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Preparation of all stereoisomers of 2-allyl-2-methyl-3-hydroxycyclopentanone by desymmetric processes based on a microbial oxidation and reduction system

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ABSTRACT

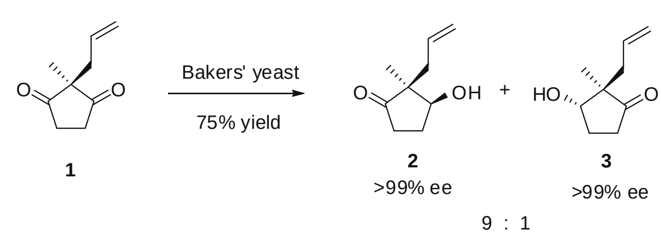
All stereoisomers of 2-allyl-3-hydroxy-2-methylcyclopentanones **2**–**5** were prepared in high conversion and in an optically pure form by microbial reduction and oxidation. The reduction of symmetric diketone **1** by *Geotrichum candidum* NBRC 4597 under anaerobic conditions gave **2** in 83% yield (98% conversion), >99% de, and >99% ee, whereas the reduction of **1** by *G. candidum* NBRC 5767 under aerobic conditions gave **3** in 75% yield (99% conversion), >99% de, and >99% ee. Oxidation of *meso*-diol **6** by *G. candidum* NBRC 5767 under aerobic conditions afforded **4** in 83% yield (99% conversion) and >99% ee, while oxidation of *meso*-diol **7** by *Mucor heimalis* IAM 6095 in the presence of cyclohexanone as a co-oxidant afforded **5** in 68% yield (75% conversion) and >99% ee.

1. Introduction

Stereoselective and regioselective reduction of 2,2-dialkylcycloalkane-1,3-diones such as 2-allyl-2-methylcyclopentane-1,3-dione **1** is a useful method for the preparation of optically active compounds possessing a chiral quaternary carbon.[1] Desymmetrization of the *meso* compound allows 100% yield of the optically pure compound, while optical resolution gives only 50% yield.[2] Bakers' yeast reduction of 2,2-dialkylcycloalkane-1,3-dione is recognized as a valuable approach for accessing highly optically active 2,2-dialkyl-3-hydroxycycloalkanones through desymmetrization. For example, bakers' yeast reduction of **1** was reported to afford (2*S*,3*S*)-2-allyl-3-hydroxy-2-methylcyclopentanone **2** and (2*R*,3*S*)-2-allyl-3-hydroxy-2-methylcyclopentanone **3** in 75% yield as a diastereomeric mixture with 80% de (**2**:**3** = 9:1).[3] Optically pure **2** is a chiral synthon for coriolin, possessing antibacterial and antitumor activities (Scheme 1).[3b]

We have reported that a single microbe afforded both enantiomers of a secondary alcohol stereoselectively by changing the reaction conditions.[4] Oxygen concentration in the reaction atmosphere, for example, changes the stereochemical course of microbial reduction (Scheme 2). Under anaerobic conditions, reduction of acetophenone by *Geotrichum candidum* NBRC 5767 afforded (*S*)-1-phenylethanol in 98% yield and >99% enantiomeric excess (ee). In contrast, the reduction of ketone by *G. candidum* NBRC 5767 under aerobic conditions afforded (*R*)-1-phenylethanol in 99% yield and >99% ee, this phenomenon is possibly due to deracemization as shown in Scheme 2.[4a] The *S*-enzyme afforded the *S*-alcohol reversibly but the *R*-enzyme afforded the *R*-alcohol irreversibly.[5] Since oxygen in air enhanced the oxidation of the *S*-alcohol, the *S*-alcohol produced by the reduction was re-oxidized to ketone in aerobic conditions, and finally the *R*-alcohol accumulated through irreversible reduction. In anaerobic conditions, oxidation of the *S*-alcohol was inhibited, and the faster reaction affording the *S*-alcohol was dominant. This procedure was considered useful for providing several enantiomers by only changing the reaction conditions. In this work we attempted to prepare an optically pure chiral synthon **2** of coriolin and its stereoisomers **3**-**5** using a microbial oxidation and reduction system (Fig. 1).

