Tetrahedron: *Asymmetry* xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

A convenient stereoselective synthesis of 5-hydroxy-3-oxoesters and 3-hydroxy-5-oxoesters

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ARTICLE INFO

Article history:
Received 12 March 2017
Revised 4 May 2017
Accepted 8 May 2017
Available online xxxx

ABSTRACT

A biocatalytic approach was employed for the asymmetric reduction of sterically demanding ketones to prepare 3-hydroxy-5-oxo-5-phenylpentanoates and 5-hydroxy-3-oxo-5-phenylpentanoates. Screening a collection of microorganisms led to the identification of stereocomplementary microbial strains that provide access to both enantiomers of 3-hydroxy-5-oxo-5-phenylpentanoates and 5-hydroxy-3-oxo-5-phenylpentanoates with high enantiomeric excess (up to 99% *ee*). Moreover, the application of *Saccharomyces cerevisiae* gave two diastereomers of 3,5-dihydroxy-5-phenylpentanoates with high enantiomeric excess (up to 99% *ee*). The applicability of the identified strains was demonstrated by transforming the obtained dihydroxy ester into the chemically valuable lactone (4*S*,6*R*)-tetrahydro-4-hydroxy-6-phenyl-pyran-2-one.

1. Introduction

A key interest in organic chemistry is the stereoselective synthesis of chiral building blocks.[1] Among these, 3,5-dioxygenated ester/amide motifs are of high interest, because they are found in many biologically active compounds, such as the anti-cancer drugs Ixempra and Berkeleyamide A (caspase-1 inhibitor),[2] shown in Scheme 1. Accordingly, various approaches have been devised to synthesize these important substructures. For instance, regio- and enantioselective reduction catalyzed by ketoreductases[3] or whole cell systems[4] were extensively used for preparing 3,5-dihydroxy acid derivatives. Moreover, several chemical and biochemical approaches have been devised for the synthesis of optically active 5-hydroxy-3-oxoesters and 3-hydroxy-5-oxoesters, including asymmetric aldol-type reactions,[5] additions of diketenes to aldehydes promoted by chiral Schiff base-titanium alkoxide complexes,[6] dithiane anion chemistry,[7] or Ru-catalyzed hydrogenation of 3,5-diketoacid derivatives.[8] In recent years, effective enzymatic reductions applying ketoreductases have been developed.[9] Although all stereoisomers were obtained, the reductions were performed on sterically less demanding 3,5-dioxohexanoates. Alternative protocols relied on enzymatic kinetic resolution[10] and dynamic kinetic resolution.[11] Although these methods were extensively investigated, they failed to deliver ideal chemo- and stereoselectivity.

Furthermore, enantiopure 5-hydroxy-3-oxoesters and 3-hydroxy-5-oxoesters are potential precursors to the tetrahydro-2*H*-pyranone ring as shown in numerous reports (Scheme 2).[12] The stereocontrolled construction is essential for the biological activity of many pharmaceuticals.[13] For instance, the antitumor polyketide (+)-discodermolide contains the (4*S*,6*R*)-4-hydroxy-6-phenyl-δ-lactone subunit while lovastatin contains a (4*R*,6*S*)-4-hydroxy-6-phenyl-δ-lactone subunit. The recently discovered diospongins A and B, isolated from the rhizomes of *Dioscorea spongiosa* exhibit promising inhibitory activities on bone resorption and have potential application for the treatment of osteoporosis.[14] In particular, diospongins can be obtained via a diastereoselective reduction of enantiomerically pure ethyl 3-hydroxy-5-phenyl-5-oxopentanoate followed by cyclization.[15] The target lactone can also be provided from enantioselective lactonization of *syn*-3,5-dihydroxy esters[16] or *anti*-3,5-dihydroxy esters.[17] Up to now, the regio- and enantioselective synthesis of these compounds remains challenging.

Previously we reported the results of screening a microbial culture collection, which led to the identification of stereocomplementary whole-cell catalysts for the preparation of ethyl 3-hydroxy-5-phenylpentanoate.[18] Herein, we report the selective reduction of sterically demanding 3,5-dioxo-5-phenylpentanoates.

