orange solid. ^{1}H NMR (600 MHz, [D$_4$]methanol): δ = 6.68 (s, 1H), 7.42−7.48 (m, 2H), 7.77−7.85 (m, 3H), 7.93 (m, 1H), 8.27 (m, 1H) ppm. ^{13}C NMR (151 MHz, [D$_4$]methanol): δ = 110.1, 125.7, 127.1, 127.2, 127.8, 128.5, 132.6, 132.7, 133.6, 141.2, 166.9 ppm. IR (neat): 2920 (O−H), 1650 (C=O) cm^{-1}. MS (ESI): m/z (%) = 213 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_{13}H_9O_3$ [M − H]$^-$ 213.0557; found 213.0557.

*3-(Naphthalene-2-yl)-2-oxopropanoic Acid (**10n**).* Starting material: piperazine-2,5-dione **9n** (120.0 mg, 0.4 mmol). 2-Oxo acid **10n** was obtained in a yield of 91% (79.4 mg, 0.4 mmol) as a brown solid. ^{1}H NMR (600 MHz, [D$_4$]methanol): δ = 4.60 (s, 2H), 7.30 (s, 1H), 7.34−7.44 (m, 4H), 7.44−7.54 (m, 3H), 7.70−7.82 (m, 4H), 7.82−7.90 (m, 3H), 8.15 (d, ^3J = 8.3 Hz, 1H), 8.26 (d, ^3J = 8.3 Hz, 1H), 8.35 (d, ^3J = 7.3 Hz, 1H) ppm. ^{13}C NMR (151 MHz, [D$_4$]methanol): δ = 106.9, 124.3, 126.4, 126.5, 127.1, 128.9, 129.0, 129.7, 131.8, 132.8, 135.1, 143.0, 168.2 ppm. IR (neat): 3400 (O−H), 1669 (C=O) cm^{-1}. MS (ESI): m/z (%) = 223 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_{13}H_9O_3$ [M − H]$^-$ 213.0557; found 213.0557.

General Procedure for the Hydrolysis of 2-Oxocarboxylic Esters 4. A solution of enol ester **4** in THF was added to an aqueous solution of LiOH (1.1 equiv). The reaction mixture was stirred for 5 h at room temperature. Then the solvent was removed by freeze-drying, and the corresponding crude product **10** was used for the enzymatic reduction without further purification.

Enantioselective Enzymatic Reductions of Li Carboxylates 10b,d−l and Acids 10m,n to 2-Hydroxy Acids 11. A solution of EDTA (0.025 mM), mercaptoethanol (0.05 mM), ammonium formate (40 mM), 2-oxocarboxylate **10b,d−l** or 2-oxo acid **10m,n** (10 mM), and NADH (0.1 mM) was diluted with water (50 mL). The pH was adjusted to 6.2−7.0 with 1 N HCl or 1 N NaOH. The enzymes D-LDH (200 units, *S. epidermidis*, activity 97 units/mg of solid) and FDH (5 units, *C. boidinii*, activity 0.45 unit/mg of solid) were added, and the suspension was stirred for 24 h at room temperature. After that time, water was removed in vacuo, and the crude product **11** was purified by flash chromatography.

*(R)-2-Hydroxy-3-(furan-3-yl)propanoic Acid (**11b**).* Starting material: 2-oxocarboxylic ester **4b** (124.43 mg, 0.74 mmol). Yield of 2-hydroxy acid **11b**: 27% (29.1 mg, 0.2 mmol), 99% *ee* (Chiralcel OJ-H; *n*-heptane/2-propanol, 95:5), brown solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 9:1 + 0.1% AcOH. $[\alpha]_D^{20}$ = +3.2 (c = 0.3 in MeOH). ^{1}H NMR (600 MHz, [D$_4$]methanol): δ = 2.82 (m, 1H), 2.93 (m, 1H), 4.29 (m, 1H), 6.40 (m, 1H), 7.38 (m, 1H), 7.40 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 30.7, 71.9, 112.6, 121.7, 141.6, 143.7, 175.1 ppm. IR (neat): 3408 (O−H), 1559 (C=O) cm^{-1}. MS (ESI): m/z (%) = 155 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_7H_7O_4$ [M − H]$^-$ 155.0350; found 155.0349.

*(R)-2-Hydroxy-3-(thiophen-2-yl)propanoic Acid (**11d**).* Starting material: 2-oxocarboxylic ester **4d** (174.26 mg, 0.95 mmol). Yield of 2-hydroxy acid **11d**: 38% (59.4 mg, 0.34 mmol), 99% *ee* (Chiralpak IA; *n*-heptane/EtOH, 95:5), brown solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 9:1 + 0.1% AcOH. $[\alpha]_D^{20}$ = +6.5 (c = 0.2 in MeOH). ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 3.18 (m, 1H), 3.38 (m, 1H), 4.30 (m, 1H), 6.94 (m, 2H), 7.19 (d, ^3J = 4.9 Hz, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 36.4, 75.0, 125.0, 127.3, 127.8, 141.4, 176.4 ppm. IR (neat): 3271 (O−H), 1585 (C=O) cm^{-1}. MS (ESI): m/z (%) = 171 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_7H_7O_3S$ [M − H]$^-$ 171.0121; found 171.0121.

