Bioscience, Biotechnology, and Biochemistry

ISSN: 0916-8451 (Print) 1347-6947 (Online) Journal homepage: http://www.tandfonline.com/loi/tbbb20

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To cite this article: Hiroshi Nago, Miwako Matsumoto & Syuryo Nakai (1993) Degradative Pathway of 2-Deceno-δ-lactone by the Lactone-producing Fungus, Fusarium solani, Bioscience, Biotechnology, and Biochemistry, 57:12, 2111-2115, DOI: 10.1271/bbb.57.2111

To link to this article: http://dx.doi.org/10.1271/bbb.57.2111

Published online: 12 Jun 2014.

Biosci. Biotech. Biochem., **57** (12), 2111–2115, 1993

Degradative Pathway of 2-Deceno-δ-lactone by the Lactone-producing Fungus, *Fusarium solani*

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Received June 10, 1993

The degradative pathway of 5-alkanolides (alkano-δ-lactones) and 2-deceno-δ-lactone (massoialactone) by *Fusarium solani* PM-1, a massoialactone-producing fungus, was investigated. (±)-Alkano-δ-lactones were shown to be degraded first to a one-carbon-atom-less methyl ketone, 4-hydroxy-2-alkanones, after hydroxylation. The 4-hydroxy-2-alkanones were then converted to 2,4-alkanediones or to 2,4-alkanediols, and are suggested to be successively degraded by modified β-oxidation. (*R*)-Massoialactone, the main compound in the volatiles produced by the strain, was first saturated to (*R*)-decano-δ-lactone, and then this saturated lactone was degraded in the same way. These observations lead to a conceptional cycle of acetate moieties throughout the production and degradation of the secondary metabolites.

In the preceding paper, we reported certain strains of *Fusarium solani* that produced (*R*)-(−)-2-deceno-δ-lactone (massoialactone, **1**) in a potato-dextrose-agar (PDA) medium. These strains had been isolated from decayed coconut and from the soil of a peach orchard. During the isolation process for the strains, the microorganisms were enriched in a medium containing alkano-δ-lactones as the sole source of carbon. The isolated strain of *F. solani* PM-1 grew well, assimilating (±)-decano-δ-lactone (**2**) as the sole source of carbon, and it could also grow when the decano-δ-lactone was substituted by massoialactone, the main compound in the volatile products of strain PM-1.

In this paper, we describe the results of experiments to investigate the mechanism by which the microorganisms convert the lactones to the primary metabolites.

Few papers have been published on the degradative pathways of secondary metabolites in producing organisms, compared with many studies on the degradative pathways in non-producing organisms.[1-5] An early work by Kalberer has shown that caffeine was degraded to allantoin, urea, and finally to carbon dioxide in the leaves of the producing organisms, *Coffea arabica* L.[6] Numerous observations on the secondary products of plants, as in this example, have unequivocally been made, showing that secondary products were subjected to turnover and degradation in the cells of mother organisms.[7,8]

For the secondary products of microorganisms, Malik and Vining have shown an example of the degradation of chloramphenicol by producing organisms to give *p*-nitrobenzyl alcohol and *p*-nitrobenzoic acid; however, no further degradation was shown.[9] In the culture of *Monilinia fructicila*, emodin, an anthraquinone derivative which has been reported from many plants and microorganisms, was transformed to a benzophenone derivatives, and then to other metabolites by the producing organisms.[10] Kominek has shown that cycloheximide was finally degraded to carbon dioxide by the producing organisms, and that the cycloheximide accumulation in a fermentation medium was a result of the balance between synthesis and degradation of this antibiotic.[11] However, in these reports, it was uncertain whether these compounds could be turned to use as energy sources or reconstructive sources of other products; in other words, the final fate of the degraded secondary products remains unidentified.

In the case of the massoialactone described in our previous report, it was obvious that the secondary metabolite was degraded to the primary metabolite, and was used as both carbon and energy sources by the producing organisms, because the microorganisms could grow in a medium containing the δ-lactones as the sole source of carbon. Massoialactone is a relatively simple compound as a secondary metabolite; therefore, it may provide a good example for studying the general nature of degradative secondary metabolites in producing organisms.

In this study, oily droplets of alkano-δ-lactones or massoialactone were added to a PDA medium on which the fungi were grown. After incubating for several days, the compounds converted from the lactone were extracted and identified.

Materials and Methods

Microorganisms. Fusarium solani PM-1, which was described in the preceding paper, was used in all experiments in this study.