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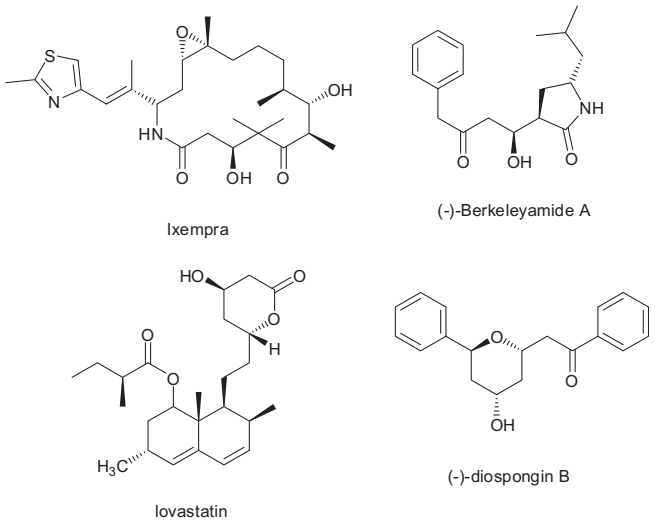
http://dx.doi.org/10.1016/j.tetasy.2017.05.005
0957-4166/

Careful selection of the microorganism enabled us to control the chemo-, regio- and stereoselective reduction of a single keto group either at the C3 or C5 position. Subsequent cyclization gave access to (4*S*,6*R*)-tetrahydro-4-hydroxy-6-phenyl-pyran-2-one with high enantiomeric purity.



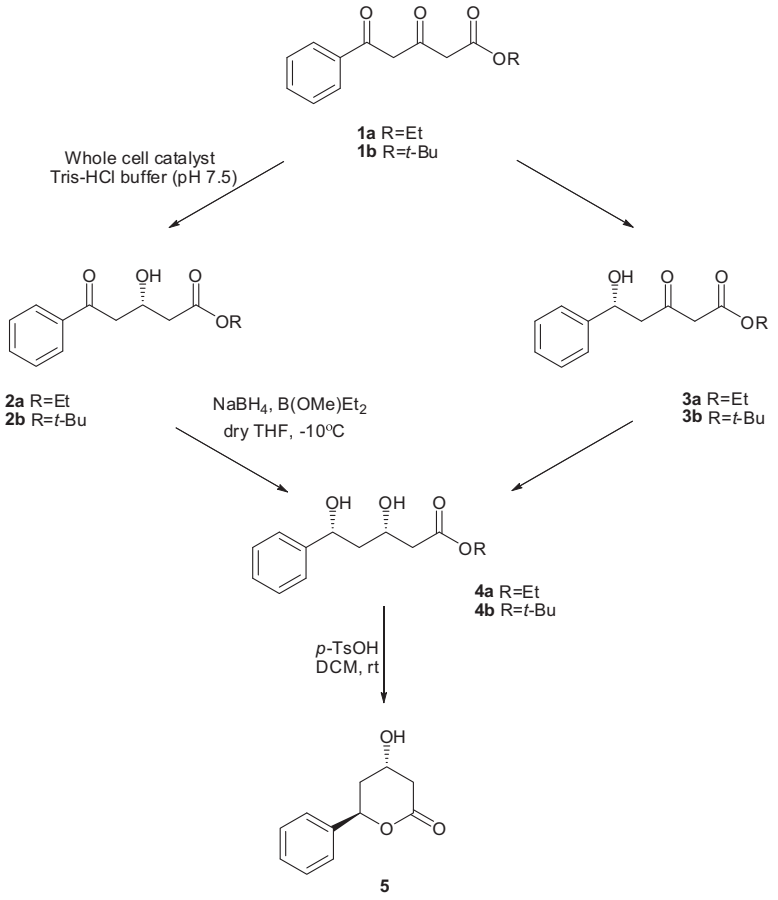
Scheme 1. Bioactive compounds.

2. Results and discussion

Identifying appropriate microorganisms possessing the enantio- and diastereocomplementary selectivity for the reduction of diketoester **1** may allow us to prepare each of the four possible diastereomeric products **4** with high enantiomeric and diastereomeric purities. However, diketoester **1** may also be asymmetrically reduced at only one carbonyl group generating multi-functionalized compounds **2** or **3** (Scheme 2).

Initially, an in-house culture collection of 250 microorganisms was screened for the reduction of compound **1a** using freeze-dried cells. Glucose dehydrogenase (GDH) and 2-propanol were used for cofactor regeneration, as well as 2-propanol to improve the solubility of the substrate.[19] Since the cofactor preference of the involved enzymes was not known, both NADH as well as NADPH were added. Probably due to the sterically hindered carbonyl groups, compound **1a** was accepted only by three microorganisms. These three biocatalysts, *Arthrobacter* sp. DSM 7325 *Pseudomonas* sp. DSM 6978 and *Actinomyces* sp. SRB-AN053 FCC 027, were selected for experiments on a preparative scale (Table 1).

