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A Two-Step, One-Pot Enzymatic Synthesis of 2-Substituted 1,3-Diols

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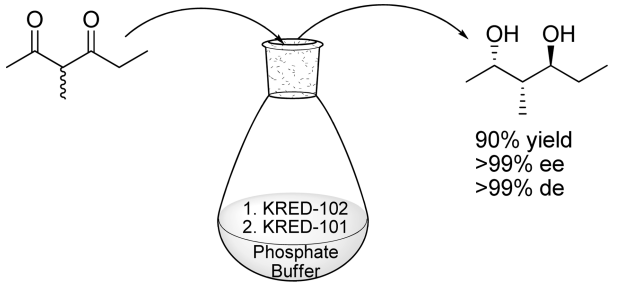

A biocatalytic cascade reaction was designed for the stereoselective synthesis of optically pure 2-alkyl-1,3-diols employing two enzymes. The cascade process consists of two consecutive steps: a stereoselective diketone reduction and a hydroxy ketone reduction. Chiral diols were formed by the addition of ketoreductases in the same vessel, in high stereoselectivity and chemical yield, without the isolation of the intermediate β-hydroxy ketones.

In the past decade, the concepts of green chemistry and sustainable development have become a strategic focus in both the chemical industry and the academic community at large.[1] A prominent feature of this drive toward sustainability is the widespread application of chemo- and biocatalytic methodologies in the manufacture of chemicals.[2] The key to successful implementation of catalytic methodologies in fine chemicals manufacture is the integration of catalytic steps in multistep organic syntheses and downstream processing. The crucial challenge is to combine several catalytic steps into a one-pot, multistep catalytic cascade process.

In the one-pot process, several reactions are conducted sequentially in the same reaction vessel, without the isolation of intermediates. By avoiding time-, effort-, and solvent-intensive steps, multistep one-pot syntheses contribute to a significantly improved process economy as well as to more sustainable synthetic routes.[3] Biotransformations can offer great applications in cascade processes.[4] Since enzymes generally function under the same or similar conditions (aqueous solution, pH ~7, rt), several biocatalytic reactions can be carried out in one pot. Thus, sequential reactions are feasible by using multienzyme systems in order to facilitate and simplify reaction processes but also to shift an unfavorable equilibrium to produce the desired product.[5] A number of examples have been published for the one-pot biocatalytic synthesis of various compounds, combining the enzymatic stereoselectivity with the simplicity of the cascade procedure.[6] The compatibility of enzymes and chemical catalysts in organic or aqueous medium can also be very useful for one-pot organic reactions.[7]

Consecutive reduction reactions can be applied for the cascade one-pot synthesis of diols starting from the corresponding diketones. More specifically, the 1,3-diols are important targets for many synthetic methodologies since they

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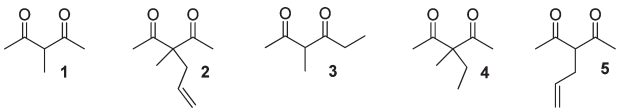

FIGURE 1. 1,3-Diketones as substrates for cascade reductions.

are high value chiral synthons or building blocks for the synthesis of many natural products and pharmaceuticals.[8] Several synthetic methods have been developed for the one-pot stereoselective synthesis of 1,3-diols. Chemoenzymatic,[9] enzymatic,[10] or simply chemical[11] procedures have been developed for the synthesis of 2-unsubstituted 1,3-diols. However, very few examples have been reported for the one-pot chemo- or chemoenzymatic formation of 2-monosubstituted 1,3-diols.[12] In all reported cases, the substituent in the 2-position was always a methyl group.

In this paper, we present the cascade enzymatic reduction of 2-alkyl-1,3-diketones utilizing commercially available ketoreductases. To the best of our knowledge, this is the first report for the enzymatic, one-pot stereoselective synthesis of optically pure 2-mono- and 2-disubstituted 1,3-diols, starting from the corresponding chiral or achiral 2-alkyl-1,3-diketones, by the consecutive addition of two reductive enzymes in the same reaction medium.

In order to accomplish the consecutive reduction, we utilized NADPH-dependent ketoreductase preparations (Kred), combined with the well-established recycling system for the regeneration of NADPH, glucose/glucose dehydrogenase.[13] In our previous studies, we have shown that ketoreductases are remarkable catalysts for the stereoselective formation of optically pure α-mono- and α-disubstituted β-hydroxy ketones starting from the corresponding 1,3-diketones. In most of the cases, the reaction was highly enantio- and diastereoselective forming exclusively one of the four possible stereoisomers.[14] These reductions rarely led directly to the formation of the corresponding diol.