Chemicals. (±)-Alkano-δ-lactones were purchased from Aldrich Chemical Co., Wisconsin. Racemic and (*R*)-(−)-massoialactone were kindly supplied by Nagaoka & Co., Osaka, Japan, and the other chemicals were purchased from Nacalai Tesque, Kyoto, Japan.

Incubation and isolation of the compounds. Twenty ml of a potato-dextrose-agar (PDA) medium in a petri dish (9 cm) was inoculated with spores of strain PM-1 and then incubated at 25°C for 3 days. On the surface of the growing culture, 20 mg of oily droplets of one of each lactone (octano-, decano-, undecano-, and dodecano-δ-lactones, and massoialactone) were spread across the surface with a glass rod. The incubation was continued for several more days, and the culture mats were then steam distilled. The steam distillates were thereafter extracted with methylene chloride, and dried over anhydrous sodium sulfate.

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Abbreviation: PDA, potato-dextrose-agar.

GC, GC-MS, and NMR measurements. The same instruments under the same operating conditions as those described in the previous paper[19] were used, unless stated otherwise for some of the cases described. For the enantiomeric analysis of 4-hydroxy-2-nonanone, CP-cyclodex-B236-M-19 (Chrompack) was used under the following conditions: column temperature, 90°C (held for 30 min) and increased at 2°C/min; carrier gas, He 1.8 kg/cm^2; flow rate, 65 ml/min.

Results and Discussion

Isolation and identification of the main degradation products (4-hydroxy-2-alkanones)

Octano(C-8)-, decano(C-10)-, undecano(C-11)-, and dodecano(C-12)-δ-lactones, which were each applied to the surface of the growing culture of *F. solani* PM-1 were readily transformed to other volatiles which had lower retention times. The gas chromatographic (GC) profiles of the volatiles obtained from the cultures containing octano-, decano-, and dodecano-δ-lactones are shown in Fig. 1A, B, and C, respectively.

The series of degraded compound **4** (**A-4**, **B-4**, and **C-4**) which were predominant compounds in the early stage of degradation, are considered to have been key compounds in this degradation reaction; therefore we first tried to characterize peak compound **B-4** derived from decano-δ-lactone. The compound was probably a carbonyl compound because it reacted, to some extent, with sodium bisulfite, although its concentration was not high enough to conduct a separation procedure. The compound was not soluble in dilute sodium hydroxide, although it was partially decomposed in an aqueous alkali to smaller compounds, one of which was identified as *n*-hexanal. Compound **B-4** was finally isolated by thin-layer silica gel chromatography.

The IR spectrum of compound **B-4** indicated a strong carbonyl absorption at 1720 cm^{-1}, a broad hydroxyl absorption at 3432 cm^{-1}, and a methylene absorption at 2957, 2931, and 2860 cm^{-1}. In the high-resolution mass spectrum of the compound, the peak that appeared at *m/z* 140.1251 (calcd. for $C_9H_{16}O$, 140.1202) is ascribed to the $M^+ - H_2O$ ion, in consideration of the ^{1}H-NMR spectrum that indicates the presence of 18 protons. In the EI-MS data, a very small peak (0.2%) of the potential molecular ion was detected at *m/z* 157 as $M^+ - 1$. The other EI-MS fragments are listed in Table I, together with those of peaks **A-4**, **C-4** and the corresponding peak from undecano-δ-lactone.

The ^{1}H-NMR spectrum at 270 MHz shown in Fig. 2 indicates a methyl signal at δ 0.89 ppm (3H), a methylene multiplet in the region of δ 1.20–1.60 ppm (8H), and a 3H singlet of methyl ketone at δ 2.18 ppm. The pattern of the multiplet in the region of δ 2.48–2.67 ppm (2H) suggests that methylene protons were deposited between the ketone and the chiral carbon of a secondary alcohol. These non-equivalent *gem*-protons centered at δ 2.53 and 2.64 ppm were coupled to each other (J = 17.7 Hz) and split by unequal vicinal coupling (J = 8.5 and 3.1 Hz) to the proton attached

