Biotransformation of (−)-Dihydromyrcenyl Acetate Using the Plant Parasitic Fungus *Glomerella cingulata* as a Biocatalyst

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The microbial transformation of (−)-dihydromyrcenyl acetate was investigated using the plant parasitic fungus *Glomerella cingulata*. As a result, (−)-dihydromyrcenyl acetate was converted to dihydromyrcenol, 3,7-dihydroxy-3,7-dimethyl-1-octene-7-carboxylate, 3,7-dihydroxy-3,7-dimethyl-1-octene, 3,7-dimethyloctane-1,2,7-triol-7-carboxylate, and 3,7-dimethyloctane-1,2,7-triol. In addition, microbial transformation of dihydromyrcenol by *G. cingulata* was carried out. The metabolic pathway of (−)-dihydromyrcenyl acetate is discussed.

Keywords: *Biotransformation; microbial transformation; Glomerella cingulata; (−)-dihydromyrcenyl acetate; dihydromyrcenol; 3,7-dihydroxy-3,7-dimethyl-1-octene-7-carboxylate; 3,7-dihydroxy-3,7-dimethyl-1-octene; 3,7-dimethyloctane-1,2,7-triol-7-carboxylate; 3,7-dimethyloctane-1,2,7-triol*

INTRODUCTION

We have reported biotransformations of acyclic terpenoids using the plant parasitic fungus *Glomerella cingulata* (Nankai et al., 1997, 1998a,b) and common cutworm larvae *Spodoptera litura* Fabricius (Miyazawa and Murata, 2000). In the biotransformation of acyclic terpenoids by *G. cingulata*, unsaturated acyclic terpenoids were regioselectively oxidized at the double bond distant from the hydroxyl or carbonyl group as a main reaction (Nankai et al., 1998a,b), whereas saturated acyclic terpenoids were mainly hydroxylated at the methine of the isopropyl moiety, which is most distant from the hydroxyl group (Nankai et al., 1997). To clarify the mode of biotransformations of acyclic terpenoids by *G. cingulata*, the biotransformation of (−)-dihydromyrcenyl acetate (7-hydroxy-3,7-dimethyl-1-octene-7-carboxylate) (**1**) was investigated. Compound **1** is not a natural product but an artificial product synthesized from α-pinene (Sprecker et al., 1986) and used in the fragrance industry. Further derivatization of **1** is of interest in producing novel biologically active compounds, in particular, perfumery ingredients. There is, however, no report of biotransformation of **1**; therefore, as part of our continuing program, we chose **1** as a substrate of biotransformation by *G. cingulata*. To elucidate the metabolic pathway, the microbial transformation of dihydromyrcenol (**2**) was also investigated. The structures of metabolites and the metabolic pathway were established. This is the first report of the biotransformations of **1** and **2**.

MATERIALS AND METHODS

General Procedure. (−)-Dihydromyrcenyl acetate (**1**) was purchased from Taiyo Perfumery Co., Ltd., and dihydromyrcenol was purchased from Nagaoka Perfumery Co., Ltd. Thin-layer chromatography (TLC) was performed on precoated plates [silica gel 60 F_{254}, 0.25 mm, Merck (Darmstadt, Germany)], and the compounds were visualized by spraying plates with 1% vanillin in 96% sulfuric acid followed by brief heating (∼120 °C, 1 min). Gas chromatography (GC) was performed on an HP 5890 series II Plus gas chromatograph equipped with a flame ionization detector (FID). The column was a fused silica capillary column [DB-5, 30 m × 0.25 mm i.d., film thickness = 1.0 μm (J&W Scientific, Folsom, CA)]. Chromatographic conditions were as follows: column temperature, 80−260 °C at 4 °C min^{-1}; injector temperature, 270 °C; detector temperature, 280 °C; carrier gas, He at 1.8 mL min^{-1}. Yields of individual constituents were determined by peak areas as measured by an HP 3396 series II integrator. FAB MS was obtained on a JEOL JMS-HX 100 mass spectrometer, and the matrix was 3-nitrobenzyl alcohol (NBA). EI-MS measurements were obtained using gas chromatography−mass spectrometry (GC-MS). GC-MS was performed on an HP 5972A mass selective detector interfaced with an HP 5890 series II Plus gas chromatograph fitted with a column (HP-5MS, 30 m × 0.25 mm i.d., film thickness = 0.25 μm), and the chromatographic conditions were the same as described above. Infrared spectra (IR) were determined with a Perkin-Elmer 1760-x IR Fourier transform spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL FX-500 NMR spectrometer (^{1}H NMR, 500.00 MHz; ^{13}C NMR, 125.65 MHz). Tetramethylsilane (TMS) was used as the internal standard (δ 0.00) for ^{1}H NMR spectra measured in $CDCl_3$. Residual $CHCl_3$ was used as internal reference (δ 77.00) for ^{13}C NMR spectra measured in $CDCl_3$. Multiplicities were determined by DEPT pulse sequence. Specific rotation was measured by JASCO DIP-1000.

