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Production of dicarboxylic acids from novel unsaturated fatty acids by laccase-catalyzed oxidative cleavage

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The establishment of renewable biofuel and chemical production is desirable because of global warming and the exhaustion of petroleum reserves. Sebacic acid (decanedioic acid), the material of 6,10-nylon, is produced from ricinoleic acid, a carbon-neutral material, but the process is not eco-friendly because of its energy requirements. Laccase-catalyzing oxidative cleavage of fatty acid was applied to the production of dicarboxylic acids using hydroxy and oxo fatty acids involved in the saturation metabolism of unsaturated fatty acids in *Lactobacillus plantarum* as substrates. Hydroxy or oxo fatty acids with a functional group near the carbon–carbon double bond were cleaved at the carbon–carbon double bond, hydroxy group, or carbonyl group by laccase and transformed into dicarboxylic acids. After 8 h, 0.58 mM of sebacic acid was produced from 1.6 mM of 10-oxo-*cis*-12,*cis*-15-octadecadienoic acid (αKetoA) with a conversion rate of 35% (mol/mol). This laccase-catalyzed enzymatic process is a promising method to produce dicarboxylic acids from biomass-derived fatty acids.

Key words: dicarboxylic acid; laccase; unsaturated fatty acid; hydroxy fatty acid; oxo fatty acid

Global warming and the exhaustion of petroleum reserves necessitate the establishment of an environmentally friendly way of producing renewable biofuels and chemicals. Over the past 10 years, scientific and technological advances have established biocatalysis as a practical and environmentally friendly alternative to traditional chemical synthesis, both in the laboratory and on an industrial scale. For instance, biocatalytic processes for the synthesis of succinic acid, 1,4-butanediol, 1,3-propanediol and biodiesel were developed[1–4] and won Green Chemistry Challenge Awards. However, it is difficult to produce oxygenated long-chain carboxylic acids because of stringent regulation of the carbon chain length and the thermodynamically unfavorable nature of ω-hydroxylation.[3,5] Long-chain dicarboxylic acids and hydroxy fatty acids are used for several polymers (e.g. polyamides and polyesters), plasticizers, lubricants, and perfumes. For instance, sebacic acid (1,10-decanedioic acid) is the material of 6,10-nylon, a polyamide representative, and is derived from biomass. Several ten thousand tons of sebacic acid are transferred from ricinoleic acid (12-hydroxy-*cis*-9-octadecenoic acid), which is abundant in castor oil, a well-known carbon-neutral compound. However, the chemical process for producing sebacic acid requires a huge amount of energy, involving alkaline conditions with high temperature and pressure.[6] Therefore, it is desirable to establish an eco-friendly process for producing dicarboxylic acids such as sebacic acid.

In a previous study, we revealed the polyunsaturated fatty acid saturation metabolism in *Lactobacillus plantarum* AKU 1009a.[7] The saturation metabolism consists of four enzymes: CLA-HY (unsaturated fatty acid hydratase), CLA-DH (hydroxy fatty acid dehydrogenase), CLA-DC (isomerase), and CLA-ER (enone reductase).[8–11] This strain produces *cis*-9,*trans*-11-conjugated linoleic acid (CLA) and *trans*-9,*trans*-11-CLA as byproducts during the saturation of linoleic acid (LA) to oleic acid (OA).[12–14] The application of these enzymes enables us to produce intermediate fatty acids such as 10-hydroxy-*cis*-12-octadecenoic acid (HYA), 10-hydroxyoctadecanoic acid (HYB), 10-oxo-*cis*-12-octadecenoic acid (KetoA), and 10-oxooctadecanoic acid (KetoB) from LA. In addition to LA, α-linolenic acid