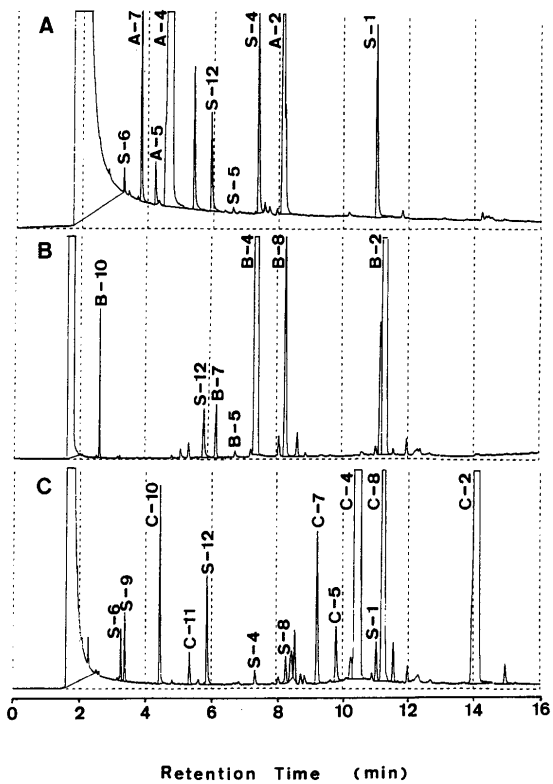

Fig. 1. Gas Chromatograms of the Volatiles Obtained from Solid Cultures of *Fusarium solani* PM-1 Containing Octano-δ-lactone (A), Decano-δ-lactone (B), and Dodecano-δ-lactone (C).

Culture conditions: incubation for 7 days after applying the lactones; GC conditions: column, 0.2 mm i.d × 50 m OT-FS bonded with CBP-1; temperature, from 80°C at a rate of 10°C/min; carrier gas, nitrogen set at 4 kg/cm^2; other conditios are as described in the Materials and Methods section. The peak compounds which are considered to have been original secondary metabolites or those derivatives are denoted by the letter S.

Table I. Mass Spectral Data for 4-Hydroxy-2-alkanones

4-Hydroxy-2-alkanone	MW	Spectral data, *m/z* (%)
4-Hydroxy-2-heptanone	130	87 (100), 55 (99), 58 (97), 97 (84), 72 (70), 112, (42), 57 (31), 69 (22), 94 (9), 115 (5)
4-Hydroxy-2-nonanone	158	56 (100), 87 (89), 58 (75), 55 (69), 57 (49), 125 (29), 82 (37), 72 (27), 71 (26), 97 (24), 111 (7), 140 (4)
4-Hydroxy-2-decanone	172	70 (100), 55 (95), 58 (67), 87 (52), 71 (50), 57 (45), 69 (42), 97 (31), 96 (30), 81 (28), 139 (27), 111 (8), 125 (4), 154 (4)
4-Hydroxy-2-undecanone	186	55 (100), 69 (99), 56 (97), 71 (70), 58 (67), 68 (46), 97 (41), 110 (37), 81 (36), 82 (33), 153 (30), 85 (29), 100 (20), 95 (20), 125 (10), 135 (4), 168 (3)

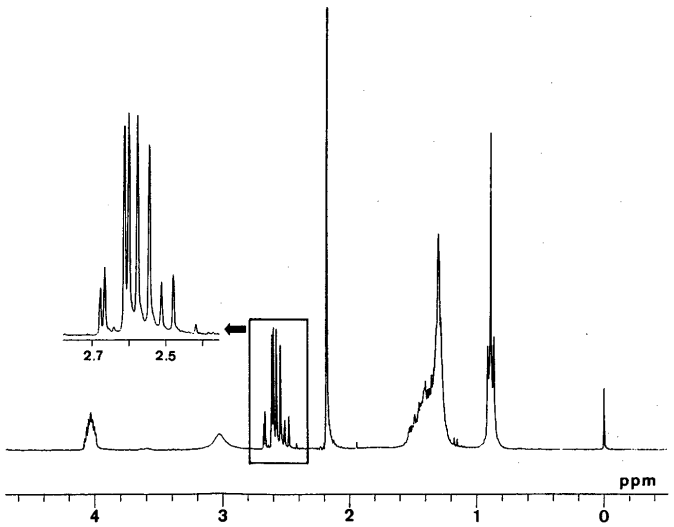

Fig. 2. ^{1}H-NMR Spectrum of 4-Hydroxy-2-nonanone at 270 MHz.

to the chiral carbon. The hydroxyl proton is indicated as a broad peak centered at δ 3.03 ppm (1H). The multiplet of the proton attached to the chiral carbon is indicated in the region of δ 3.99–4.10 ppm centered at δ 4.04 ppm of the spectrum.