Preculture of Fungi. Spores of *G. cingulata* (the strain had been isolated from diseased grape and was received from Dr. Hyakumachi, M., Gifu University, Japan), which have been preserved on potato dextrose agar (PDA) at 4 °C, were inoculated into 200 mL of sterilized culture medium (1.5% saccharose, 1.5% glucose, 0.5% polypepton, 0.05% $MgSO_4 \cdot 7H_2O$, 0.05% KCl, 0.1% K_2HPO_4, and 0.001% $FeSO_4 \cdot 7H_2O$ in distilled water) in a 500 mL shaking flask, and the flask was shaken (reciprocating shaker, 100 rpm) at 27 °C for 3 days (Nankai et al., 1997).

Time Course Experiment. Precultured *G. cingulata* (1 mL) was transferred into a 200 mL Erlenmeyer flask containing 100 mL of medium (same medium as used in preculture) and stirred under the same conditions as for preculture. After 3 days, the organism matured, compound **1** or **2** (50 mg) was added to the medium, and the organism was cultivated for 10 more days. The culture medium (5 mL) was removed daily for

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Table 1. ^{1}H NMR Spectral Data of Compounds 2−6[a]

H	2	3	4	5	6
1	4.96 ddd (17.0, 2.0, 1.0)	5.21 dd (17.5, 1.5)	5.21 dd (17.5, 1.5)	3.54 m	3.50 m
1′	4.91 ddd (10.5, 2.0, 1.0)	5.06 dd (11.0, 1.5)	5.06 dd (11.0, 1.5)		
2	5.69 ddd (17.0, 10.5, 7.5)	5.91 dd (17.5, 11.0)	5.92 dd (17.5, 11.0)	3.69 m	3.70 m
3	2.13 m			1.67−1.79 m	1.52−1.64 m
4	1.24−1.38 m	1.44−1.57 m	1.32−1.58 m	1.12−1.33 m	1.40−1.51 m
5	1.24−1.38 m	1.29−1.39 m	1.32−1.58 m	1.12−1.33 m	1.40−1.51 m
6	1.39−1.50 m	1.70−1.75 m	1.32−1.58 m	1.51−1.62 m	1.23−1.31 m
7					
8	1.21 s	1.42 s	1.22 s	1.422/1.421 s	1.22 s
9	1.21 s	1.42 s	1.22 s	1.422/1.421 s	1.22 s
10	0.99 d (6.5)	1.28 s	1.29 s	0.90/0.93 d (7)	0.89/0.92 d (7)
OAc		1.97 s		1.97 s	

[a] Chemical shifts in ppm; coupling constants in Hz.

Table 2. ^{13}C NMR Spectral Data of Compounds 2−6[a]

C	2	3	4	5	6
1	112.5 (CH_2)	111.6 (CH_2)	111.7 (CH_2)	64.7/65.1 (CH_2)	64.6/65.0 (CH_2)
2	144.7 (CH)	145.0 (CH)	145.1 (CH)	76.1/75.5 (CH)	76.0/75.3 (CH)
3	37.8 (CH)	73.2 (C)	73.3 (C)	36.0/35.5 (CH)	36.0/35.6 (CH)
4	37.1 (CH_2)	42.3 (CH_2)	42.6 (CH_2)	33.1/32.6 (CH_2)	32.9/33.4 (CH_2)
5	22.0 (CH_2)	18.2 (CH_2)	18.7 (CH_2)	21.2/21.4 (CH_2)	21.4/21.7 (CH_2)
6	44.0 (CH_2)	41.0 (CH_2)	44.1 (CH_2)	40.8/40.9 (CH_2)	43.80/43.83 (CH_2)
7	71.1 (C)	82.4 (C)	71.1 (C)	82.34/82.31 (C)	71.12/71.08 (C)
8	29.2 (CH_3)	26.0 (CH_3)	29.3 (CH_3)	26.1/26.0 (CH_3)	29.1/29.2 (CH_3)
9	29.2 (CH_3)	26.0 (CH_3)	29.3 (CH_3)	26.1/26.0 (CH_3)	29.1/29.2 (CH_3)
10	20.2 (CH_3)	27.8 (CH_3)	27.8 (CH_3)	15.2/14.5 (CH_3)	15.4/14.6 (CH_3)
$\underline{C}OCH_3$		170.7 (C)		170.5 (C)	
$\overline{C}O\underline{C}H_3$		22.4 (CH_3)		22.5/22.6 (CH_3)	