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Abbreviations: LA, linoleic acid; OA, oleic acid; CLA, conjugated linoleic acid; NADH, nicotinamide adenine dinucleotide; FAD, flavin adenine dinucleotide; BSA, bovine serum albumin; HBT, 1-hydroxybenzotriazole; TEMPO, 2,2,6,6-tetramethylpiperidine 1-oxyl; ABTS, 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid ammonium salt); GC, gas–liquid chromatography; MS, mass spectrometry; HYA, 10-hydroxy-*cis*-12-octadecenoic acid; HYB, 10-hydroxyoctadecanoic acid; KetoA, 10-oxo-*cis*-12-octadecenoic acid; KetoB, 10-oxooctadecanoic acid; αHYA, 10-hydroxy-*cis*-12,*cis*-15-octadecenoic acid; αKetoA, 10-oxo-*cis*-12,*cis*-15-octadecadienoic acid; γHYA, 10-hydroxy-*cis*-6,*cis*-12-octadecenoic acid; γKetoA, 10-oxo-*cis*-6,*cis*-12-octadecenoic acid.

and γ-linolenic acid are also converted into 10-hydroxy-*cis*-12,*cis*-15-octadecadienoic acid (αHYA) and 10-hydroxy-*cis*-6,*cis*-12-octadecadienoic acid (γHYA) by CLA-HY.[15] These novel fatty acids are potential materials for the production of biopolymers because they are produced from LA, α-linolenic acid, or γ-linolenic acid in biomass-derived oils, and have functional groups such as a hydroxy group or an oxo group.

Laccase belongs to the multi-copper oxidase family and catalyzes four-electron oxidation by reducing oxygen to water.[16,17] *Trametes* sp. Ha-1, the white-rot fungus, shows lignolytic oxidation activity and produces commercial laccase, which has high oxidation activity and thermostability.[18] Laccase can directly oxidize phenolic lignin structures and also non-phenolic lignin compounds in the presence of suitable mediators.[19] For example, the laccase-mediator system is applied to dye-decolorization[20] and rice straw treatment for bioethanol production.[21] In addition, it is reported that azelaic acid (nonanedioic acid) was produced from linoleic acid and oleic acid using laccase mediator system.[22] However the substrates investigated were only common unsaturated fatty acids and there is no report to produce C10 dicarboxylic acid enzymatically. Therefore, in this study, we attempted to establish microbial processes to produce dicarboxylic acids especially for C10 dicarboxylic acid, *e.g.* sebacic acid from biomass-derived fatty acids, for example, ricinoleic acid and intermediate fatty acids, during the saturation of linoleic acid to oleic acid.