The ^{13}C-NMR spectrum at 67.80 MHz measured by the DEPT (distortionless enhancement by polarization transfer) method indicate the presence of two methyl carbons at δ 13.98 and 30.73 ppm, a methine carbon at 67.52 ppm, five methylene carbons at 22.56, 25.10, 31.70, 36.32, and 49.92 ppm, and a carbonyl carbon at 210.04 ppm.

All these spectral data suggest the structure of volatile compound **B-4** to be 4-hydroxy-2-nonanone. Corey,[12] Molander,[13] and Eichenauer *et al.*[14] have synthesized 4-hydroxy-2-nonanone and reported its spectral data. The data just described are almost identical to those reported. We then synthesized the compound by a simple aldol condensation, using *n*-hexanal, acetone, and aqueous sodium hydroxide. The dominant product in the reaction was purified by TLC, and its IR, and ^{1}H-NMR spectra were obtained. These spectral data perfectly matched those of the microbially degraded product of (±)-decano-δ-lactone. Furthermore, 4-hydroxy-2-heptanone was synthesized, and it was confirmed to be identical to compound **A-4**, the main degradation product of (±)-octano-δ-lactone by the strain.

2-Alkanones as degraded products from n-alkanoic acids by strain PM-1 of Fusarium solani

At the beginning of this series of studies, the δ-lactone was assumed to be directly derived from *n*-alkanoic acids; accordingly, feeding decano-, dodecano-, and tetradecanoic acids to the growing culture was attempted. However, no appreciable stimulation of lactone production by adding these fatty acids was observed, and the most dominant degraded products from those fatty acids at the early stage of decomposition were 2-nonanone, 2-undecanone and 2-tridecanone accompanying the corresponding 2-alkanols (data are not shown). This suggested that the alkano-δ-lactones added to the culture medium of the strain were first hydrolyzed to 5-hydroxy alkanoic acids (**3**), and then decarboxylated to 4-hydroxy-2-alkanones. The GC peak for the hydrolyzed hydroxy-fatty acid appeared when the culture mats were extracted directly by an organic solvent without steam distillation. However, it was not resolved whether the hydrolysis had been catalyzed by an enzyme.

Identification of 2,4-alkanediones (**5**), *2,4-alkanediols* (**8**), *3-alken-2-ones* (**7**), *and other volatiles*

2,4-Alkanediones were synthesized by a Claisen condensation using 2-pentanone, 2-nonanone, and ethyl acetate.[15] The products yielded peaks identical to A-**5** (2,4-heptanedione) and C-**5** (2,4-undecanedione) with three types of OT-FS columns. Synthesized 4-hydroxy-2-heptanone and 4-hydroxy-2-nonanone were reduced by sodium borohydride in ethylene glycol. The peaks of the products, 2,4-heptanediol and 2,4-nonanediol, were identical to those of A-**8** and B-**8**. Peak B-**8** derived from microbial degradation, as well as the peak for the synthesized diols, were split into two diastereomeric peaks in the other OT-FS columns, OV-1701 and PEG-20M; however, the stereochemistry of the diols was not investigated.

Synthesized 4-hydroxy-2-heptanone and 4-hydroxy-2-nonanone were heated in dilute sulfuric acid, and the respective dehydrated products, 3-hepten-2-one and 3-nonen-2-one,[16] were identical to compounds A-**7** and B-**7**, respectively. The 3-alken-2-ones were discovered to have

Table II. Compounds from the Cultures of *F. Solani*

Applied lactone	Peak number	Compound
Octano-δ-lactone (Fig. 1A)	A-2	Octano-δ-lactone
	A-4	4-Hydroxy-2-heptanone
	A-5	2,4-Heptanedione
	A-7	3-Heptene-2-one
	S-1	Massoialactone
	S-4	4-Hydroxy-2-nonanone
	S-5	2,4-Nonanedione
	S-6	2-heptanone
	S-12	β-Phenyl ethanol
Decano-δ-lactone (Fig. 1B)	B-2	Decano-δ-lactone
	B-4	4-Hydroxy-2-nonanone
	B-5	2,4-Nonanedione
	B-7	3-Nonen-2-one
	B-8	2,4-Nonanediol
	B-10	*n*-Hexanal
	S-12	β-Phenyl ethanol
Dodecano-δ-lactone (Fig. 1C)	C-2	Dodecano-δ-lactone
	C-4	4-Hydroxy-2-undecanone
	C-5	2,4-Undecanedione
	C-7	3-Undecen-2-one
	C-8	2,4-Undecanediol
	C-10	*n*-Octanal
	C-11	*n*-Octanol
	S-1	Massoialactone
	S-4	4-Hydroxy-2-nonanone
	S-6	2-Heptanone
	S-8	2,4-Nonanediol
	S-9	2-Heptanol
	S-12	β-Phenyl ethanol