[a] Chemical shifts in ppm; multiplicities were determined by the DEPT pulse sequence.

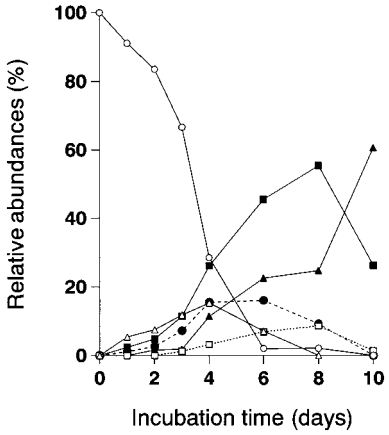


Figure 1. Time course for the biotransformation of **1** by *G. cingulata*: (○) (−)-dihydromyrcenyl acetate (**1**); (△) dihydromyrcenol (**2**); (□) 3-hydroxydihydromyrcenyl acetate (**3**); (●) 3-hydroxydihydromyrcenol (**4**); (■) 3,7-dimethyloctane-1,2,7-triol-7-carboxylate (**5**); (▲) 3,7-dimethyloctane-1,2,7-triol (**6**).

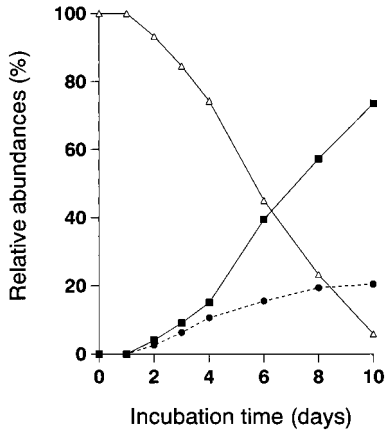


Figure 2. Time course for the biotransformation of **2** by *G. cingulata*: (△) dihydromyrcenol (**2**); (●) 3-hydroxydihydromyrcenol (**4**); (■) 3,7-dimethyloctane-1,2,7-triol (**6**).

4 days and then every 2 days; sampling was continued for more 6 days. The culture medium was extracted with EtOAc (1 mL) and the solvent then evaporated. This extract was analyzed by TLC, GC, and GC-MS. The ratios between the substrate and metabolic products were determined on the basis of GC peak areas (Figures 1 and 2).

Biotransformation of (—)-Dihydromyrcenyl Acetate (1) for 4 Days. Precultured *G. cingulata* (5 mL) was transferred into a 3 L stirred fermentor containing 2 L of medium. Cultivation was carried out at 27 °C with stirring (~100 rpm) for 3 days under aeration. After 3 days, the organism matured, compound **1** (1.0 g) was added to the medium, and the organism was cultivated for an additional 4 days.