TABLE 1. Enzymatic Reduction of Diketones 1−5

Substrate	Kred-No 1	Kred-No 2	Yield[a]	Time (h)	ee%,[b] de%[c]	Product
1	102	101	88%	48	>99, >99	 **1a**
2	112	114	91%	36	>99, 98	 **2a**
3	102	101	90%	48	>99, >99	 **3a**
3	102	A1B	85%	48	>99, 96	 **3ai**
4	118	101	90%	36	>99, 99	 **4a**
5	108	111	92%	48	>99, 98	 **5a**

[a]Isolated yield. [b]ee (%) was measured by chiral GC analysis. [c]de (%) was determined by chiral GC analysis and ^{1}H NMR spectra.

It is possible to prepare single diastereomers of the product diol by tailoring the choice of enzyme. The substrates for this study are three monoalkyl- and two dialkyl-substituted 1,3-diketones. Four of them were nonchiral compounds (**1**, **2**, **4**, **5**), and one was chiral (**3**) (Figure 1). The reductions were carried out in a phosphate buffer (200 mM, pH 6.5−6.9) in the presence of ketoreductases, glucose dehydrogenase, glucose, and NADPH. In all cases, the first enzymatic reduction led to the β-hydroxy ketone,[14] and the corresponding diol was formed by the addition of a second ketoreductase without the isolation of the intermediate product. The results of the enzymatic reductions are summarized in Table 1.

In an achiral environment, the reduction of these diketones would yield a mixture of all possible diastereomers. Reductive enzymes, on the other hand, are both stereo- and regioselective and can distinguish between the faces of prochiral ketones reducing them in a highly stereoselective fashion. It is clearly demonstrated that by the cascade addition of these biocatalysts, 2-substituted 1,3-diols were formed in high optical purity and high isolated yield (Table 1). In all cases, the chemical purity of the products was very high, and the diols were isolated without any chromatographic purification. The efficiency of this methodology is due to the complete enzymatic reduction of starting material, with the simultaneous absence of any detectable byproduct. The enzymes chosen for the first reduction step led to quantitative formation of hydroxy ketone[14a,c] with no further reduction to the 1,3-diol. This first step was highly stereoselective, producing only one of the four possible stereoisomers, which is crucial for the optical purity of the final product. It is also important to note that the absolute configuration of the intermediate product was already known.[14c] The completion of the first step of this reaction (24 h for substrates **1**, **3**, and **5**, 12 h for substrates **2** and **4**) was followed by the addition of ketoreductase no. 2. The reaction was monitored by gas chromatography. In all cases, the second reduction was also

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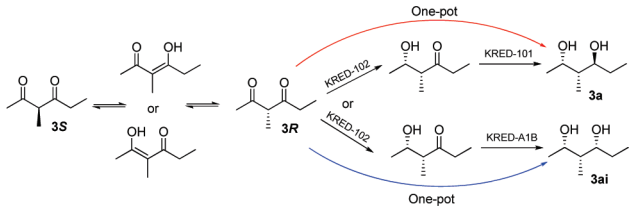
SCHEME 1. Enzymatic Reduction through Dynamic Kinetic Resolution



highly stereoselective, producing only one stereoisomer as the final product, in 24 h. The absolute configuration of the 1,3-diols **1a**, **2a**, **4a**, and **5a** was easily determined by ^{1}H NMR spectroscopy. Only the diol **3a** was converted to its di-MPA ester in order to determine its absolute configuration, and therefore, the absolute configuration of **3ai** was assigned too.[15]

Because of symmetry reasons (plane of symmetry), in all but one of the substrates shown in Table 1, both carbonyl carbons are enantiotopic and chemically equivalent in a nonchiral environment. However, in the asymmetric biocatalytic environment, a regio- and stereoselective reduction of the keto group leads to the formation of a single diastereomer of the corresponding hydroxy ketone. In the case of substrate **3**, the two keto groups are chemically different (diastereotopic) because of the nonsymmetrical structure of the molecule. In this case, two diastereomers would have been expected to be formed. However, only one stereoisomer (**3a** or **3ai**) was formed with high chemical yield and optical purity. This interesting result was rationalized by the equilibrium between the two enantiomeric diketones **3*S*** and **3*R***, through their enolate tautomers, under the enzymatic reaction conditions. This example illustrates impressively the application of dynamic kinetic resolution (Scheme 1).[16] In this case, we were able to synthesize both possible stereoisomers of the final product under the proper selection of the second enzyme (Kred-101 or Kred-A1B).