Compound **1** was reduced under normal conditions by *G. candidum* NBRC 5767 to obtain **2** in 92% conversion with 76% diastereomeric excess (de) (Table 1, entry 1). To control the diastereoselectivity of microbial reduction, a reduction system using XAD-7 under anaerobic conditions was employed (Table 1, entry 2).[6] However, the de of **2** decreased to 8%. Thus reduction under anaerobic conditions gave **2** in 80% conversion, 80% de, and >99% ee together with the minor stereoisomer **3** (>99% ee) (Table 1, entry 3). High diastereoselectivity and excellent enantioselectivity were observed on the



Scheme 1.

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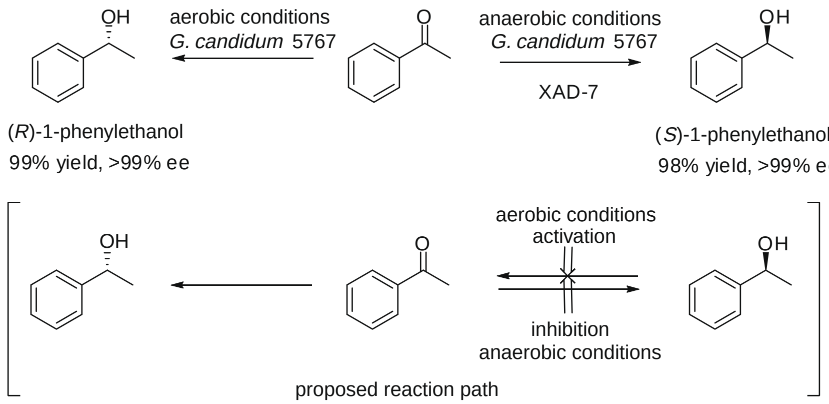
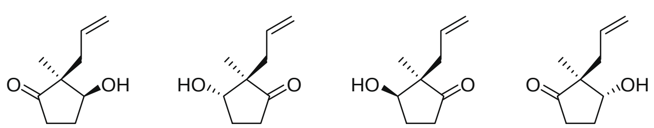


Scheme 2.



2 (2*S*,3*S*) **3** (2*R*,3*S*) **4** (2*R*,3*R*) **5** (2*S*,3*R*)

Figure 1. Four stereoisomers of 2-allyl-3-hydroxy-2-methylcyclopentanone (**2**–**5**).

reduction of **1** by *G. candidum* NBRC 5767. It was found that the obtained **2** was the same major stereoisomer as that of bakers' yeast reduction. On the other hand, the reduction in aerobic conditions gave **3** in 95% conversion with 98% de and 99% ee (Table 1, entry 4). The reduction by *G. candidum* NBRC 5767 has been found to afford two stereoisomers by changing only reaction atmosphere.[4] The time course of the reaction under aerobic conditions is shown in Figure 2. Initially, reduction of **1** by *G. candidum* NBRC 5767 under aerobic conditions afforded **2** dominantly over **3**, the degree of conversion of **2** reached 60% after 6 h, and reduced with increasing reaction time. The degree of conversion of **3** transiently increased and reached 98% after 40 h. In order to improve the diastereoselectivity of the reduction affording **2**, another strain *G. candidum* NBRC 4597 was employed for the reduction of **1** to afford **2** in 98% conversion with 99% de and >99% ee (Table 1, entry 5). Finally, we succeeded in the preparation of **2** and **3** in high yield with satisfactory stereoselectivities. The high stereoselectivity of the reduction system under aerobic conditions was due to the high stereoselectivity of oxidation.[6] Moreover, the enzyme catalyzing oxidation of **2** recognized the chirality of the adjacent quaternary carbon at the 2-position of **2**.

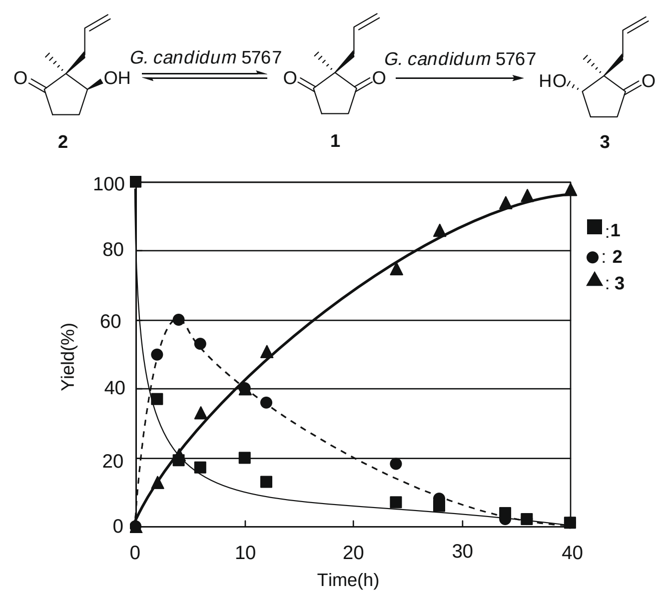
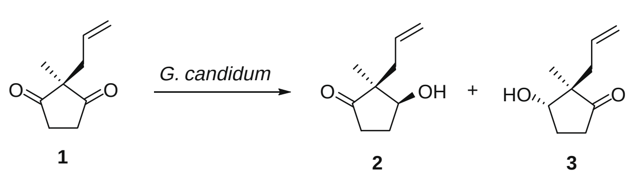


