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One-Pot Enzymatic Synthesis of Cyclic Vicinal Diols from Aliphatic Dialdehydes via Intramolecular C−C Bond Formation and Carbonyl Reduction Using Pyruvate Decarboxylases and Alcohol Dehydrogenases

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Abstract. An enzymatic cascade reaction was developed for one-pot enantioselective conversion of aliphatic dialdehydes to chiral vicinal diols using pyruvate decarboxylases (PDCs) and alcohol dehydrogenases (ADHs). The PDCs showed promiscuity in catalysing the cyclization of aliphatic dialdehydes through intramolecular stereoselective carbon−carbon bond formation. Consequently, 1,2-cyclopentanediols in three different stereoisomeric forms and 1,2-cyclohexanediols in two different stereoisomeric forms could be prepared with high conversion and stereoisomeric ratio from the respective initial substrates, glutaraldehyde and adipaldehyde. These cascade reactions represent a promising approach to the biocatalytic synthesis of important chiral vicinal diols.

Keywords: Intramolecular stereoselective carboligation; cascade biocatalysis; ThDP-dependent enzyme; α-hydroxy ketone; vicinal diol

Introduction

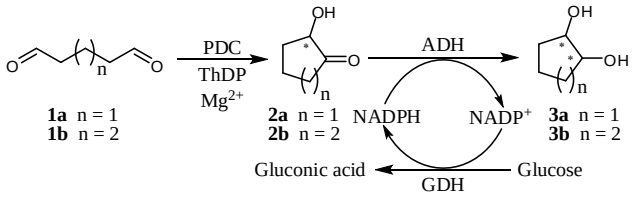
Intramolecular stereoselective carbon−carbon bond formation is a useful strategy to construct cyclic molecules with chiral center in synthetic organic chemistry. Numerous approaches have been developed previously, such as aldol reactions catalyzed by proline and its derivatives,[1] Michael reactions catalyzed by chiral amines,[2] cation−olefin reactions,[3] and benzoin reactions catalyzed by *N*-heterocyclic carbenes.[4] In addition to chemical methods, biocatalytic intramolecular cyclizations involving the formation of C-C bonds have also achieved, e.g., squalene-hopene cyclases, Pictet−Spenglerases, berberine bridge enzyme, and terpene synthase.[5] However, the asymmetric intramolecular carboligation reactions catalyzed by thiamine diphosphate (ThDP)-dependent enzymes had less been developed. Recently, Clapés *et al.* reported the intramolecular benzoin reaction between aromatic and heteroaromatic moieties connected by a spacer containing ether bonds, which was catalyzed by a ThDP-dependent benzaldehyde lyase.[6] Yields of the intramolecular products greater than 60% and *ee* values between 64% and 98% were reported.

Cyclic α-hydroxy ketones are very valuable chiral building blocks and pharmaceutical ingredients.[7] For their synthesis, various chemical methods have been reported, such as intramolecular acyloin condensation of dimethyl ester[8] and hydroxylation of cyclic ketones by hypervalent iodine compounds.[9] Recently, Reetz *et al.* reported the conversion of cyclohexane, cyclohexanol or cyclohexanone through three steps, two steps or one step to form 2-hydroxycyclohexanone (**2b**) using P450-BM3 monooxygenase from *Bacillus megaterium*.[10] Alcohol dehydrogenases BDHA (2,3-butanediol dehydrogenase from *Bacillus subtilis* BGSC1A1) was engineered as an efficient biocatalyst for the stereoselective oxidation of 1,2-cyclopentanediol (**3a**) and 1,2-cyclohexanediol (**3b**) to the corresponding cyclic (*R*)-α-hydroxy ketones.[11]

Chiral **3a** are the key intermediates for the preparation of chiral ligands of enantioselective catalysts and hepatitis C virus NS3-NS4A protease inhibitors.[12] Chiral **3b** could be applied as a chiral auxiliary,[13] in addition to serving as a starting material for the synthesis of several anticancer compounds.[14] Various synthetic methods of chiral vicinal diols have been reported, e.g., intramolecular pinacol coupling in the presence of SmI_2, Bu_3SnH or