Thus, 236 mg (1 mmol) of diketo ester **1a** were subjected to a biotransformation, which reached completion within 72 h at 30 °C. Two main products, namely **2a** and **3a** were identified (Scheme 2). Out of the tested biocatalysts, *Arthrobacter* sp. transformed diketoester **1a** into a mixture of two products, (*R*)-configured **2a** (49% *ee*, Table 1, entry 1) and (*S*)-configured **3a** (96% *ee*). The separation of these products by column chromatography was not feasible. Thus, *Arthrobacter sp.* allowed to reduce both keto



Scheme 2. Synthesis of (4*R*,6*S*)-tetrahydro-4-hydroxy-6-phenylpyran-2-one.

Table 1
Reduction of ethyl 3,5-dioxo-5-phenylpentanoate **1a** employing freeze-dried microorganisms[a]

Entry	Microorganism	NAD^+	$NADP^+$	GDH/glucose	Yield **2a** (%)	*ee* (%)	Yield **3a** (%)	*ee* (%)
1	*Arthrobacter* sp.	+	+	+	36	49 (*R*)	29	96 (*S*)
2	*Arthrobacter* sp.	+			34	59 (*R*)	22	71 (*S*)
3	*Arthrobacter* sp.		+		27	55 (*R*)	18	66 (*S*)
4	*Pseudomonas* sp.	+	+	+	16	94 (*S*)	<1	nd
5	*Pseudomonas* sp.	+			17	>99 (*S*)	<1	nd
6	*Pseudomonas* sp.		+		20	78 (*S*)	<1	nd
7	*Saccharomyces cerevisiae*			+	17	23 (*S*)	<1	nd

[a] Conditions: 30 °C, 120 rpm in a thermoshaker for 72 h, 2 g of lyophilized whole-cell biocatalyst in 100 mL of reaction solution, containing 20 mM glucose, glucose dehydrogenase (1 mg mL^{-1}), 0.5 mM NADH or/and 0.5 mM NADPH, 1 mmol substrate in a mixture of buffer (100 mM Tris-HCl pH 7.5) and 2-propanol (90:10, v/v). Yield refers to isolated product **2a** and **3a** after column chromatography. The *ee*s of **2a** and **3a** were determined by HPLC equipped with a Chiralcel OB-H column.

functionalities. In contrast, *Pseudomonas* sp. reduced the diketone in a regio- and enantioselective fashion transforming only the keto moiety at the β-position to (*S*)-**2a** with high enantiomeric excess (94% *ee*, Table 1, entry 4). It is worth noting that the *Pseudomonas* sp. gave access to the (*S*)-enantiomer of **2a** while *Arthrobacter* sp. provided the (*R*)-enantiomer. *Actinomyces* sp. gave only trace amounts of the product on a millimolar scale. Optimization of the cofactors led to enantiomerically pure 3-hydroxy-5-keto ester (*S*)-**2a** (>99% *ee*, Table 1, entry 5), a useful chiral synthon and building block, which is difficult to synthesize otherwise. An additional experiment with Yeast from *Saccharomyces cerevisiae*, which is known for its versatility, led to (*S*)-**2a** with low yield and low enantiomeric excess (Table 1, entry 7).

Due to the presence of various types of enzymes in whole-cell catalysts, conversions were very high (>85%), while the isolated product yields were quite low (16–36%). Whole-cell catalysts contain besides dehydrogenases also hydrolases, and since all investigated compounds **1a**–**4a** possess an ester functional group, they are susceptible to enzymatic hydrolysis. For this reason, the ethyl ester group was replaced by the sterically demanding *t*-butyl ester, which is less susceptible to hydrolysis.