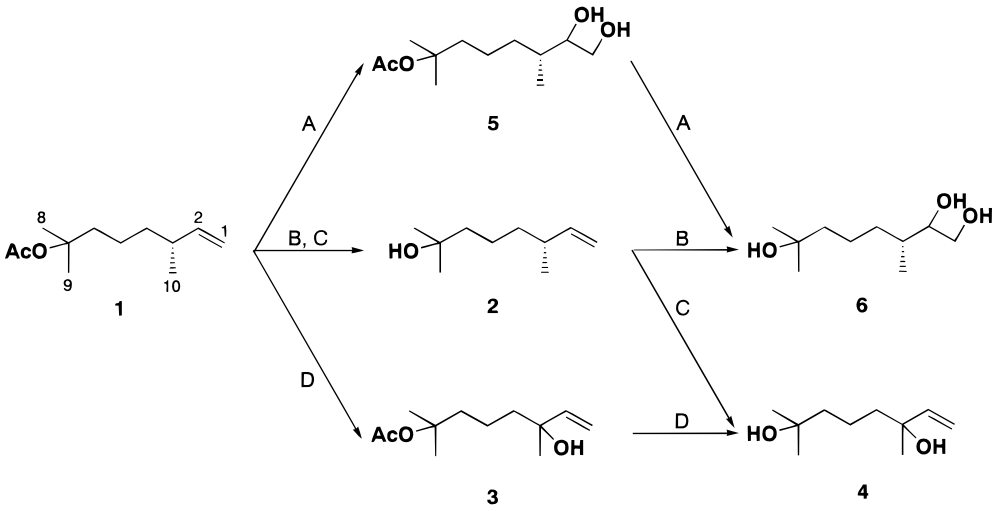
Isolation of Metabolites 2—6. After the cultivation described above, the culture medium and mycelia were separated by filtration. The medium was saturated with NaCl and extracted with CH_2Cl_2 (~800 mL), and the mycelia were also extracted with CH_2Cl_2 (~200 mL). Both CH_2Cl_2 extracts were mixed, the solvent was evaporated, and a crude extract (897 mg) was obtained. The extract was chromatographed on a Si-60 column with hexane/EtOAc (stepwise 19:1 to 1:19) to yield metabolites **2** (92 mg), **3** (19 mg), **4** (92 mg), and **5** (157 mg). Furthermore, the high polar fraction was chromatographed on a Si-60 column with chloroform/MeOH (stepwise 19:1 to 1:1), and **6** (68 mg) was isolated.

*Compound **2**:* oil; $[\alpha]^{25}_D$ −2.71° ($CHCl_3$; *c* 0.5); EI-MS, *m*/*z* (rel int) 141 $[M - CH_3]^+$ (0.3), 138 $[M - H_2O]^+$ (0.2), 123 $[M - CH_3 - H_2O]^+$ (9), 109 (2), 95 (6), 83 (10), 81 (7), 67 (12), 59 (100), 55 (25), 43 (36), 41 (26); IR ν_{max} cm^{-1} 3385, 2966, 2933, 1465, 1375, 1162, 909; ^{1}H, ^{13}C NMR (Tables 1 and 2).

*Compound **3**:* oil; $[\alpha]^{25}_D$ +3.76° ($CHCl_3$; *c* 0.4); EI-MS, *m*/*z* (rel int) 154 $[M - CH_3COOH]^+$ (0.2), 139 $[M - CH_3COOH - CH_3]^+$ (6), 136 $[M - CH_3COOH - H_2O]^+$ (2), 131 (8), 121 (11), 109 (5), 93 (12), 81 (23), 71 (100), 68 (14), 56 (39), 43 (85); IR ν_{max} cm^{-1} 3429, 2927, 1734, 1457, 1369, 1262, 1158; ^{1}H, ^{13}C NMR (Tables 1 and 2).

*Compound **4**:* oil; $[\alpha]^{25}_D$ +2.27° ($CHCl_3$; *c* 0.3); EI-MS, *m*/*z* (rel int) 154 $[M - H_2O]^+$ (0.1), 139 $[M - H_2O - CH_3]^+$ (8), 136

Scheme 1. Possible Metabolic Pathways of Compound 1 by *G. cingulata*



$[M - 2H_2O]^+$ (0.8), 121 (12), 109 (5), 93 (6), 81 (30), 71 (100), 68 (43), 59 (36), 43 (72); IR ν_{max} cm^{-1} 3380, 2971, 2927, 1459, 1374, 1186, 1167, 1035, 918; ^1H, ^{13}C NMR (Tables 1 and 2).

Compound ***5****:* oil; $[\alpha]^{25}_D$ +5.38° ($CHCl_3$; *c* 0.5); HRFAB MS (pos), *m/z* 233.1733 $[MH]^+$, calcd for $C_{12}H_{25}O_4$ 233.1753; EI-MS, *m/z* (rel int) 172 $[M - CH_3COOH]^+$ (1), 157 $[M - CH_3COOH - CH_3]^+$ (1), 141 (15), 123 (42), 112 (5), 101 (10), 95 (11), 81 (33), 69 (33), 55 (32), 43 (100); IR ν_{max} cm^{-1} 3405, 2938, 2877, 1734, 1369, 1261, 1207, 1155, 1082, 1050, 1020; ^1H, ^{13}C NMR (Tables 1 and 2).