Cp_2TiPh,[15] and olefins oxidation using $KMnO_4$, H_2O_2 in the presence of resin-supported sulfonic acid catalyst or polysulfone-based microencapsulated osmium tetroxide.[16] In addition, alkanes could be selectively converted to vicinal *cis*-diols under transition-metal-free and ambient reaction conditions.[17] Remarkably, vinyl boronate diboration was shown to have the ability to accommodate alkyl halide substituents. This enabled the construction of vicinal diols from 1,1,2-tris(boronates).[18] Owing to the excellent features of biotransformation,[19] some biocatalytic systems for the synthesis of vicinal diols had been developed. For instance, epoxide hydrolases from *Rhodococcus erythropolis* DCL 14(LEH), *Aspergillus niger* (ANEH) and *Sphingomonas sp*. HXN-200 (SpEH) or their mutants were used for enantioselective hydrolysis of *cis*-epoxides to give chiral vicinal diols.[20] Reetz *et al.* developed a new approach to synthesize chiral **3b** from cyclohexane, cyclohexanol, or cyclohexanone using *Escherichia coli* cells co-expressing P450-BM3 mutants and alcohol dehydrogenases (ADHs).[10]

ThDP-dependent PDC (EC 4.1.1.1) is a rather well established family of enzymes in the making and breaking of C-C bonds,[21] which has been combined with ADHs to synthesize the acyclic vicinal chiral diols.[22] Herein, we explored the new utilization of ThDP-dependent PDCs that catalyzed the cyclization of aliphatic dialdehydes to α-hydroxyketones through intramolecular stereoselective carboligation. Subsequently, the asymmetric reduction of α-hydroxyketones to chiral vicinal diols catalyzed by ADHs together with a conventional glucose dehydrogenase (GDH)-driven NADPH regeneration system was also investigated (**Scheme 1**).



Scheme 1. One-pot two-step enzymatic synthesis of chiral vicinal diols from aliphatic dialdehydes via cascade biocatalysis using PDC, ADH, and GDH.

Results and Discussion

The protein sequence of a well characterized ThDP-dependent pyruvate decarboxylase from *Zymomonas mobilis* (ZmPDC) with a broad substrate specificity[23] and solved tertiary structure[24] was used as a query sequence in BLAST searches. According to the sequence similarity (30%-70%), twelve hypothetical PDC candidates were selected (**Table S1** in the Supporting Information). We also made a phylogenetic tree showing the relationship between the new enzymes described herein and the literature-reported ThDP-dependent enzymes. The comparison shows that the selected enzymes are generally not on the same branch with most of ThDP-dependent enzymes which have been reported (**Figure S1** in the Supporting Information). The respective synthetic genes including that of ZmPDC were expressed in *E. coli*.

After initial screening, six out of the thirteen phylogenetically-different PDCs were found to catalyze the cyclization of glutaraldehyde (**1a**) to give 2-hydroxycyclopentanone (**2a**) (**Table 1**), and adipaldehyde (**1b**), which could be prepared from cyclohexene by ozonation,[25] to give 2-hydroxycyclohexanone (**2b**) (**Table 2**). They were ZmPDC and five new enzymes (SpPDC from *Streptococcus pneumoniae*, CbPDC from *Corynebacterium bouchesdurhonense*, GmPDC from *Gimesia maris*, AmPDC from *Acidomonas methanolica* NBRC 104435 and AsPDC from *Ancylobacter sp.* FA202). Depending on the biocatalyst, the substrate conversion and stereoselectivity by GC analysis revealed that glutaraldehyde (**1a**) conversion to 2-hydroxycyclopentanone (**2a**) could reach 65% *ee* value in the case of AsPDC, and up to 96% conversion in the case of ZmPDC (**Table 1**). The *ee* value of the product decreased with time. By virtue of an *ee* value in excess of 30%, five of the PDCs with the exception of AmPDC are regarded as catalytically useful for the designated carboligation. Although no catalyst could give excellent *ee* values, ZmPDC appeared to be the best performing enzyme.