Employing *t*-butyl 3,5-dioxo-5-phenylpentanoate **1b** as the substrate resulted in higher product yields (up to 40%) as well as lower conversions. The latter is most likely due to the even more bulky substrate. *Arthrobacter* sp. catalyzed the reduction of substrate **1b** exclusively at the δ-carbonyl group to afford the (*R*)-enantiomer of **3b** as the only product (Table 2, entries 1–3). Thus, by changing the ester moiety, the regioselectivity of the biocatalyst could be controlled. Additionally, the *t*-butyl group led to a switch of stereopreference compared to the ethyl ester **1a**. The reduction of **1b** catalyzed by *Pseudomonas* sp. took place again preferentially at the β-carbonyl group to afford the (*R*)-configured **2b**, which also corresponded to a switch in stereoselectivity compared to the reduction of the ethyl ester. Independent of the cofactor added, high *ee* values were obtained (92–96% *ee*, Table 2, entries 4–6). For this substrate *Actinomyces sp.* proved to be stereocomplementary to *Pseudomonas* sp. leading to (*S*)-configured **2b** with 62% *ee* (Table 2, entry 9). In all cases, the determined conversions were independent of the presence or absence of glucose and GDH. The developed method is a convenient synthetic pathway to obtain both enantiomers of 3-hydroxy-5-oxo-5-phenylpentanoic esters. According to the literature, such compounds may be chemically reduced in a highly diastereoselective manner to all diastereoisomers of 3,5-dihydroxy-5-phenylpentanoates and then cyclized to a desired lactone.[12]

As an alternative, racemic **3a** was reduced with the whole-cell catalysts at the β-carbonyl group, which may lead to the formation of four stereoisomers of dihydroxyester **4** (Scheme 2). The isolation of *syn*-(3*S*,5*R*) might be very valuable in the synthetic pathway leading to desired lactone (4*S*,6*R*)-tetrahydro-4-hydroxy-6-phenyl-pyran-2-one. Whole cells of *Saccharomyces cerevisiae* were selected as the biocatalyst. Cells were shaken under fermenting and non-fermenting conditions in water at room temperature for 24 h. An inexpensive carbon source (glucose) was added for the internal cofactor regeneration in the metabolism of the cells. Unreacted substrate and the obtained products were isolated and analyzed (Table 3).

The addition of glucose was found to accelerate the yeast-mediated reduction from 38% to 66% product yield (Table 3, entries 1 vs 2). Based on the sign of the specific rotation of the unreacted substrate, it was noticed that yeast transformed preferentially the (*R*)-configured substrate, while the (*S*)-enantiomer was recovered.[10] 5-Hydroxy-3-oxoester **3a** was reduced by yeast to give the corresponding *syn*-product (3*S*,5*R*)-**4** and *anti*-product (3*S*,5*S*)-**4** with good enantiomeric excess (Table 3, entry 2). Only 60–80% of the recovered substrate and product were isolated because of

Table 2
Reduction of *t*-butyl 3,5-dioxo-5-phenylpentanoate **1b** with whole-cell biocatalysts

Entry	Microorganism	NADH	NADPH	GDH/glucose	Yield **2b** (%)	*ee* **2b** (%)	Yield **3b** (%)	*ee* **3b** (%)
1	*Arthrobacter* sp.	+	+	+	<1	nd	34	84 (*R*)
2	*Arthrobacter* sp.	+			<1	nd	33	80 (*R*)
3	*Arthrobacter* sp.		+		<1	nd	20	76 (*R*)
4	*Pseudomonas* sp.	+	+	+	27	92 (*R*)	<1	nd
5	*Pseudomonas* sp.	+			27	96 (*R*)	<1	nd
6	*Pseudomonas* sp.		+		25	93 (*R*)	<1	nd
7	*Actinomyces* sp.	+	+	+	40	34 (*S*)	<1	nd
8	*Actinomyces* sp.	+			36	52 (*S*)	<1	nd
9	*Actinomyces* sp.		+		40	62 (*S*)	<1	nd
10	*Saccharomyces cerevisiae*			+	<1	nd	<1	nd

Conditions: 30 °C, 120 rpm in a thermoshaker for 72 h, 2 g of lyophilized whole-cell biocatalyst in 100 mL of reaction solution, containing 20 mM glucose, glucose dehydrogenase (1 mg mL^{-1}), 0.5 mM NADH or/and 0.5 mM NADPH, 1 mmol substrate in a mixture of buffer (100 mM Tris-HCl, pH 7.5) and 2-propanol (90:10, v/v). Yield refers to isolated product **2b** and **3b** after column chromatography. The *ee* of **3a** and **3b** was determined by HPLC equipped with a Chiralcel OB-H or Chiralpak IA column; nd—non defined.