Compound ***6****:* oil; $[\alpha]^{25}_D$ +6.60° ($CHCl_3$; *c* 0.5); HRFAB MS (pos), *m/z* 191.1671 $[MH]^+$, calcd for $C_{10}H_{23}O_3$ 191.1647; EI-MS, *m/z* (rel int) 157 $[M - CH_3 - H_2O]^+$ (2), 141 $[M - 2CH_3 - H_2O]^+$ (10), 123 (36), 95 (7), 81 (33), 71 (32), 59 (100), 43 (89), 41 (29); IR ν_{max} cm^{-1} 3420, 2937, 1658, 1466, 1380, 1212, 1157, 1081, 1050; ^1H, ^{13}C NMR (Tables 1 and 2).

RESULTS AND DISCUSSION

To investigate the time course of relative abundance between substrate and metabolites on the microbial transformation of **1** by *G. cingulata*, a small amount of **1** was incubated with the organism for 10 days. Five major metabolites and some minor metabolites were detected by TLC, GC, and GC-MS analysis. These metabolites were not detected by TLC and GC analysis of the culture of *G. cingulata* to which no substrate (**1**) had been fed or when the mixture of **1** and the culture medium had been incubated under static conditions for 10 days. It was demonstrated that *G. cingulata* transformed **1** into various metabolites. The time course of relative concentration changes of substrate (**1**) and metabolites (**2**−**6**) was monitored by TLC and quantitatively measured by using a GC method (Figure 1). Almost all beginning substrate **1** was consumed in 6 days. Metabolites **2**−**4** disappeared by 8−10 days. Metabolite **5** increased after 3 days and then decreased rapidly after 8 days, whereas metabolite **6** increased rapidly after 8 days. To isolate metabolites **2**−**6**, a large-scale incubation of **1** using *G. cingulata* was carried out for 4 days. After the biotransformation, the culture was extracted and metabolites **2**−**6** were isolated from the crude extract. The structures of **2**−**6** were determined by spectral analysis.

The molecular formula of metabolite **2** was shown to be $C_{10}H_{20}O$ on the basis of its mass spectrum. Other spectral data indicated the loss of the acetyl group and the presence of a tertiary hydroxyl group (δ_C 71.1; ν_{max} 3385, 1162 cm^{-1}). The ^1H and ^{13}C NMR spectra (Tables 1 and 2) were assigned by comparison with the spectral data for **1** and the previous paper (Bohlmann et al., 1975); in addition, these spectral data corresponded to an authentic sample of dihydromyrcenol. On the basis of the above results, metabolite **2** was identified as dihydromyrcenol. It had been reported that metabolite **2** was formed by chemical hydration of dihydromyrcene (Matsubara et al., 1973); however, there was no report of the production of **2** by biotransformation.

The mass spectrum indicated that metabolite **3** had a molecular formula of $C_{12}H_{22}O_3$. From other spectral data, **3** had an acetyl group (δ_H 1.97; δ_C 170.7, 22.4; ν_{max} 1734, 1262 cm^{-1}) and a tertiary hydroxyl group (δ_C 73.2; ν_{max} 3429, 1158 cm^{-1}). The ^1H and ^{13}C NMR spectra (Tables 1 and 2) were assigned by comparison with the spectral data for **1** and **2**. On the basis of these spectral data, metabolite **3** was identified as 3,7-dihydroxy-3,7-dimethyl-1-octene-7-carboxylate. Rapp and Mandery (1988) reported that metabolite **3** was formed on the biotransformation of linalool by *Botrytis cinerea*.

Metabolite **4** had a molecular formula of $C_{10}H_{20}O_2$ that was estimated by its mass spectrum. Other spectral data indicated the presence of two tertiary hydroxyl groups (δ_C 71.1, ν_{max} 3380, 1167 cm^{-1}; and δ_C 73.3, ν_{max} 3380, 1186 cm^{-1}). The ^1H and ^{13}C NMR spectra (Tables 1 and 2) were assigned by comparison with the spectral data for **1**−**3** and the previous paper (Williams et al., 1980). These spectral data suggested that metabolite **4** was 3,7-dihydroxy-3,7-dimethyl-1-octene. There was a report that metabolite **4** was synthesized from isoprene (Takabe et al., 1975).