Materials and methods

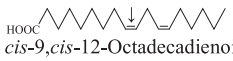
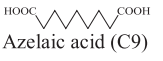
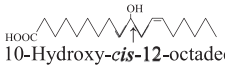
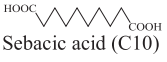
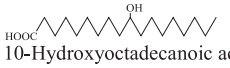
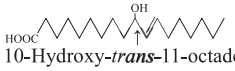
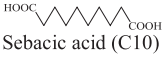
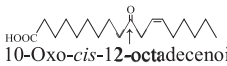
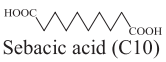
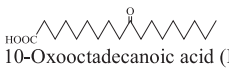
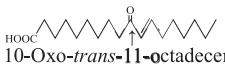
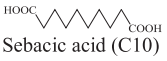
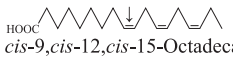
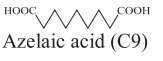
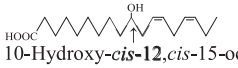
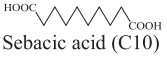
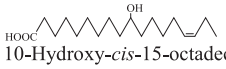
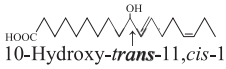
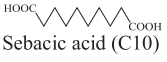
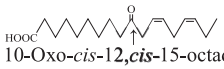
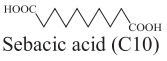
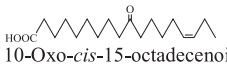
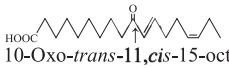
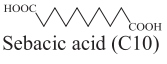
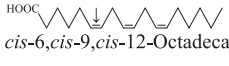
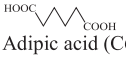
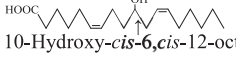
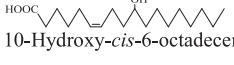
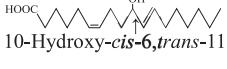
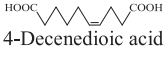
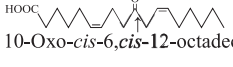
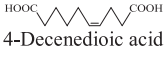
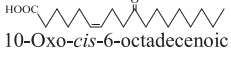
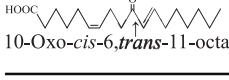
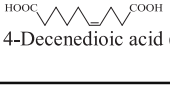
Materials. Laccase (from *Trametes* sp. Ha-1) was purchased from Daiwa Fine Chemicals Co., Ltd. (Kobe, Japan). OA, nicotinamide adenine dinucleotide, flavin adenine dinucleotide, and 1-hydroxybenzotriazole were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). LA and fatty acid-free (<0.02%) bovine serum albumin were purchased from Sigma (St. Louis, MI, USA). α-Linolenic acid and γ-linolenic acid were purchased from Nu-Chek-Prep, Inc. (Elysian, MN, USA). HYA, HYB, αHYA, and γHYA were produced from OA, LA, α-linolenic acid, and γ-linolenic acid, respectively, by *Escherichia coli* Rosetta2/pCLA-HY.[15] 10-Hydroxy-*trans*-11-octadecenoic acid and 10-oxo-*trans*-11-octadecenoic acid were produced from LA as described previously.[7] 10-Hydroxy-*cis*-15-octadecenoic acid, 10-hydroxy-*trans*-11,*cis*-15-octadecadienoic acid, 10-oxo-*cis*-15-octadecenoic acid, and 10-oxo-*trans*-11,*cis*-15-octadecadienoic acid were produced from α-linolenic acid as described previously.[7] 10-Hydroxy-*cis*-6-octadecenoic acid, 10-hydroxy-*cis*-6,*trans*-11-octadecadienoic acid, 10-oxo-*cis*-6-octadecenoic acid, and 10-oxo-*cis*-6,*trans*-11-octadecadienoic acid were produced from γ-linolenic acid as described previously.[7] 10-Oxo-*cis*-12-octadecenoic acid (KetoA), 10-oxooctadecanoic acid (KetoB), 10-oxo-*cis*-12,*cis*-15-octadecadienoic acid (αKetoA), and 10-oxo-*cis*-6,*cis*-12-octadecadienoic acid (γKetoA) were produced from the above hydroxy fatty acids by Jones oxidation, which is oxidation of a hydroxy group with CrO_3.[23]

Reaction conditions. As standard reaction condition, the reaction with laccase was conducted with shaking (300 strokes/min) at 37 °C for 8 h in a test tube (16.5 × 105 mm) that contained 1 mL of reaction mixture (20 mM of sodium acetate buffer, pH 4.0) with 11.3 U/mL laccase, 1.5 mM of αKetoA, and 1 mM of HBT. One unit was defined as the amount of enzyme that catalyzes the oxidation of 1 μmol of 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid ammonium salt) (ABTS) per minute. All experiments were performed in triplicate. For substrate specificity experiments, we prepared 23 kinds fatty acids including hydroxy and oxo fatty acids. Twenty-three different fatty acids were tested under the standard reaction condition except for the substrate and reaction time. Reaction time was 24 h. The concentration of dicarboxylic acids from reaction mixture with αKetoA was defined as 100%. For experiments of mediators effects, 1 mM of six mediators [HBT, benzotriazole, veratryl alcohol, violuric acid, ABTS, 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO)] were used. For experiments of mediator concentration effects, HBT was used with a range of 0–5 mM. For experiments of reaction temperature effects, reaction temperature was 18–52 °C. For experiments of reaction pH effects, sodium acetate buffer, HEPES buffer, and Tris-HCl buffer were used for pH 3–5, 6–7.5, and 7–9, respectively. For time course of sebacic acid production, reaction was conducted with 20 mM of sodium acetate buffer (pH 5.0) at 40 °C for 0–8 h.