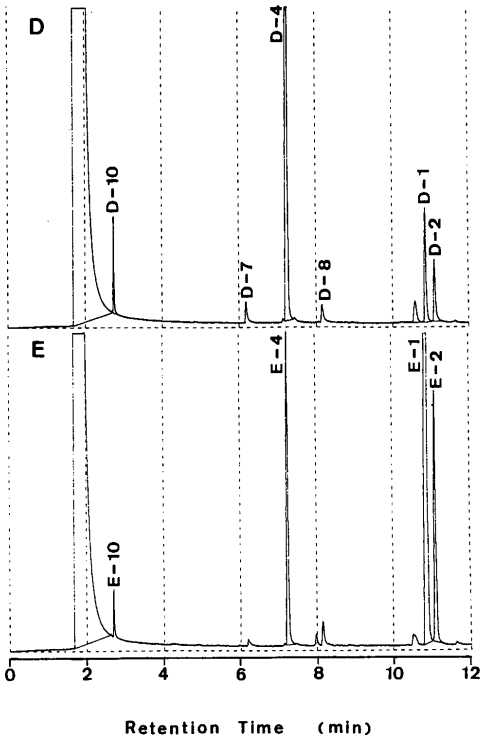

Fig. 3. Gas Chromatograms of Microbially Converted Products from (*R*)-(−)-Massoialactone (D), and (±)-Massoialactone (E).
Conditions are the same as those in the legend to Fig. 1.

Table III. Yield (%) and Enantiomeric Composition (% *e.e.*) of Products in the Degradation Process of δ-Lactones by *F. solani* PM-1 after Incubating for 5 Days

Substrate	Residual substrate		Products			
			Decano-δ-lactone		4-Hydroxy-2-nonanone	
	Recovery (%)	Enant. Comp. (%)	Yield (%)	Enant. Comp. (%)	Yield (%)	Enant. Comp. (%)
(−)-Massoialactone	—[a]	(*R*): 100 (*S*): 0	—[a]	(*R*): 100 (*S*): 0	—[a]	(*R*): 100 (*S*): 0
(±)-Massoialactone	32[b]	(*R*): 45.8 (*S*): 54.2	5[b]	(*R*): 31.7 (*S*): 68.3	2	(*R*): 70.9 (*S*): 29.1
(±)-Decano-δ-lactone	10	(*R*): 41.5 (*S*): 58.5	—	— —	5	(*R*): 70.3 (*S*): 29.7

[a] Not determined.
[b] Recovery or yield is expressed as % to that of the added δ-lactones (20 mg, 100%) in a petri dish.

been mostly generated during the isolation process of steam distillation by comparing the steam distillates with the solvent extracts of the cultures without steam distillation.

The identified volatiles derived from octano-, decano-, and dodecano-δ-lactone, including the compounds just described, and listed in Table II. Some other lower molecular-weight compounds identified by GC-MS and retention indices, using the other OT-FS column, from the culture containing octano-δ-lactone were furfural, 1-hepten-4-ol, 3-methyl-1-butanol, 2-heptanone, 1-butanol, ethyl *n*-butyrate, 1-butanal, and acetone. Most of these volatiles were probably the original secondary products of the fungi, or otherwise the by-products due to the scavenging pathways for the products derived from the added lactone.

Identified volatiles derived from (R)-(−) and racemic massoialactone

The major volatile compound in the secondary metabolites of strain PM-1, (*R*)-(−)-massoialactone (**1**), was accumulated in the cells of the fungi as described in the preceing paper. In this experiment, two kinds of commercial massoialactone, one obtained from the bark oil of *Cryptocarya massoia*,[17,18] and the other being synthesized racemic lactone, were decomposed by strain PM-1. We found that these two massoialactones were also transformed by the microorganisms like the saturated δ-lactones were. The gas chromatographic profiles of the products derived from (*R*)-(−)-massoialactone and racemic massoialactone are shown in Fig. 3. Peak compounds D-**2** and E-**2** appearing in Fig. 3 were identified as decano-δ-lactone based on GC-MS retention and fragmentation. These results demonstrate that massoialactone was first saturated to decano-δ-lactone, which was then degraded in the same way as that already described, although a little difference is apparent between the two profiles of D and E in Fig. 3; for example, the absence of a peak at 8.0 min for D. This difference is probably due to slight difference in degradation mechanism between (*R*)- and (*S*)-massoialactone.