Interestingly, adipaldeyde (**1b**) could be cyclized to form 2-hydroxycyclohexanone (**2b**) in good *ee* value (>91%) in most of the cases, and the conversion by SpPDC was up to 99% (**Table 2**). Unlike **2a**, the *ee* value of **2b** did not change within 20 h. From the results, it can be seen that the enzyme activity and stereoselectivity of the same PDC appear to be substrate dependent. For instance, SpPDC catalyzed the cyclization of adipaldehyde (**1b**) to form 2-hydroxycyclohexanone (**2b**) in 99% conversion and 91% *ee* value after 20 hours of incubation, whereas the conversion and *ee* value for glutaraldehyde (**1a**) were only 36% and 55%, respectively (**Table 1** and **Table 2**). Conversely, ZmPDC could catalyze the conversion of glutaraldehyde (**1a**) to 2-hydroxycyclopentanone (**2a**) in 96% conversion and 46% *ee* value, while those were 82% and 91% for adipaldehyde (**1b**) respectively (**Table 1** and **Table 2**). Clearly, both the number of methylene in the dialdehyde substrates and the available enzymes affect the conversion and stereoselectivity of the intramolecular cyclization. Interestingly, the tested PDCs towards **1a** or **1b** are predominantly *R*-selective, which is consistent with the results of intermolecular C−C bond formation catalyzed by PDCs.[21c] Although the *ee* values of the various products can be improved by enzyme engineering further,[21c, 26] the present results provide us a new approach and sound basis for the synthesis of cyclic α-hydroxy ketones through biocatalytic

intramolecular C−C bond formation catalyzed by PDCs.

Table 1. Intramolecular stereoselective carboligation of glutaraldehyde (**1a**) to 2-hydroxycyclopentanone (**2a**) catalyzed by PDCs.

Enzymes	10 h[a)]		20 h[a)]	
	ee (%)[b)]	Conv.(%) [b)]	*ee* (%)[b)]	Conv.(%) [b)]
SpPDC	55(*R*)	15	55(*R*)	36
CbPDC	47(*R*)	12	59(*R*)	22
GmPDC	36(*R*)	20	31(*R*)	35
AsPDC	65(*R*)	60	59(*R*)	82
AmPDC	5(*R*)	62	7(*R*)	82
ZmPDC	55(*R*)	92	46(*R*)	96

[a)] Reaction conditions: 0.1 mM ThDP, 2.5 mM $MgSO_4$, 10 mM glutaraldehyde, 1 mg/ml purified enzymes, 50 mM potassium phosphate buffer (pH 6.5), 30°C. [b)] The conversion and *ee* of 2-hydroxycyclopentanone (**2a**) were determined by GC analysis.

Table 2. Intramolecular stereoselective carboligation of adipaldehyde (**1b**) to 2-hydroxycyclohexanone (**2b**) catalyzed by PDCs.

Enzymes	10 h[a)]		20 h[a)]	
	ee (%)[b)]	Conv.(%) [b)]	*ee* (%)[b)]	Conv.(%) [b)]
SpPDC	91(*R*)	97	91(*R*)	99
CbPDC	91(*R*)	12	90(*R*)	37
GmPDC	84(*R*)	59	87(*R*)	74
AsPDC	91(*R*)	74	90(*R*)	85
AmPDC	91(*R*)	56	91(*R*)	68
ZmPDC	91(*R*)	75	91(*R*)	82

[a)] Reaction conditions: 0.1 mM ThDP, 2.5 mM $MgSO_4$, 10 mM adipaldehyde (**1b**), 1 mg/ml purified enzymes, 50 mM potassium phosphate buffer (pH 6.5), 30°C. [b)] The conversion and *ee* of 2-hydroxycyclohexanone (**2b**) were determined by GC analysis.