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Table 3
Enzymatic reduction of racemic ethyl 5-hydroxy-5-phenyl-3-oxopentanoate **3a**

Entry	System[a]	Additives	Yield **4** (%)	*dr* (*syn*:*anti*)	ee_{syn}	ee_{anti}	Substrate **3a** recovery (%)	*ee* **3a**
1	A	None	38	77:23	88	>99	23	50
2	B	None	66	74:26	83	>99	15	70
3	B	5% v/v hexane	45	78:22	83	91	45	32
4	B	5% v/v 2-propanol	52	78:22	75	99	17	64
5	B	5% v/v diethylether	40	76:24	78	98	19	58
6	B	5% v/v acetone	54	75:25	80	96	23	54
7	B	Allylbromide[b]	65	56:44	94	98	6	54
8	B	Allylalcohol[b]	59	60:40	79	98	4	50
9	B	Ethyl bromoacetate[b]	57	60:40	98	>99	8	94

Conditions: [a]system A—non-fermenting: *Saccharomyces cerevisiae* (10 g) was suspended in 100 mL of water. After stirring for 30 min, compound **3a** (200 mg) dissolved in 4 mL of water or in organic solvent was added. The resulting cell suspension was shaken at room temperature for 24 h; system B—fermenting: 4 g glucose was added; [b]100 mg of inhibitor was added. Yield refers to isolated product **4** after column chromatography. Substrate **3a** recovery refers to isolated substrate **3a** after column chromatography. The *ee* of **3a**, **4** and *dr* were determined by HPLC equipped with a Chiralcel OB-H column and by ^{1}H NMR.

by-product formation. Possible explanations for this include the hydrolysis of the ester moiety, oxidation of the hydroxyl group, side reactions with the fermentation products, while the product and starting material might be retained by lipids in the whole cells.

According to the literature, the stereoselectivity and chemoselectivity can be tuned by the addition of organic solvents, immobilization of biocatalysts or selective inhibition of one of the various enzymes present in the microorganism.[20] In order to investigate the effect of organic solvent addition, reactions were performed under fermenting conditions with 5% by volume of organic co-solvent. Hexane, 2-propanol, diethyl ether and acetone led to slightly reduced yields without a significant influence on the enzyme enantioselectivity (Table 3, entries 3–6), hence none of them were used in further optimization studies.

The stereochemical direction of the reduction reaction may be controlled by the careful design of the substrate or by selective inhibition of one of the involved dehydrogenases. Ethyl bromoacetate, allyl bromide and allyl alcohol were found to be suitable inhibitors. When using ethyl bromoacetate (Table 3, entry 9), the highest enantiomeric purity (94% *ee*) of the recovered substrate and obtained products (3*S*,5*R*)-**4** (98% *ee*) and (3*S*,5*S*)-**4** (>99% *ee*) were found. The product diastereoisomers were separated by column chromatography on silica gel. The absolute configuration of the products was assigned based on the specific rotation measurements and chemical correlation.[10,12,15,21]

Finally, to show the applicability of the developed procedure, (3*S*,5*R*)-**4** (98% *ee*) was lactonized to the chemically valuable lactone (4*S*,6*R*)-**5** by using *p*-toluenesulfonic acid (See Supporting Information).

The biocatalytic reduction may be developed into a convenient synthetic pathway to obtain nonracemic 5-aryl-5-hydroxy-3-oxopentanoates and 5-aryl-3-hydroxy-5-oxopentanoates. Such compounds can be chemically reduced in a highly diastereoselective manner to 5-aryl-3,5-dihydroxypentanoates and then cyclized to a synthetically valuable substituted tetrahydro-2*H*-pyranone ring. Furthermore, two diastereoisomers (3*S*,5*R*)-**4** and (3*S*,5*S*)-**4** were obtained with high enantiomeric excess (>98% *ee*) by stereoselective reduction of racemic **3a** using whole cells of *Saccharomyces cerevisiae*.