In conclusion, a straightforward and quantitative method has been demonstrated for the synthesis of high valuable synthons, with less waste and greater economic benefits. This is an environmentally benign process, where NADPH-dependent ketoreductases were utilized for two-step, one-pot enzymatic reduction of 2-alkyl 1,3-diketones. These enzymes proved excellent catalysts for the stereoselective preparation of optically pure 2-substituted 1,3-diols. They were able to catalyze the formation of chiral diols by cascade addition in the same reaction buffer without isolation of the intermediate β-hydroxy ketones. More importantly, no by-products were identified and the final products were isolated easily without any chromatographic separation.

Experimental Section

General Methods. Enzymes were purchased from Biocatalytics-Codexis. The progress of the enzymatic reactions and the selectivities were determined by gas chromatographical analysis of crude EtOAc extracts and of isolated products, using a gas chromatograph equipped with an FID detector (column: 30 m × 0.25 mm × 0.25 μm chiral capillary column, 20% permethylated (*R*)-cyclodextrin). ^{1}H and ^{13}C NMR spectra were recorded on 300 and 500 MHz spectrometers in $CDCl_3$ solutions using Me_4Si as the internal standard. Chemical shifts are reported in ppm downfield from Me_4Si. Thermo LTQ-OrbitrapXL with an ETD ion trap mass spectrometer was used for the high resolution mass spectra.

Enzymatic Reduction of 1,3-Diketones 1−5. In every enzymatic reaction, diketones **1**−**5** were used as substrates.[14a,c] The reduction was performed as follows. In a phosphate buffer solution (23 mL, 200 mM, pH 6.5 for substrates **1** and **3** or 6.9 for substrates **2**, **4**, and **5**), the 1,3-diketone (75 mM, 200 mg for **1**, 270 mg for **2**, 224 mg for **3**, 245 mg for **4**, and 242 mg for **5**), 20 mg of the corresponding ketoreductase no. 1, 10 mg of glucose dehydrogenase, 10 mg of NADPH, and 500 mg of glucose were added. The reaction was performed at rt until GC analysis of the crude extracts showed a complete reaction. Periodically, the pH was readjusted accordingly to 6.5 or 6.9 with NaOH (2 M). After completion of the first reductive step, the pH was readjusted to 6.9 and to the same buffer solution were added 20 mg of the corresponding ketoreductase no. 2, 10 mg of glucose dehydrogenase, 10 mg of NADPH, and 315 mg of glucose. The second step was also performed at rt until completion of the reaction as shown by GC analysis of the crude extracts. Periodically, the pH was readjusted to 6.9 with NaOH (2 M). The product was isolated by extracting the crude reaction mixture with EtOAc (30 mL × 2). The combined organic layers were then extracted with saturated NaCl solution, dried over $MgSO_4$, and evaporated to dryness. Pure, optically active diols were obtained in 88−92% yield. The products were analyzed by NMR spectroscopy. Their optical purity was determined by chiral GC chromatography using 20% permethylated cyclodextrin column.

(2*S*,4*S*)-3-Methyl-2,4-pentanediol (diol 1a): isolated yield 88% (182 mg); NMR δ_H (500 MHz; $CDCl_3$; Me_4Si) 4.08−4.14 (1H, m, C*H*OH), 3.83−3.89 (1H, m, C*H*OH), 2.81 (2H, bs, OH), 1.54−1.61 (1H, m, CH), 1.24 (3H, d, J = 6.5 Hz, Me), 1.19 (3H, d, J = 6.5 Hz, Me), 0.88 (3H, d, J = 7.0 Hz, Me); NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 71.0, 69.7, 44.5, 22.1, 19.0, 12.2; HRMS (ESI) calcd for $C_6H_{14}O_2$ m/z (M + H) 119.1072, obsd 119.1064; GC data (column: 30 m × 0.25 mm × 0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C isothermal; carrier gas: N_2, press 85 kPa); t_R = 8.51 min.