With these results in hand, the cascade reaction from aliphatic dialdehydes to chiral vicinal diols was investigated using PDCs and ADHs. Identities of 24 ADH candidates availabe in our laboratory can be found in **Table S3** in the Supporting Information. **2a** obtained with ZmPDC and **2b** obtained with SpPDC were used as the substrate for the bioreduction. Screening of the 24 ADH enzymes at a substrate concentration of 10 mmol/L gave rise to different configuration forms of **3a** and **3b** (**Table S4** and **S5** in the Supporting Information). A typical format in these reactions is that after **1a** was completely converted to the intermediate **2a** catalyzed by ZmPDC, various ADHs were added to the reactions. All three stereoisomeric diols were obtained with high to comparable enantio- and diastereoselectivity on an optional basis. Notable results are shown in **Table 3**. CMCR of *Candida* origin provided *cis*-**3a** ((1*S*, 2*S*)/(1*R*, 2*R*)/*cis* =1/15/84), whereas the TbADH of *Thermoethanolicus brockii* and BDHA of *Bacillus subtilis* favored (1*R*, 2*R*)-**3a** ((*1S, 2S*)/(*1R, 2R*)/*cis* = 1/82/17 and 0/91/9). Although *trans*-**3a** only accounted for 40% of production catalyzed by PfADH (*Pyrococcus furiosus*) , *trans*-**3a** was mainly (*S,S*)-**3a** ((*1S, 2S*)/(*1R, 2R*)/*cis* = 40/0/60) (**Table 3**).

To synthesize **3b**, SpPDC was used in conjunction with the 24 ADHs and the results are presented in **Table S5** in the Supporting Information. As shown in **Table 4**, *cis*-and (1*R*, 2*R*)-**3b** were obtained with high diastereo- and enantioselectivity on an optional basis. The SpPDC and CMCR or PfADH cascade provided *cis*-**3b** whereas the following combinations of SpPDC with TbADH, SpPDC with YMR226c, SpPDC with BDHA, and SpPDC with ReADH favored (1*R*, 2*R*)-**3b** (**Tables 3 and 4**).

Table 3. One-pot two-step enantioselective conversion of **1a** to **3a** catalyzed by ZmPDC and ADHs. [a, b)]

ADHs	(1*S*, 2*S*)/(1*R*, 2*R*)/*cis*	Conv.(%)
CMCR	1/15/84	99
TbADH	1/82/17	99
BDHA	0/91/9	99
PfADH	40/0/60	98

[a)] The conversion and absolute configuration were determined by GC analysis. [b)] Reaction conditions: 1 ml 50 mM potassium phosphate buffer (pH 6.5) containing 0.1 mM ThDP, 2.5 mM $MgSO_4$, 10 mM **1a**, 1 mg/mL purified enzymes, 30°C and 200 rpm for 20h. Then 2 mg GDH (0.4 U/mg), 30 μmol glucose, 50 mU ADHs purified protein, 0.5 mg $NADP^+$ or NAD^+ , pH8.0, 30°C for 20 h. [c)] Not applicable.

Table 4. One-pot two-step enantioselective conversion of **1b** to **3b** catalyzed by *Sp*PDC and ADHs. [a, b)]

ADHs	(1*S*, 2*S*)/(1*R*, 2*R*)/*cis*	Conv.(%)
CMCR	3/0/97	99
TbADH	0/97/3	99
PfADH	8/0/92	99
YMR226c	5/95/0	99
BDHA	2/94/4	99
ReADH	2/92/6	94

[a)] The conversion and absolute configuration were determined by GC analysis. [b)] Reaction conditions: 1 ml 50 mM potassium phosphate buffer (pH 6.5) containing 0.1 mM ThDP, 2.5 mM $MgSO_4$, 10 mM **1b**, 1 mg/mL purified enzymes, 30°C and 200 rpm for 20h. Then 2 mg GDH (0.4 U/mg), 30 μmol glucose, 50 mU ADHs purified protein, 0.5 mg $NADP^+$ or NAD^+ , pH8.0, 30°C for 20 h. [c)] Not applicable.

It could also be shown that the intramolecular C−C bond formation could be achieved without loss of enantioselectivity by employing *E. coli* whole cells harboring PDC genes. Therefore, the applicability of this new type of cascade biocatalysis was examined at laboratory-preparative scale by using PDCs wet cells and purified ADHs in a 100 mL-scale reaction at a substrate concentration of 10 mmol/L. *Cis*-**3a** and **3b** were obtained by the combinations of ZmPDC or SpPDC with CMCR in 56% and 68% isolated yields, respectivley. The ZmPDC and BDHA combination

for the cascade conversion of **1a** gave (1*R*, 2*R*)-**3a** in 98% *ee* and *trans*/*cis* = 96:4 with 48% isolated yield, while SpPDC and TbADH for **1b** gave (1*R*, 2*R*)-**3b** in 99% *ee* and *trans*/*cis* > 99:1 with 71% isolated yield. Although the conversion into the desired products were essentially quantitative, some compounds were lost during workup, probably as a result of their excellent water solubility.