Fatty acid analysis. Lipids were extracted from the reaction mixture with ethyl acetate (containing 10% methanol) and then concentrated by evaporation under reduced pressure. The resulting lipids were dissolved in 5 mL of benzene/methanol (3:2, by volume) and methylated with 300 μL of 1% trimethylsilyldiazomethane (in hexane) at 28 °C for 30 min. The resulting fatty acid methyl esters were concentrated by evaporation under reduced pressure and analyzed by gas–liquid chromatography (GC) using a Shimadzu (Kyoto, Japan) gas chromatograph equipped with a flame ionization detector and a split injection system and fitted with a capillary column (SPB-1, 30 m × 0.25 mm I.D.; Supelco, Bellefonte, PA, USA). The column temperature was initially 180 °C for 30 min, was raised to 220 °C at a rate of 40 °C/min, and was then maintained at that temperature for 9 min. The injector and detector were operated at 250 °C. Helium was used as a carrier gas at a flow rate of 1.9 mL/min in the column. Heptadecanoic acid (17:0) was used as an internal standard for quantification.

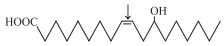
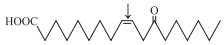
GC-MS analysis. Methyl esters of fatty acids were subjected to GC-MS analysis using GCMS-QP2010 Plus (Shimadzu) with a GC-2010 gas chromatograph. The GC separation of fatty acid methyl esters was performed on an SPB-1 column as described above. The column temperature was initially 180 °C for 30 min, was raised to 220 °C at a rate of 30 °C/min, and was then maintained at that temperature for 40 min. The injector and MS interface were operated at 220 °C.

Table 1. Substrate specificity.

Substrate	Product	Relative activity [%]
 *cis*-9,*cis*-12-Octadecadienoic acid (Linoleic acid)	 Azelaic acid (C9)	19
 10-Hydroxy-***cis*-12**-octadecenoic acid (HYA)	 Sebacic acid (C10)	12
 10-Hydroxyoctadecanoic acid (HYB)	—[c]	
 10-Hydroxy-***trans*-11**-octadecenoic acid	 Sebacic acid (C10)	17
 10-Oxo-*cis*-12**-octa**decenoic acid (KetoA)	 Sebacic acid (C10)	13
 10-Oxooctadecanoic acid (KetoB)	—	
 10-Oxo-*trans*-**11-o**ctadecenoic acid	 Sebacic acid (C10)	*tr*.[b]
 *cis*-9,*cis*-12,*cis*-15-Octadecatrienoic acid (α-Linolenic acid)	 Azelaic acid (C9)	13
 10-Hydroxy-***cis*-12**,*cis*-15-octadecadienoic acid (αHYA)	 Sebacic acid (C10)	14
 10-Hydroxy-*cis*-15-octadecenoic acid	—	
 10-Hydroxy-***trans*-**11,*cis*-15-octadecadienoic acid	 Sebacic acid (C10)	88
 10-Oxo-*cis*-12**,*cis*-**15-octadecadienoic acid (αKetoA)	 Sebacic acid (C10)	100[a]
 10-Oxo-*cis*-15-octadecenoic acid	—	
 10-Oxo-*trans*-**11,*cis***-15-octadecadienoic acid	 Sebacic acid (C10)	42
 *cis*-6,*cis*-9,*cis*-12-Octadecatrienoic acid (γ-Linolenic acid)	 Adipic acid (C6)	*tr*.
 10-Hydroxy-***cis*-6,*cis***-12-octadecadienoic acid (γHYA)	 4-Decenedioic acid (C10)	7.1
 10-Hydroxy-*cis*-6-octadecenoic acid	—	
 10-Hydroxy-***cis*-6,*trans***-11-octadecadienoic acid	 4-Decenedioic acid (C10)	66
 10-Oxo-*cis*-6,***cis*-12**-octadecadienoic acid (γKetoA)	 4-Decenedioic acid (C10)	44
 10-Oxo-*cis*-6-octadecenoic acid	—	
 10-Oxo-*cis*-6,***trans***-11-octadecadienoic acid	 4-Decenedioic acid (C10)	17

(*Continued*)

Table 1. (*Continued*).