3. Conclusion

Herein microbial catalysts for the stereoselective synthesis of 3,5-dihydroxyesters, 3-hydroxy-5-oxoesters and 5-hydroxy-3-oxoesters were investigated. The set-up of the stereogenic centers of the examined compounds is very demanding, due to the sterical hindrance of the corresponding ketone, but is of high interest. Due to the presence of the ester groups in these molecules, they are susceptible to side reactions such as hydrolysis. Despite these challenges, the developed method allowed us to obtain both enantiomers of 5-hydroxy-5-phenyl-3-oxopentanoate **3** and 3-hydroxy-5-phenyl-5-oxopentanoate **2** with high enantiomeric excess and two diastereoisomers of 3,5-dihydroxy-5-phenylpentanoate **4** with excellent enantiomeric and diastereomeric purities. The applicability of the developed method was demonstrated by converting ethyl (3*S*,5*R*)-dihydroxy-5-phenylpentanoate into the chemically valuable lactone (4*S*,6*R*)-tetrahydro-4-hydroxy-6-phenyl-pyran-2-one.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ solution on a Bruker 400 MHz Spectrometer. Chemical shifts are expressed in parts per million values using TMS as an internal standard. Commercial enzyme preparations were purchased from Sigma-Aldrich and Novozymes. Wild-type whole-cell microorganisms are from the collection of the Institute of Chemistry - Organic and Bioorganic Chemistry, University of Graz. All chemicals were commercial products of the analytical grade. Optical rotation measurements were done on a Jasco P-2000 polarimeter. The HPLC analyses were performed with a Varian ProStar instrument equipped with chiral-phase columns (Chiralcel OB-H, Chiralpak IA; Daicel, Japan). The mobile phase was a mixture of hexane and 2-propanol, the proportion of solvents and flow rate vary for different compounds. TLC was done on silica gel 60 F_{254} aluminum sheets (Merck). For more details see Supporting Information.

4.2. Bioreduction with whole-cell biocatalysts

The whole cell biocatalyst (2 g) was suspended in 100 mL of reaction solution, containing glucose dehydrogenase (1 mg mL^{-1}), 20 mM glucose, 0.5 mM NAD^+, 0.5 mM $NADP^+$, 1 mmol substrate **1a** or **1b** in a mixture of buffer (100 mM Tris-HCl, pH 7.5) and 2-propanol (90:10; v/v). Biotransformations were conducted at 30 °C and 120 rpm in a thermoshaker for 48 h. After this time, the biocatalyst was removed by centrifugation and the reaction mixture was extracted with ethyl acetate. The organic phase was separated, dried ($MgSO_4$), evaporated under reduced pressure and the product was purified by column chromatography on silica gel with hexane/ethyl acetate as an eluent.

4.3. Bioreduction with *Saccharomyces cerevisiae*

Saccharomyces cerevisiae (10 g) and sucrose (4 g) were suspended in water (100 mL). After stirring for 30 min, ethyl

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5-hydroxy-5-phenyl-3-oxopentanoate **3b** (200 mg) dissolved in 4 mL of organic solvent was added. The resulting cell suspension was shaken at room temperature (21 °C) for 24 h. After this time, the cells were centrifuged and the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried over $MgSO_4$. The solvent was evaporated and the product was purified by column chromatography on silica gel using hexane/ethyl acetate.

4.4. Ethyl 3,5-dioxo-5-phenylpentanoate 1a

^{1}H NMR ($CDCl_3$, 400 MHz, ppm, enol:ketone = 92:8) δ 15.77 (s, 0.9H, OH), 7.95–7.93 (d, 0.2H), 7.89–7.87 (d, 1.96H, Ar), 7.53–7.43 (m, 3H, Ar), 6.29 (s, 1H, CH), 4.25–4.20 (m, 2H, O*CH*$_2$CH$_3$), 3.64 (s, 0.2H), 3.47 (s, 1.6H, CH_2), 1.33–1.23 (m, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 189.2, 182.6, 167.5, 134.1, 132.6, 128.7, 127.1, 96.7, 61.5, 45.9, 14.1; HR-MS (ESI, [M+H+] calcd for: $C_{13}H_{14}O_4Na$, 257.0790, found, 257.0784; Element. Anal. calcd. for $C_{13}H_{14}O_4$: C, 66.66; H, 6.02; found: C, 66.52; H, 5.99.

4.5. Ethyl 3-hydroxy-5-oxo-5-phenylpentanoate 2a

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.96–7.94 (m, 2H, Ar), 7.60–7.56 (m, 1H, Ar), 7.48–7.44 (m, 1H, Ar), 4.65 (quin, 1H, J = 6.2 Hz, CH), 4.20–4.15 (q, 2H, J = 7.2 Hz, O*CH*$_2$CH$_3$), 3.55 (br. s., 1H, OH), 3.23–3.21 (d, 2H, J = 5.6 Hz, CHC*H*$_2$COO), 2.63–2.61 (d, 2H, J = 6.4 Hz, COC*H*$_2$CH), 1.29–1.25 (t, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 200 MHz, ppm)δ 199.4, 171.9, 136.1, 133.6, 128.7, 128.1, 64.8, 60.7, 44.3, 40.9, 14.2; HR-MS (ESI, [M+H+] calcd for: $C_{13}H_{16}O_4Na$, 259.0946, found, 259.0945; (*S*)-**2a**: $[\alpha]_D$ = +17.5 (*c* 0.75, $CHCl_3$) corresponding to >99% *ee* determined by HPLC.