Conclusion

We found that PDCs could catalyze aliphatic dialdehydes to form cyclic α-hydroxy ketone through intramolecular asymmetric C-C bond formation. One-pot two-step process was also developed to synthesize chiral cyclopentane-1,2-diols from glutaraldehyde (**1a**) and chiral cyclohexane-1,2-diols from adipaldehyde (**1b**) using PDCs and ADHs. Three different stereoisomeric forms of cyclopentane-1,2-diols and cyclohexane-1,2-diols were accessible in high conversion and stereoisomeric ratio. This study provides the first example for synthesis of chiral cyclopentane-1,2-diols and cyclohexane-1,2-diols from glutaraldehyde (**1a**) and adipaldehyde (**1b**), respectively. In addition, alternative substrate-coupled cofactor regeneration may make this approach more economical and feasible.[22a] Further protein engineering of selected PDCs is underway in our laboratory to reveal the stereoselective mechanism of intramolecular asymmetric C-C bond formation.

Experimental Section

Materials

Glutaraldehyde and adipaldehyde were purchased from J&K Scientific. 2-Hydroxycyclohexanone dimer, thiamine pyrophosphate and (±)-*trans*-cyclohexane-1, 2-diol were purchased from Aladdin Industrial Corporation. (±)-*Trans*-cyclopexane-1,2-diol and *cis*-cyclopexane-1, 2-diol were purchased from Sigma-Aldrich Corporation. *Cis*-cyclohexane-1,2-diol was purchased from ACROS ORGANICS. DifcoTM LB (Luria-Bertani) Broth, Miller was purchased from Becton Dickinson and Company. Ampicilin was purchased from Beijing Probe Bioscience Co., Ltd. Isopropyl β-D-1-thiogalactopyranoside (IPTG) was purchased from AMRESCO Inc. All other chemicals were purchased from Sinopharm Chemical Reagent Co., Ltd. The GC analysis was performed on an Agilent 7890A GC system. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 600 MHz NMR spectrometer. Purified GDH from *Bacillus megaterium* and various ADHs were stored in our laboratory.

Construction of the Expression Vectors

The ZmPDC gene was amplified from *Zymomonas mobilis* genomic DNA and cloned into plasmid pET21a with C-terminal 6×His-tag.

Nucleotide sequences of PDC genes were obtained from the National Center for Biotechnology Information (NCBI) GeneBank® using ZmPDC gene as a query sequence. Twelve putative PDC genes were selected in this study. The gene sequences were optimized based on the codon bias of *E. coli* (see Supporting Information), synthesized by GENEWIZ Suzhou (China), and cloned into pET21a-vector containing a C-terminal His-tag (**Table S1** in the Supporting Information).

Expression and Purification of PDCs

The plasmids were transformed into *E. coli* BL21(DE3) cells. Recombinant *E. coli* BL21(DE3) was propagated in 1 L of LB medium containing 1 mM ampicillin at 25°C or 30°C (**Table S2** in the Supporting Information). The culture was induced by addition of IPTG with a final concentration of 0.0 to 1.0 mM when the optical density (λ=600 nm) reached 0.25 and then incubated for additional 12 h or 20 h at 25°C or 30°C with 200 rpm. After centrifugation at 6000 ×*g* and 4°C for 20 min and the recombinant cells were suspended in 100 mL of 50 mM potassium phosphate buffer containing 2.5 mM $MgSO_4$ and 0.1 mM ThDP and lysed by French press at an operating pressure of 12000 psi. The cell debris was removed by centrifugation at 10,000×*g* for 30 min at 4°C. The resulting cell-free extract were purified by Ni-NTA-chromatography (washing buffer: 50 mM potassium phosphate buffer, pH 6.5, 50 mM imidazole, 500 mM NaCl), elution buffer: 50 mM potassium phosphate buffer, pH 6.5, 500 mM imidazole, 500 mM NaCl)). The target protein fraction was collected and desalted by dialysis with 50 mM potassium phosphate buffer (pH 7.0) and ultrafiltration at 4000 ×*g* and 4°C for 30 min. Protein concentration was measured using the Bradford method.[27] These enzymes were diluted with 30% (V/V) glycerol and stored at -80°C.