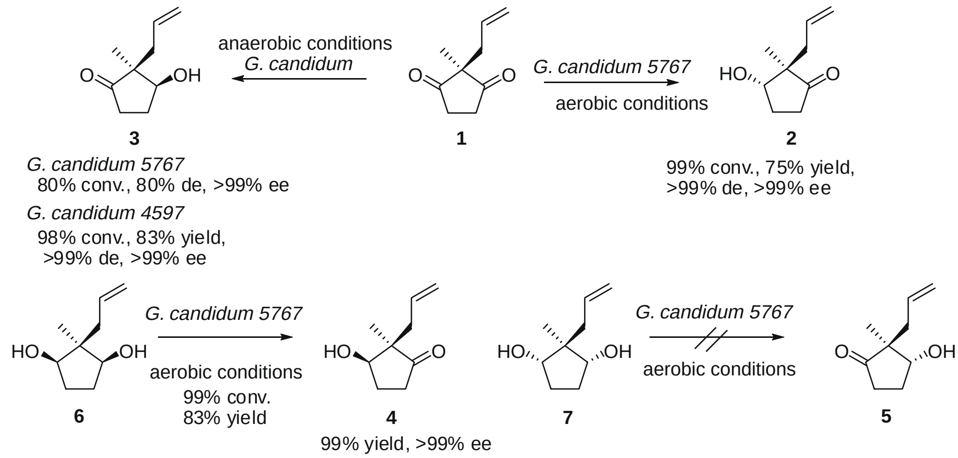
Figure 2. Time course of the reduction of **1** by *G. candidum* 5767 under aerobic conditions.

Table 1
Stereochemical control on reduction of **1** by *G. candidum*



Entry	Microbe	Conditions	Conv. (%)	de (%)	ee (%) (**2**)	ee (%) (**3**)
1	*G. candidum* NBRC 5767		92	76 (**2**)	>99	>99
2	*G. candidum* NBRC 5767	Ar, XAD-7[4]	54	8 (**2**)	>99	>99
3	*G. candidum* NBRC 5767	Ar[4]	80	80 (**2**)	>99	>99
4	*G. candidum* NBRC 5767	Aerobic[4]	95	98 (**3**)	—[a]	>99
5	*G. candidum* NBRC 4597	Ar[4]	98	>99 (**2**)	>99	—[b]

Conditions: see Ref. 4 (reaction time: 24 h.).
GC analysis: after acetylation of products treated with acetic anhydride and pyridine, GC analysis was performed (Chirasil-DEX CB, 110 °C, 0.25 mm × 25 m, Ar: 2 mL/min). Retention time: **2**-acetate; 23.3 min, **5**-acetate; 24.4 min, **4**-acetate; 22.3 min, **3**-acetate; 19.8 min.
[a] Compound **5** was not observed.
[b] Compound **4** was not observed.



Scheme 3.

Reduction on a preparative scale was performed under both conditions. Reduction of **1** under anaerobic conditions gave **2** in 83% isolated yield and >99% ee (Scheme 3).[7] As with the reduction of **1** by *G. candidum* NBRC 5767 under anaerobic conditions, a prolonged reaction time was employed and **3** was obtained in 75% isolated yield (99% conv.) with >99% de and >99% ee.[8]