Metabolite **5** had a molecular formula of $C_{12}H_{24}O_4$ based on its HRFAB MS. Other spectral data indicated the presence of an acetyl group (δ_H 1.97; δ_C 170.5, 22.5/22.6; ν_{max} 1734, 1261 cm^{-1}), a primary hydroxyl group (δ_H 3.54; δ_C 64.7/65.1; ν_{max} 3405, 1020 cm^{-1}), and a secondary hydroxyl group (δ_H 3.69; δ_C 76.1/75.5; ν_{max} 3405, 1082 cm^{-1}). The ^1H and ^{13}C NMR spectra (Tables 1 and 2) were assigned by comparison with the spectral data for compounds **1**−**4**. It was concluded that metabolite **5** was a novel compound, 3,7-dimethyloctane-1,2,7-triol-7-carboxylate.

Metabolite **6** had a molecular formula of $C_{10}H_{22}O_3$ based on its HRFABMS. The results of the spectral data indicated the presence of a primary hydroxyl group (δ_H 3.50; δ_C 64.6/65.0; ν_{max} 3420, 1057 cm^{-1}), a secondary hydroxyl group (δ_H 3.70; δ_C 76.0/75.3; ν_{max} 3420, 1081

cm^{-1}), a tertiary hydroxyl group (δ_C 71.12/71.08; ν_{max} 3420, 1157 cm^{-1}), and no acetyl group. The ^1H and ^{13}C NMR spectra (Tables 1 and 2) were assigned by comparison with the spectral data for compounds **1**−**5**. On the basis of these spectral data, metabolite **6** was determined to be a novel compound, 3,7-dimethyloctane-1,2,7-triol.

The metabolic pathways for the biotransformation of **1** by *G. cingulata* (Scheme 1) were derived from the time course experiment (Figure 1) and the structures of the metabolites. The major metabolite **6** was considered to be formed by way of two pathways (A, **1** → **5** → **6**; B, **1** → **2** → **6**). In route A, the substrate **1** was oxidized at the double bond to glycol (**1** → **5**). This glycol (**5**) was possibly formed via epoxidation and subsequent hydrolysis of the epoxide, although the intermediate epoxide could not be detected. Then compound **5** was deacetylated (**5** → **6**); from Figure 1, this route is suggested to be the main metabolic pathway. Metabolite **6** was also formed through route B, that is, the deacetylation of **1** (**1** → **2**) and subsequent oxidation at the double bond to glycol (**2** → **6**). To clarify the probability that **6** was produced not only from **5** but also from **2**, a small amount of **2** (authentic sample) was incubated with *G. cingulata* for 10 days. As a result, two major metabolites were detected by TLC, GC, and GC-MS analysis. The time course of relative concentration changes of **2** and two metabolic products was monitored by TLC and quantitatively measured by using a GC method (Figure 2). Their retention time on GC and mass spectra given by GC-MS corresponded to compounds **4** and **6**, respectively. These results demonstrated that metabolite **2** was converted into metabolites **4** and **6** by *G. cingulata*. Because the rate of this conversion was slow (Figure 2), route B (**1** → **2** → **6**) was considered to be a minor pathway.

Metabolite **4** was formed via two possible pathways (C, **1** → **2** → **4**; D, **1** → **3** → **4**). In route C, the substrate **1** was deacetylated (**1** → **2**) with subsequent introduction of the hydroxyl group at the C-3 position of **2** to give **4**. This route was proved from the time course experiment (Figure 2). In route D, however, first the hydroxyl group was introduced at the C-3 position of **1** (**1** → **3**) and then deacetylated (**3** → **4**), although it was not verified that **4** was produced from **3**.

The above results demonstrated that the oxidation of the remote double bond, deacetylation, and introduction of a hydroxyl group into the C-3 position of **1** proceeded enzymatically by *G. cingulata*. These results were similar to our previous results of biotransformation of acyclic terpenoids by *G. cingulata* [see, for instance, Nankai et al. (1997, 1998a,b)]. We are now considering the investigation of the biotransformations of other acyclic terpenoids using this fungus and the larvae of common cutworm (*S. litura*) (Miyazawa and Murata, 2000).

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