4.6. Ethyl 5-hydroxy-3-oxo-5-phenylpentanoate 3a

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.37–7.34 (m, 4H, Ar), 7.30–7.26 (m, 1H, Ar), 5.20–5.17 (dd, 1H, J_1 = 3.6 Hz, J_2 = 9.2 Hz, CH), 4.21–4.16 (q, J = 7.2 Hz, O*CH*$_2$CH$_3$), 3.47 (s, 2H, COC*H*$_2$CO), 3.03–2.97 (dd, J_1 = 9.2 Hz, J_2 = 17.2 Hz, CHC*H*$_2$CO), 2.93–2.88 (dd, J_1 = 3.2 Hz, J_2 = 17.2 Hz, CHC*H*$_2$CO), 1.29–1.25 (t, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 200 MHz, ppm) δ 202.8, 166.8, 142.5, 128.5, 127.8, 125.6, 69.8, 61.5, 51.6, 49.9, 14.0; HR-MS (ESI, [M+H+] calcd. for: $C_{13}H_{16}O_4Na$, 259.0946, found, 259.0945; Element. Anal. calcd for $C_{13}H_{16}O_4$: C, 66.09; H, 6.83; found: C, 65.99, 6.93; (*S*)-**3a**: $[\alpha]_D$ = −36.6 (*c* 0.75, $CHCl_3$) corresponding to 72% *ee* determined by HPLC.

4.7. Ethyl 3,5-dihydroxy-5-phenylpentanoate 4a

^{1}H NMR ($CDCl_3$, 400 MHz, ppm, dr 90:10) δ 7.36–7.32 (m, 3H, Ar), 7.28–7.24 (m, 2H, Ar), 5.13–5.09 (dd, 0.10 H), 4.97–4.94 (dd, 0.95H, J_1 = 3.3 Hz, J_2 = 9.7 Hz), 4.35–4.28 (m, 1H), 4.19–4.13 (q, 2H, O*CH*$_2$CH$_3$), 3.69 (s, 2H, OH), 2.53–2.44 (m, 2H), 1.97–1.88 (m, 1H), 1.79–1.74 (dt, 1H, J_1 = 2.9 Hz, J_2 = 14.4 Hz), 1.27–1.24 (t, 3H, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 200 MHz, ppm) δ 172.5, 144.1, 128.4, 127.5, 125.7, 74.4, 68.6, 60.8, 44.8, 41.5, 14.1; HR-MS (ESI, [M+H+] calcd for: $C_{13}H_{18}O_4Na$, 261.1103, found, 261.1101; (3*S*,5*R*)-**4a**: $[\alpha]_D$ = +17.5 (*c* 0.75, $CHCl_3$) corresponding to 99% *ee* determined by HPLC.

4.8. *t*-Butyl 3,5-dioxo-5-phenylpentanoate 1b

Ketone–enol equilibrium is shifted toward enol (92:8). ^{1}H NMR ($CDCl_3$, 400 MHz, ppm, enol:ketone = 92:8) δ 15.8 (br s, 0.9H, OH), 7.89–7.87 (d, 2H, Ar), 7.53–7.47 (m, 1H, Ar), 7.47–7.43 (m, 2H, Ar), 6.29 (s, 1H, CH), 3.39 (s, 2H), 1.49 (s, 9H, 3×CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 189.7, 182.6, 166.8, 134.3, 132.5, 128.7, 127.1, 96.7, 82.0, 47.2, 28.0; HR-MS (ESI, [M+H+] calcd. for: $C_{15}H_{18}O_4Na$, 285.1103, found, 285.1100; Element. Anal. calcd for $C_{15}H_{18}O_4$: C 68.68; H 6.92; found: C 68.70, 6.94.