Substrate	Product	Relative activity [%]
 12-Hydroxy-*cis*-9-octadecenoic acid (Ricinoleic acid)	 Azelaic acid (C9)	1.0
 12-Oxo-*cis*-9-octadecenoic acid	 Azelaic acid (C9)	7.6

[a]The mole amount of products from 10-Oxo-*cis*-12,*cis*-15-octadecadienoic acid under the condition (1 mM of HBT, 37 °C, pH 4.0, 24 h) was defined as 100%.
[b]*tr*., trace, <0.001%.
[c]not detected.
Cleavage positions were indicated by arrows.

Helium was used as a carrier gas at a flow rate of 1.7 mL/min in the column.

Results and discussion

Substrate specificity

Twenty-three different fatty acids were applied to the oxidative reaction by laccase, and shorter products were observed by GC analysis (Table 1). As a representative result, the GC chromatogram and mass spectrum of products from 10-oxo-*cis*-12,*cis*-15-octadecadienoic acid (αKetoA) are shown in Fig. 1. In terms of the results of GC-MS analysis, the product was identified as sebacic acid because the retention time and MS fragments of the methyl-esterified product corresponded to those of the methyl-esterified sebacic acid standard (Fig. 1(b)). The byproduct was expected to be C8 compounds, but was not detected under these conditions. Dicarboxylic acids were produced from almost all of the fatty acids, except for six hydroxy and oxo fatty acids that have no carbon–carbon double bond near a hydroxy or oxo group, such as HYB, 10-hydroxy-*cis*-6-octadecenoic acid, 10-hydroxy-*cis*-15-octadecenoic acid, KetoB, 10-oxo-*cis*-6-octadecenoic acid, and 10-oxo-*cis*-15-octadecenoic acid (Table 1). The oxidative cleavage of fatty acids by laccase occurred in the unsaturated fatty acids which have carbon–carbon double bond, hydroxy group, or carbonyl group at allylic or homoallylic position. The cleavage positions were indicated by arrows in Table 1. αKetoA was used in the following experiments because the amount of products was the highest among these various fatty acids.

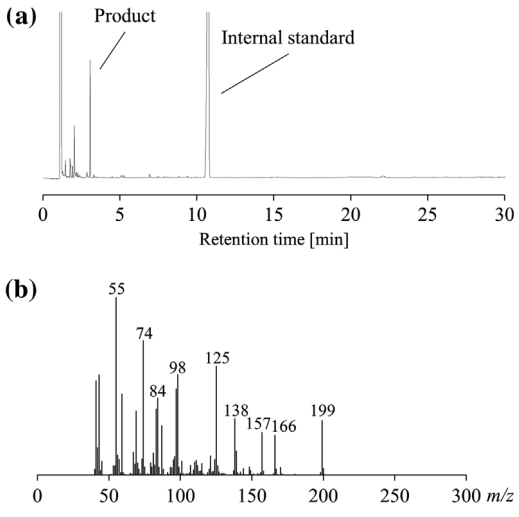


Fig. 1. Gas-chromatography chromatogram (a) and mass spectrum (b) of the product from αKetoA.

Effect of mediators for dicarboxylic acid production

Six mediators were examined for their ability to mediate laccase-catalyzed oxidation of fatty acids (Table 2). Among these six, HBT and TEMPO gave highest production of sebacic acid (0.40 mM). Among six mediators, TEMPO, HBT, and violuric acid belong to N–OH-type mediator.[20] N–OH is necessary but not sufficient for efficient production of dicarboxylic acid. The productivity is determined by combination of enzymatic activity for mediator oxidation and reactivity of oxidized mediator toward substrate. Mediator concentration was varied from 0 to 5 mM. The production of sebacic acid depended on mediator concentration (Fig. 2). Sebacic acid production increased depending on HBT concentration under 1 mM, but was constant over 1 mM.

Effects of reaction pH and temperature

The effects of reaction pH and temperature were examined. The optimal reaction pH was found to be 5.0 (Fig. 3), although the optimum pH of laccase for ABTS oxidation was 3.0 (data not shown). The difference of optimum pH between the cleavage of αKetoA and the oxidation of ABTS was probably caused by the difference in the stability of αKetoA and laccase at each pH. The optimal reaction temperature was found to be 40 °C (Fig. 4). The time course of oxidative cleavage of αKetoA by laccase is shown in Fig. 5. After 8 h, 0.58 mM of sebacic acid was produced from

Table 2. Effect of mediator on sebacic acid production.