Biosynthesis of 2-Hydroxycyclopentanone and 2-Hydroxycyclohexanone

The tested PDC (1 mg/mL purified enzyme) was added into 1 mL 50 mM potassium phosphate buffer (pH 6.5) containing 10 mM glutaraldehyde (**1a**) or adipaldehyde (**1b**), 0.1 mM ThDP and 2.5 mM $MgSO_4$. The reaction mixture was incubated at 30°C, 200 rpm for 24 h and extracted with ethyl acetate. The conversion and *ee* value of 2-hydroxycyclopentanone (**2a**) and 2-hydroxycyclohexanone (**2b**) were determined by GC analysis. The absolute configuration was determined by comparing the relative retention times of the reference (**Table S6** in the Supporting Information).[11]

Cascade Reactions to Synthesize Cyclopentane-1,2-diol (3a) and Cyclohexane-1,2-diol (3b)

Glutaraldehyde (**1a**) and adipaldehyde (**1b**) were used as substrates for ZmPDC and SpPDC, respectively. The purified enzyme (1 mg/mL) was added to 1 mL 50 mM potassium phosphate buffer (pH 6.5) containing 10 mM **1a** or **1b**, 0.1 mM ThDP and 2.5 mM $MgSO_4$. The reactions were performed at 30°C and 200 rpm and monitored by GC analysis. After **1a** or **1b** was consumed, the reaction pH was adjusted to 8.0 with 1 M NaOH. Then 30 mM glucose, 0.5 mg of $NADP^+$ or NAD^+, 50 mU purified ADHs (One unit of activity was defined as the amount of enzyme that converted 1 μmol of NAD(P)H to $NAD(P)^+$ per minute using acetophenone as substrate at 30°C) and 2 mg GDH (0.4 U/mg) were added into reaction mixtures. The reaction was performed at 30°C and 200 rpm. The conversion and *ee* of cyclopentane-1,2-diol and cyclohexane-1,2-diol were determined by GC analysis. The absolute configuration was determined by comparing the relative retention times of the reference (**Tables S4 and S5** in the Supporting Information).[11]

Laboratory-Preparative Scale Synthesis of Chiral *trans*-3a/3b and *cis*-3a/3b

General procedure for the synthesis of 1,2-cyclopentanediols (**3a**) and 1,2-cyclohexanediols (**3b**) was carried out as follows: The biosynthesis of cyclic α-hydroxy ketones (**2a** and **2b**) was performed with fresh wet cells (5.0 g) of recombinant strain *E.coli* (ZmPDC) or

E.coli (SpPDC) in 100 mL potassium phosphate buffer (pH 6.5, 50 mM) containing dialdehyde (1.00 mmol of **1a** or **1b**), ThDP (5 mg, 0.01 mmol) and $MgSO_4$ (62 mg, 0.25 mmol). The reactions were performed at 30°C and 200 rpm and monitored by GC analysis. After dialdehyde reacted completely, the pH of the reaction mixtures was adjusted to 8.0 with 1 M NaOH. Then glucose (595 mg, 3.00 mmol), 25 mg of $NADP^+$ or NAD^+, 20 U of purified ADHs, GDH (200 mg, 80 U) were added into the reaction mixtures. The reactions were performed at 200 rpm and 30°C and monitored by GC analysis. Once the reaction was finished, the reaction solution was centrifuged to remove precipitate, and the solutions were saturated with NaCl and extracted with *n*-butyl alcohol (100 mL×3) three times. The combined organic extracts were dried over Na_2SO_4, filtered and evaporated in vacuo. The desired product was obtained after purification by column silica gel chromatography.

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