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*(R)-2-Hydroxy-3-(thiophen-3-yl)propanoic Acid (**11e**).* Starting material: 2-oxocarboxylic ester **4e** (57.11 mg, 0.31 mmol). Yield of 2-hydroxy acid **11e**: 23% (11.8 mg, 0.07 mmol), 99% *ee* (Chiralpak IA; *n*-heptane/EtOH, 95:5), brown solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 9:1 + 0.1% AcOH. $[\alpha]_D^{20}$ = +12.6 (*c* = 0.5 in MeOH). ^{1}H NMR (600 MHz, [D$_4$]methanol): δ = 3.11 (m, 1H), 3.30 (m, 1H), 4.35 (m, 1H), 7.07 (m, 1H), 7.16 (m, 1H), 7.31 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 36.2, 75.0, 123.3, 125.9, 130.1, 139.6, 176.4 ppm. IR (KBr): 3401 (O−H), 1721 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 171 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_7H_7O_3S$ [M − H]$^-$ 171.0121; found 171.0121.

*(R)-2-Hydroxy-3-(thiazol-2-yl)propanoic Acid (**11f**).* Starting material: 2-oxocarboxylic ester **4f** (27.6 mg, 0.15 mmol). Yield of 2-oxo acid **11f**: 66% (22.2 mg, 0.13 mmol), 99% *ee* (Chiralpak IA; *n*-heptane/EtOH, 80:20), red solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 7:3 + 0.1% AcOH. $[\alpha]_D^{20}$ = +4.1 (*c* = 0.3 in MeOH). ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 3.41 (m, 1H), 3.55 (m, 1H), 4.45 (m, 1H), 7.49 (m, 1H), 7.72 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 39.2, 73.4, 119.0, 120.9, 142.8, 170.4 ppm. IR (neat): 3342 (O−H), 1559 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 172 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_6H_6NO_3S$ [M − H]$^-$ 172.0074; found 172.0074.

*(R)-2-Hydroxy-3-(pyridin-3-yl)propanoic Acid (**11g**).* Starting material: 2-oxocarboxylic ester **4g** (98.5 mg, 0.55 mmol). Yield of 2-hydroxy acid **11g**: 38% (34.7 mg, 0.21 mmol), 99% *ee* (Chiralpak IA; *n*-heptane/EtOH, 70:30), white solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 7:3 + 0.1% AcOH. $[\alpha]_D^{20}$ = +4.2 (*c* = 0.2 in MeOH). ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 2.92 (m, 1H), 3.12 (m, 1H), 4.19 (m, 1H), 7.35 (m, 1H), 7.78 (m, 1H), 8.19−8.66 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 39.2, 85.3, 108.9, 120.8, 139.7, 144.3, 147.8, 185.5 ppm. IR (neat): 3204 (O−H), 1584 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 166 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_8H_8NO_3$ [M − H]$^-$ 166.0510; found 166.0510.

*(R)-2-Hydroxy-3-(pyridin-4-yl)propanoic Acid (**11h**).* See ref 13.

*(R)-2-Hydroxy-3-(pyridin-2-yl)propanoic Acid (**11i**).* Starting material: 2-oxocarboxylic ester **4i** (50.0 mg, 0.30 mmol). Yield of 2-hydroxy acid **11i**: 99% (50.0 mg, 0.30 mmol), 99% *ee* (Chiralpak IA; *n*-heptane/EtOH, 85:15), brown solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 1:1 + 0.1% AcOH. $[\alpha]_D^{20}$ = +9.5 (*c* = 0.2 in MeOH). ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 3.09 (m, 1H), 3.35 (m, 1H), 4.46 (m, 1H), 7.28 (m, 1H), 7.40 (m, 1H), 7.76 (m, 1H), 8.45 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$): δ = 43.3, 73.7, 123.4, 125.9, 138.8, 149.4, 160.5, 196.2 ppm. IR (neat): 3274 (O−H), 1559 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 166 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_8H_8NO_3$ [M − H]$^-$ 166.0510; found 166.0512.

*(R)-2-Hydroxy-3-(pyrazin-2-yl)propanoic Acid (**11j**).* Starting material: 2-oxocarboxylic ester **4j** (45.9 mg, 0.26 mmol). Yield of 2-hydroxy acid **11j**: 70% (30.0 mg, 0.18 mmol), 99% *ee* (Chiralpak IA; *n*-heptane/2-propanol, 85:15), brown solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 1:1 + 0.1% AcOH. $[\alpha]_D^{20}$ = +11.2 (*c* = 0.6 in MeOH). ^{1}H NMR (600 MHz, [D$_4$]methanol): δ = 3.10 (m, 1H), 3.38 (m, 1H), 4.43 (m, 1H), 8.45 (m, 1H), 8.56 (m, 1H), 8.59 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 41.7, 71.5, 143.4, 145.3, 146.6, 156.8, 179.5 ppm. IR (KBr): 3293 (O−H), 1559 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 167 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_7H_7N_2O_3$ [M − H]$^-$ 167.0462; found 167.0462.