Mediator	Sebacic acid production (mM)
TEMPO	0.40
1-Hydroxybenzotriazole (HBT)	0.39
Veratryl alcohol	0.22
Violuric acid	0.22
ABTS	0.22
Benzotriazole	0.19

TEMPO: 2,2,6,6-tetramethylpiperidine 1-oxyl, HBT: 1-hydroxybenzotriazole, ABTS: 2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid) ammonium salt. The reaction mixture contained 1.5 mM of 10-oxo-*cis*-12,*cis*-15-octadecadienoic acid, laccase, and 1 mM of each mediator. Experimental conditions: temperature, 37 °C; shaking frequency, 300 rpm; reaction time; 8 h.

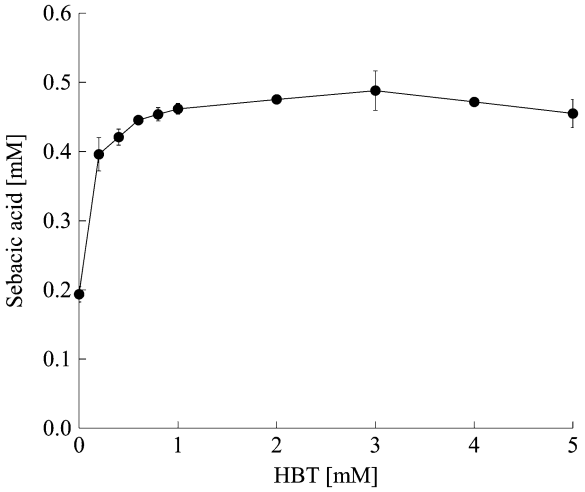


Fig. 2. Effect of mediator concentration on sebacic acid production.
Note: The reaction mixture containing 1.5 mM of αKetoA, 11.3 U/mL laccase, and 1-hydroxybenzotriazole (HBT) (0–5 mM). Reaction conditions: temperature, 37 °C; shaking frequency, 300 strokes/min; reaction time, 8 h.

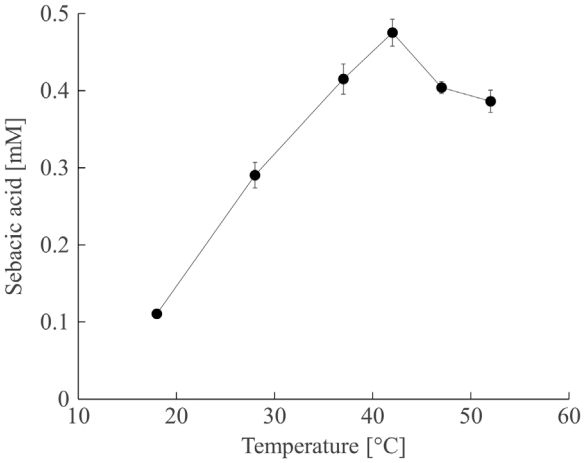


Fig. 4. Effect of reaction temperature on sebacic acid production.
Note: The reaction mixture contained 1.5 mM of αKetoA, 11.3 U/mL laccase, 1 mM of HBT, and 20 mM of sodium acetate buffer (pH 4.0). Reaction conditions: temperature, 18–52 °C; shaking frequency, 300 strokes/min; reaction time, 8 h.

1.6 mM of αKetoA with a conversion rate of 35% (mol/mol).