(2*S*,4*S*)-3-Allyl-3-methyl-2,4-pentanediol (diol 2a): isolated yield 91% (252 mg); NMR δ_H (500 MHz; $CDCl_3$; Me_4Si) 5.87−5.96 (1H, m, C*H*=CH_2), 5.08−5.16 (2H, m, CH=CH_2), 3.94−4.00 (1H, m, C*H*OH), 3.85−3.92 (1H, m, C*H*OH), 3.16 (1H, bs, OH), 2.74 (1H, bs, OH), 2.41−2.47 (1H, m, CH_2), 1.92−1.98 (1H, m, CH_2), 1.21 (3H, d, J = 6.5 Hz, Me), 1.17 (3H, d, J = 6.5 Hz, Me), 0.82 (3H, s, CCH_3); NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 134.9, 117.7, 73.0, 72.6, 42.7, 36.9, 19.1, 17.5, 17.4; HRMS (ESI) calcd for $C_9H_{18}O_2$ m/z (M + H) 159.1385, obsd 159.1377; GC data (column: 30 m × 0.25 mm × 0.25 μm chiral capillary column, 20% permethylated cyclodextrin 160 °C isothermal; carrier gas: N_2, press 85 kPa); t_R = 9.08 min.

(2*S*,3*R*,4*S*)-3-Methyl-2,4-hexanediol (diol 3a): isolated yield 90% (208 mg); NMR δ_H (500 MHz; $CDCl_3$; Me_4Si) 4.09−4.17 (1H, m, C*H*OH), 3.55−3.63 (1H, m, C*H*OH), 2.84 (1H, bs, OH), 2.72 (1H, bs, OH), 1.48−1.66 (3H, m, CH_3CH_2, C*H*), 1.18 (3H, d, J = 7.0 Hz, Me), 0.96 (3H, t, J = 7.5 Hz, Me), 0.91 (3H, d, J = 7.0 Hz, Me); NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 76.7, 69.2, 41.9, 28.1, 19.5, 11.9, 9.8; HRMS (ESI) calcd for $C_7H_{16}O_2$ m/z (M + H) 133.1229, obsd 133.0758; GC data (column: 30 m × 0.25 mm × 0.25 μm chiral capillary column, 20% permethylated cyclodextrin 130 °C isothermal; carrier gas: N_2, press 85 kPa); t_R = 11.63 min.

(2*S*,3*R*,4*R*)-3-Methyl-2,4-hexanediol (diol 3ai): isolated yield 85% (193 mg); NMR δ_H (500 MHz; $CDCl_3$; Me_4Si) 4.06−4.13 (1H, m, C*H*OH), 3.75−3.80 (1H, m, C*H*OH), 2.55 (1H, bs, OH), 2.40 (1H, bs, OH), 1.41−1.60 (3H, m, CH_3CH_2, C*H*), 1.20 (3H, d, J = 6.5 Hz, Me), 0.93 (3H, t, J = 7.5 Hz, Me), 0.91 (3H, d, J = 7.0 Hz, Me); NMR δ_C (75 MHz; $CDCl_3$; Me_4Si) 78.7, 72.9, 41.4,

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28.2, 21.5, 10.4, 3.8; HRMS (ESI) calcd for $C_7H_{16}O_2$ m/z (M + H) 133.1229, obsd 133.1220; GC data (column: 30 m × 0.25 mm × 0.25 μm chiral capillary column, 20% permethylated cyclodextrin 130 °C isothermal; carrier gas: N_2, press 85 kPa); t_R = 10.83 min.

(2*S*,4*S*)-3-Ethyl-3-methyl-2,4-pentanediol (diol 4a): isolated yield 90% (224 mg); NMR δ_H (500 MHz; $CDCl_3$; Me_4Si) 3.95−3.99 (1H, m, C*H*OH), 3.90−3.94 (1H, m, C*H*OH), 3.02 (1H, bs, OH), 2.97 (1H, bs, OH), 1.59−1.66 (2H, m, CH_2CH$_3$), 1.18 (3H, d, J = 6.5 Hz, Me), 1.16 (3H, d, J = 6.5 Hz, Me), 0.88 (3H, t, J = 7.5 Hz, CH$_2$CH_3), 0.80 (3H, s, CCH_3); NMR δ_C(75 MHz; $CDCl_3$; Me_4Si) 73.0, 72.4, 41.9, 24.5, 18.2, 17.7, 17.6, 7.6; HRMS (ESI) calcd for $C_8H_{18}O_2$ m/z (M + H) 147.1385, obsd 147.1378; GC data (column 30 m × 0.25 mm × 0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C isothermal; carrier gas: N_2, press 85 kPa); t_R = 11.43 min.