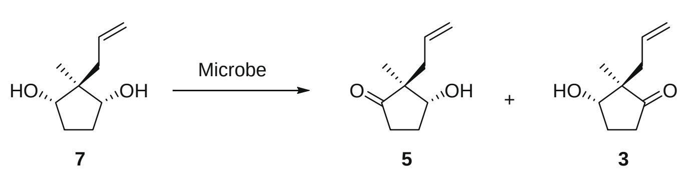
Next we attempted to obtain the other stereoisomers of **2**. Stereoselective and regioselective oxidation of *meso*-diols, such as (1*R*,2*S*,3*S*)-2-allyl-2-methylcyclopentane-1,3-diol (**6**) and (1*R*,2*R*,3*S*)-2-allyl-2-methylcyclopentane-1,3-diol (**7**), are also desymmetrization processes capable of producing optically active **4** and **5** in high yield. For the preparation of *meso*-diol substrates, **1** was reduced by excess $NaBH_4$ to afford **6** (31%), racemic (1*S**,3*S**)-2-allyl-2-methylcyclopentane-1,3-diol (41%), and **7** (15%).[9]

The oxidation of **6** by *G. candidum* NBRC 5767 under aerobic conditions afforded **4** in 99% conversion (83% isolated yield)[10] with >99% ee; further oxidation to diketone **1** was not observed. We succeeded in affording three stereoisomers (**2**, **3**, and **4**) in high yield and high ee using *G. candidum* (Scheme 3). Stereoselective oxidation of **7** by *G. candidum* NBRC 5767 as a pathway to **5** was unsuccessful. In the reduction of **1**, the enzyme catalyzing the oxidation of the alcohol appears to recognize the stereochemistry at the 2-position, leading to the oxidation of **7** to afford **5**. That is, although alcohols possessing the (2*S*,3*S*) configuration, such as **2** and **6**, were oxidized by *G. candidum* NBRC 5767, alcohols possessing the (2*R*,3*S*) configuration, such as **3** and **7**, could not be oxidized by *G. candidum* NBRC 5767.

The ability of several microbes to afford **5** selectively was tested (Table 2). *Mucor heimalis* IAM 6095 (entry 5) had comparatively higher activity in affording **5** than the other microbes tested. In our experience, oxidation of secondary alcohols by *Mucor* species is not promoted by aerobic conditions. Thus, a biphasic system using cyclohexanone as a co-oxidant in a water–hexane co-solvent system was applied to the oxidation of **7** to enhance oxidation.[11] The addition of 45 mM cyclohexanone to the reaction system increased the conversion rate of **7** into **5** to 45% (entry 8). The addition of 90 mM cyclohexanone further increased the conversion rate up to 75% (entry 9), and optically pure **5** was isolated in 68% yield.[12]

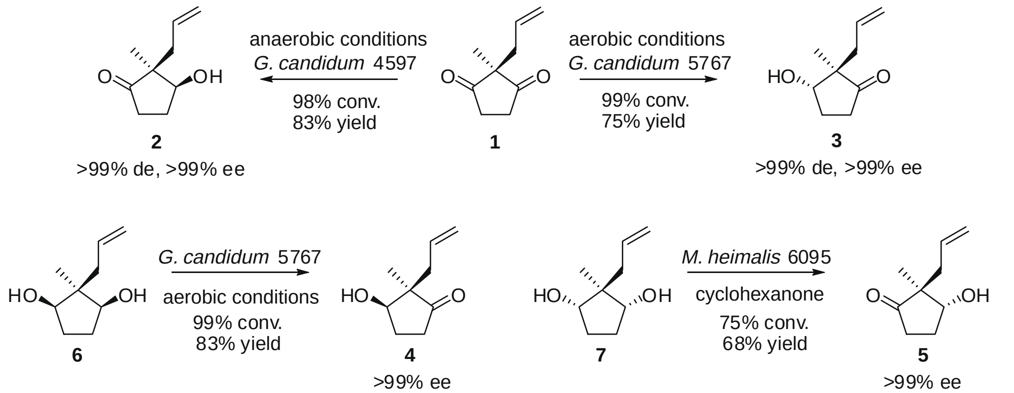
In summary, we demonstrated a microbial oxidation and reduction system affording four different isomers of 2-allyl-3-hydroxy-2-methylcyclopentanones **2**–**5** in high conversion and in an enantiomerically pure form (Scheme 4). Moreover, by changing the reaction conditions, the reduction of **1** by *G. candidum* NBRC 5767 afforded two stereoisomers (**2** and **3**) and the oxidation of **6** by *G. candidum* NBRC 5767 under aerobic conditions afforded **4** (Scheme 3). In our previous study,[4,5] reversible reductases, *S*-en-