In a previous study, we established a process for producing hydroxy fatty acids using linoleic acid hydratase from *L. plantarum* AKU 1009a.[15] These hydroxy fatty acids have health-supporting activities such as anti-inflammatory, anti-obesity, and immunomodulatory effects.[24,25] In this study, these hydroxy fatty acids were also shown to be promising starting materials for bioplastic production because dicarboxylic acids were produced from hydroxy and oxo fatty acids by laccase. Hydroxy and oxo unsaturated fatty acids are favorable compounds to control the chain length of products of oxidative reactions for dicarboxylic acid production (Table 1). The mechanism is expected that dihydroxy fatty acid generated by epoxidation and hydration of carbon–carbon double bond is cleaved and converted into dicarboxylic acid by the same mechanism as azelaic acid (nonanedioic acid) generation as an end product of LA peroxidation.[26] The rate of conversion from αKetoA to sebacic acid was low level [about 35% (mol/mol)] because of the difficulty of controlling the radical reaction (Fig. 5). However, the laccase-catalyzed enzymatic process appears to be promising for eco-friendly production of dicarboxylic acid from biomass-derived fatty acids because this process does not require high energy and highly alkaline condition compared with chemical process. Innovation Commercialization Venture Support Project from the New Energy and Industrial Technology Development Organization (NEDO) of Japan (to collaboration of NITTO PHARMA and J. O.) Science and Technology Promotion Program for Agriculture Forestry, Fisheries, and Food Industry from the Ministry of Agriculture,

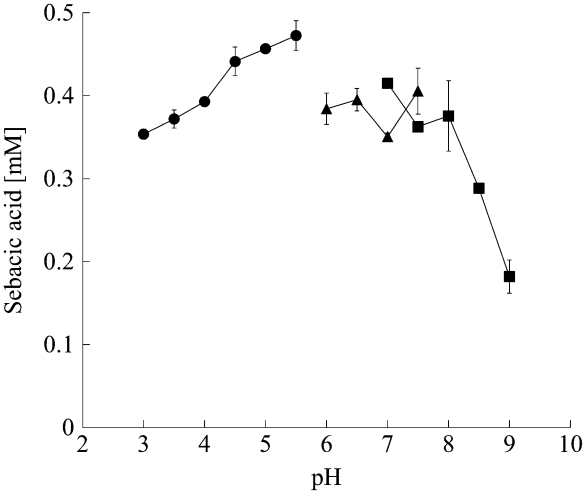


Fig. 3. Effect of reaction pH on sebacic acid production.
Note: The reaction mixture contained 1.5 mM of αKetoA, 11.3 U/mL laccase, 1 mM of HBT, and 20 mM of buffer. Reaction conditions: temperature, 37 °C; shaking frequency, 300 strokes/min; reaction time, 8 h; circle, sodium acetate buffer; triangle, HEPES buffer; square, Tris-HCl buffer.

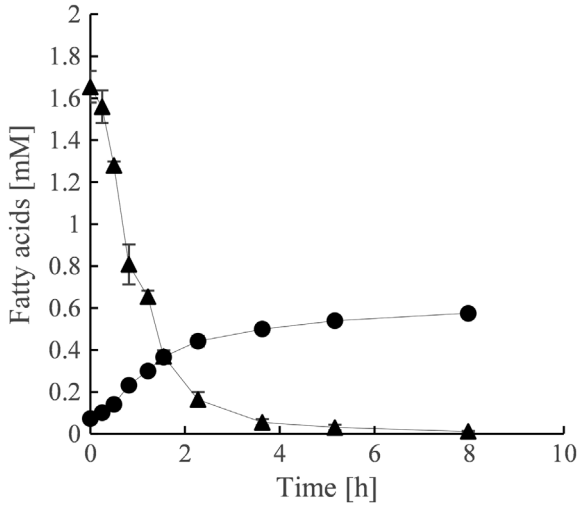


Fig. 5. Time course of sebacic acid production from αKetoA.
Note: The reaction mixture contained 1.6 mM of αKetoA, 11.3 U/mL laccase, 1 mM of HBT, and 20 mM of sodium acetate buffer (pH 5.0). Reaction conditions: temperature, 40 °C; shaking frequency, 300 strokes/min; triangle, αKetoA; circle, sebacic acid.

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Author contributions

All members conceived and designed the experiments, and discussed the results for the completion of the manuscript. MT, SK, SBP, NK, HW, and AS performed the experiments. MT analyzed the data and wrote the manuscript in consultation with SK, MH, KY, and JO.

Disclosure statement

No potential conflict of interest was reported by the authors.

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