(2*S*,4*S*)-3-Allyl-2,4-pentanediol (diol 5a): isolated yield 92% (228 mg); NMR δ_H(500 MHz; $CDCl_3$; Me_4Si): 5.76−5.86 (1H, m, CH=CH$_2$), 5.02−5.11 (2H, m, CH=CH_2), 4.23−4.28 (1H, m, C*H*OH), 4.01−4.06 (1H, m, C*H*OH), 2.97 (1H, bs, OH), 2.67 (1H, bs, OH), 2.21−2.28 (1H, m, CH$_2$), 2.07−2.14 (1H, m, CH$_2$), 1.43−1.49 (1H, m, CH), 1.27 (3H, d, J = 6.5 Hz, Me), 1.22 (3H, d, J = 6.5 Hz, Me); NMR δ_C(75 MHz; $CDCl_3$; Me_4Si) 137.4, 116.3, 69.1, 67.7, 48.8, 30.8, 22.1, 19.4; HRMS (ESI) calcd for $C_8H_{16}O_2$ m/z (M + H) 145.1229, obsd 145.1216; GC data (column: 30 m × 0.25 mm × 0.25 μm chiral capillary column, 20% permethylated cyclodextrin 140 °C isothermal; carrier gas: N_2, press 85 kPa); t_R = 12.10 min.

Preparation of MPA Diester of (2*S*,3*R*,4*S*)-3-Methyl-2,4-hexanediol, 3a. To a solution of the corresponding diol (0.1 mmol, 13 mg) in dry CH_2Cl_2 were added 2.2 equiv of DCC (0.22 mmol, 46 mg), 2.2 equiv of the corresponding (*R*)- or (*S*)-MPA ester (0.22 mmol, 36 mg), and a catalytic amount of DMAP, and the reaction mixture was stirred at 0 °C for 6 h and at rt for 12 h. After completion of the reaction, the produced urea was filtered, and the filtrate was evaporated and then chromatographed with 5/1 (v/v), Hex/EtOAc, producing the corresponding MPA diester (38 mg, 90% isolated yield).

(*R*,*R*)-MPA diester of (2*S*,3*R*,4*S*)-3-Methyl-2,4-hexanediol: NMR δ_H (500 MHz; $CDCl_3$; Me_4Si): 7.28−7.45 (10H, m, 2 × CHC$_6H_5$), 5.04−5.09 (1H, m, C*H*O$_2$C), 4.77−4.82 (1H, m, C*H*O$_2$C), 4.76 (1H, s, C*H*OMe), 4.75 (1H, s, C*H*OMe), 3.45 (3H, s, OMe), 3.44 (3H, s, OMe), 1.72−1.79 (1H, m, C*H*CH$_3$), 1.44−1.53 (1H, m, CH_2), 1.25−1.38 (1H, m, CH_2), 1.02 (3H, d, J = 6.0 Hz, CH_3CHO$_2$C), 0.83 (3H, d, J = 7.0 Hz, CH_3CH), 0.43 (3H, t, J = 7.5 Hz, CH_3CH$_2$).

(*S*,*S*)-MPA diester of (2*S*,3*R*,4*S*)-3-Methyl-2,4-hexanediol: δ_H (500 MHz; $CDCl_3$; Me_4Si) 7.29−7.42 (10H, m, 2×CHC$_6H_5$), 4.67−4.72 (1H, m, C*H*O$_2$C), 4.69 (1H, s, C*H*OMe), 4.66 (1H, s, C*H*OMe), 4.45−4.50 (1H, m, C*H*O$_2$C), 3.40 (3H, s, OMe), 3.39 (3H, s, OMe), 1.59−1.65 (1H, m, C*H*CH$_3$), 1.23−1.32 (2H, m, CH_2), 1.09 (3H, d, J = 6.0 Hz, CH_3CHO$_2$C), 0.64 (3H, t, J = 7.5 Hz, CH_3CH$_2$), 0.55 (3H, d, J = 7.0 Hz, CH_3CH).

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.