Table 2
Screening of microbes to afford **5**



Entry	Microbe	Conditions	Conv. (%)	ee (%)
1	*G. candidum* NBRC 5767	Aerobic[4,5]	0	–
2	*G. candidum* NBRC 4597	Aerobic[4,5]	7	38 (**3**)
3	*G. candidum* ATCC 34614	Aerobic[4,5]	3	4 (**3**)
4	*M. javanicus* IAM 6101	Aerobic[4,5]	13	>99[a] (**5**)
5	*M. heimalis* IAM 6095	Aerobic[4,5]	17	>99[a] (**5**)
6	*A. niger* IAM 4091	Aerobic[4,5]	0.4	>99[a] (**5**)
7	*D. magnusii* NBRC 4600	Aerobic[4,5]	3	>99[a] (**5**)
8	*M. heimalis* IAM 6095	Cyclohexanone: 45 M[11]	45	>99[a] (**5**)
9	*M. heimalis* IAM 6095	Cyclohexanone: 90 M[11]	75	>99[a] (**5**)

Conditions: see Refs. 4 and 5 for entries 1–7 and Ref. 11 for entries 8 and 9 (reaction time: 3 d).
[a] Compound **3** was not observed.



Scheme 4.

zymes, affording *S*-alcohols, and irreversible reductases, *R*-enzymes, were involved in the reaction to afford both enantiomers independently under different conditions. This work has found that the reversible reductase affording the *S*-alcohol recognizes the (2*S*,3*S*)-configuration of **2** and irreversible *S*-enzymes affording **3** are involved in the reaction. In fact, *S*-enzymes possessing different stereoselectivities on the reduction of ethyl 2-methyl-3-oxobutanoate have been reported.[13] Normally, a single microbe could not afford different isomers in high enantio- and diastereoselectivity. However the unique enantio- selective and diastereoselective oxidase in *G. candidum* was able to afford three isomers in high enantio- and diastereoselectivity. Application of the reversibility of the enzyme is a useful method for the preparation of optically active compounds in high yield.

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7. Compound **2**: From **1** (300 mg, 1.97 mmol) to (2*S*,3*S*)-**2** (255 mg, 1.66 mmol, 83%, >99% ee); $[\alpha]_D$ +106.2 (*c* 0.43, $CHCl_3$), lit.[3a] $[\alpha]_D$ +80.7 (*c* 0.4, $CHCl_3$). IR (neat) ν: 3457, 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.97 (s, 3H), 1.70–2.56 (m, 7H), 3.98–4.14 (m, 1H), 5.01–5.18 (m, 2H), 5.76–5.95 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz); δ 19.6, 27.7, 34.0, 35.3, 53.2, 77.3, 118.1, 134.3, 221.0; Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.89; H. 9.15.
8. Compound **3**: From **1** (100 mg, 0.64 mmol) to (2*R*,3*S*)-**3** (76 mg, 0.49 mmol, 75%, >99% ee); $[\alpha]_D$ −81.0 (*c* 0.59, $CHCl_3$), lit.[3a] $[\alpha]_D$ −86.5 (*c* 0.26, $CHCl_3$); IR (neat) ν: 3434, 1732, 1640 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 0.98 (s, 3H), 1.78–1.194 (m, 1H) 2.01–2.50 (m, 6H), 4.48 (t, 1H, J = 6.4 Hz), 5.01–5.14 (m, 2H), 5. 26–5.83 (m, 1H); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.0, 27.5, 34.9, 39.7, 53.0, 75.2, 118.7, 133.5, 220.2; Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.94; H. 9.09.
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10. Compound **4**: From (1*R*,2*R*,3*S*)-**6** (100 mg, 0.64 mmol) to (2*R*,3*R*)-**4** (81 mg, 0.53 mmol, 83%, >99% ee). $[\alpha]_D$ −105.0 (*c* 0.58, $CHCl_3$). Spectral data including ^1H NMR and ^{13}C NMR were identical to those of **2**.
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12. Compound **5**: From (1*R*,2*R*,3*S*)-**7** (120 mg, 0.77 mmol) to (2*R*,3*R*)-**5** (80 mg, 0.52 mmol, 68%, >99% ee). $[\alpha]_D$ +85.4 (*c* 0.58, $CHCl_3$). Spectral data including ^1H NMR and ^{13}C NMR were identical to those of **3**.
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