4.9. *t*-Butyl 3-hydroxy-5-oxo-5-phenylpentanoate 2b

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.90–7.87 (m, 2H, Ar), 7.53–7.49 (m, 1H, Ar), 7.42–7.38 (m, 2H, Ar), 4.53 (quin, 1H, J = 5.2 Hz, CH), 3.52 (br s, 1H, OH), 3.15–3.09 (m, 2H, CHC*H*$_2$COO), 2.49–2.46 (m, 2H, COC*H*$_2$CH), 1.40 (s, 9H, 3×CH_3); ^{13}C NMR ($CDCl_3$, 200 MHz, ppm)δ 199.4, 171.4, 136.8, 133.5, 128.7, 128.1, 81.2, 64.9, 44.4, 41.9, 28.1; HR-MS (ESI, [M+H+] calcd for: $C_{15}H_{20}O_4Na$, 287.1259, found, 287.1259; (*R*)-**2b**: $[\alpha]_D$ = +13.6 (*c* 0.28, $CHCl_3$) corresponding to 93% *ee* determined by HPLC; (*S*)-**2b**: $[\alpha]_D$ = −8.8 (*c* 0.75, $CHCl_3$) corresponding to 62% *ee* determined by HPLC.

4.10. *t*-Butyl 5-hydroxy-3-oxo-5-phenylpentanoate 3b

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.40–7.26 (m, 5H, Ar), 5.22–5.19 (dd, 1H, J_1 = 3.6 Hz, J_2 = 9.2 Hz, CH), 4.41 (s, 2H, CO*H*$_2$CO), 3.14 (br s, 1H, OH), 3.04–2.90 (m, 2H, CHC*H*$_2$CO), 1.49 (s, 9H, 3xCH_3);^{13}C NMR ($CDCl_3$, 200 MHz, ppm)δ 203.4, 166.1, 142.6, 128.6, 127.7, 125.6, 82.3, 69.8, 51.6, 51.2, 28.0; Element. Anal. calcd for $C_{15}H_{20}O_4$: C, 68.16; H, 7.63; found: C, 68.07, 7.68; HR-MS (ESI, [M+H+] calcd. for: $C_{15}H_{20}O_4Na$, 287.1259, found, 287.1256; (*R*)-**3b**: $[\alpha]_D$ = −26.6 (*c* 1.15, $CHCl_3$) corresponding to 80% *ee* determined by HPLC.

4.11. *t*-Butyl 3,5-dihydroxy-5-phenylpentanoate 4b

^{1}H NMR ($CDCl_3$, 400 MHz, ppm, dr 53:47) δ 7.31–7.17 (m, 5H, Ar), 4.97 (dd, 0.5H, J_1 = 7.3 Hz, J_2 = 3.9 Hz), 4.89 (dd, 0.5H, J_1 = 3.3 Hz, J_2 = 9.7 Hz), 4.21–4.16 (m, 1H), 3.6 (br s, 2H, 2×OH), 2.42–2.30 (m, 2H) 1.85–1.65 (m, 2H), 1.38 (m, 9H, 3×CH_3);^{13}C NMR ($CDCl_3$, 200 MHz, ppm) δ172.1, 144.3, 128.4, 128.4, 127.5, 127.5, 125.7, 125.6, 81.6, 74.4, 71.3, 68.8, 65.8, 44.9, 44.0, 42.5, 42.0, 28.1; HR-MS (ESI, [M+H+] calcd for: $C_{15}H_{22}O_4Na$, 289.1416, found, 289.1411.

4.12. (4*S*,6*R*)-Tetrahydro-4-hydroxy-6-phenyl-pyran-2-one 5

^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.41–7.32 (m, 5H, Ar), 5.74 (dd, 1H, J_1 = 3.2 Hz, J_2 = 11.3 Hz, CH), 4.41 (m, 2H, COC*H*$_2$CH), 2.86 (dd, J_1 = 4.9 Hz, J_2 = 17.5 Hz, 1H, CH), 2.73 (m, 1H, CH_2), 2.21–2.01 (m, 3H); ^{13}C NMR ($CDCl_3$, 200 MHz, ppm) δ 170.1, 139.3, 128.7, 128.4, 125.9, 76.9, 62.7, 38.7, 38.4.

Acknowledgements

This work was supported by COST Action CM1303 Systems Biocatalysis and Polish National Science Center project No. 2013/11/B/ST5/02199.

A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetasy.2017.05.005.

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Please cite this article in press as: Żądło-Dobrowolska, A. ; et al. *Tetrahedron: Asymmetry* (2017), http://dx.doi.org/10.1016/j.tetasy.2017.05.005