*(R)-2-Hydroxy-3-(pyridazin-3-yl)propanoic Acid (**11k**).* Starting material: 2-oxocarboxylic ester **4k** (82.9 mg, 0.46 mmol). Yield of 2-hydroxy acid **11k**: 29% (21.6 mg, 0.13 mmol), 99% *ee* (Chiralcel OJ-H; *n*-heptane/2-propanol, 85:15), brown solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 1:1 + 0.1% AcOH. $[\alpha]_D^{20}$ = +10.1 (*c* = 0.4 in MeOH). ^{1}H NMR (600 MHz, [D$_4$]methanol): δ = 3.20 (m, 1H), 3.50 (m, 1H), 4.37 (m, 1H), 7.67 (m, 1H), 7.76 (m, 1H), 9.06 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 42.5, 73.0, 128.8, 130.2, 151.0, 163.5, 179.8 ppm. IR (KBr): 3362 (O−H), 1579 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 167 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_7H_9N_2O_3$ [M + H]$^+$ 169.0608; found 169.0609.

*(R)-2-Hydroxy-3-(pyrimidin-4-yl)propanoic Acid (**11l**).* Starting material: 2-oxocarboxylic ester **4l** (85.8 mg, 0.48 mmol). Yield of 2-hydroxy acid **11l**: 57% (45.4 mg, 0.27 mmol), 99% *ee* (Chiralcel OJ-H; *n*-heptane/2-propanol, 85:15), brown solid. Solvent for chromatographic purification: ethyl acetate/MeOH, 1:1 + 0.1% AcOH. $[\alpha]_D^{20}$ = +5.7 (*c* = 0.3 in MeOH). ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 3.10 (m, 1H), 3.35 (m, 1H), 4.49 (m, 1H), 7.53 (m, 1H), 8.59 (m, 1H), 9.06 (m, 1H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 43.7, 72.8, 123.5, 157.6, 158.9, 169.9, 179.5 ppm. IR (KBr): 3271 (O−H), 1557 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 167 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_7H_7N_2O_3$ [M − H]$^-$ 167.0462; found 167.0462.

*(R)-2-Hydroxy-3-(naphthalen-1-yl)propanoic Acid (**11m**).* Starting material: 2-oxo acid **10m** (70.0 mg, 0.3 mmol). Yield of 2-hydroxy acid **11m**: 75% (53.0 mg, 0.3 mmol), 99% *ee* (Chiralcel OD-H; *n*-heptane/2-propanol, 90:10), red solid. Solvent for chromatographic purification: ethyl acetate + 0.1% AcOH. $[\alpha]_D^{20}$ = +7.7 (*c* = 0.3 in MeOH). ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 3.03 (m, 1H), 3.28 (m, 1H), 4.32 (m, 1H), 7.36−7.52 (m, 3H), 7.71−7.82 (m, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$): δ = 41.7, 72.9, 126.4, 126.5, 126.8, 126.9, 128.5, 128.8, 129.0, 133.8, 134.9, 136.1, 175.7 ppm. IR (KBr): 3371 (O−H), 1632 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 215 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_{13}H_{11}O_3$ [M − H]$^-$ 215.0714; found 215.0715.

*(R)-2-Hydroxy-3-(naphthalen-2-yl)propanoic Acid (**11n**).* Starting material: 2-oxo acid **10n** (70.0 mg, 0.3 mmol). Yield of 2-hydroxy acid **11n**: 75% (53.0 mg, 0.3 mmol), 99% *ee* (Chiralcel OD-H; *n*-heptane/2-propanol, 90:10), orange solid. Solvent for chromatographic purification: ethyl acetate + 0.1% AcOH. $[\alpha]_D^{20}$ = +2.8 (*c* = 0.2 in MeOH). ^{1}H NMR (400 MHz, [D$_4$]methanol): δ = 3.04 (m, 1H), 3.30 (m, 1H), 4.35 (m, 1H), 7.25−7.60 (m, 3H), 7.65−8.13 (m, 4H) ppm. ^{13}C NMR (151 MHz, [D$_4$]methanol): δ = 42.5, 74.3, 126.2, 126.7, 126.8, 127.4, 128.5, 128.6, 128.7, 130.1, 131.2, 133.7, 134.1, 134.9, 136.4, 137.6, 172.9 ppm. IR (KBr): 3369 (O−H), 1625 (C═O) cm^{-1}. MS (ESI): *m*/*z* (%) = 215 (100) [M − H]$^-$. HRMS (ESI): calcd for $C_{13}H_{11}O_3$ [M − H]$^-$ 215.0714; found 215.0715.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: scherkenbeck@uni-wuppertal.de. Homepage: http://www.bioorganik.uni-wuppertal.de/.

Notes

The authors declare no competing financial interest.

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