Stereo-selectivity of the catabolic reaction

The enantiomeric compositions of the degraded products and residual substrates derived from the degradation of massoialactone and decano-δ-lactone were determined by GC,[19] the results being listed in Table III. The original secondary product of the strain, (*R*)-massoialactone, was

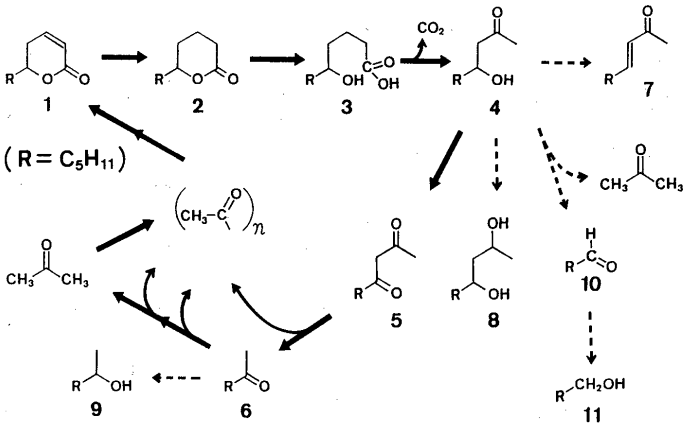

Fig. 4. Proposed Degradative Pathway for Massoialactone by Massoialactone-producing Fungi *F. solani* PM-1.

⟶ shows the suspected main route, and ⟶ shows the suspected bypass routes to by-products. Compounds: **1**, massoialactone; **2**, 2-decano-δ-lactone; **3**, 5-hydroxydecanoic acid; **4**, 4-hydroxy-nonanone; **5**, nonan-2,4-dione; **6**, 2-heptanone; **7**, 3-nonen-2-one; **8**, 2,4-dihydroxy-nonane; **9**, 2-hydroxy-heptan; **10**, *n*-hexanal; **11**, *n*-hexanol.

stereochemically pure, the results showing that both (*R*)- and (*S*)-massoialactone that were added in the racemic form were degraded with low stereo-selectivity, the former being slightly faster than the latter. However, this seems quite reasonable because strain PM-1 is considered to be a parasite of coconut which contains both (*R*)- and (*S*)-alkano-δ-lactones.[20]

All of the described observations lead to the degradative pathway for massoialactone that is proposed in Fig. 4. Decano-δ-lactone derived from massoialactone is suggested to have been continuously degraded by modified β-oxidation releasing acetyl moieties.

(R)-4-Hydroxy-nonanone detected in the culture containing octano-δ-lactone

In Fig. 1A, medium-sized peak S-**4**, which was identified to be 4-hydoxy-2-nonanone by GC-MS, can be seen, as well as a large peak of 4-hydroxy-2-heptanone derived from the added octano-δ-lactone. The former is considered to have been derived from (*R*)-decano-δ-lactone, a hydrogenated product of (*R*)-massoialactone (S-**1**), which is the original secondary metabolite of the fungi. Peak S-**4** in Fig. 1A was found to consist of 100% (*R*)-4-hydroxy-2-nonanone enantiomerically. The appearance of this

compound in the culture containing octano-δ-lactone suggests that (*R*)-massoialactone produced in the cells was subjected to continuous degradation, and that the accumulation of massoialactone was the result of balance between the production and degradation of the lactone as in the case of the cycloheximide.[11] This compound, which was not found in the culture without the addition of δ-lactone, was probably accumulated as a result of the catabolite repression or inhibition promoted by the degraded products downstream; for example, 4-hydroxy-2-heptanone or other methylketones.[21] In Fig. 1 and Table II, the compounds which are presumed to have been derived from the secondary metabolites of the fungi are designated by the letter S.

Concluding comments on the degradative reactions

Yagi *et al.* have reported that wide varieties of filamentous fungi, which were classified into *Ascomycotina*, *Basidiomycotina*, *Mastigomycotina*, *Zygomycotina*, and *Deuteromycotina*,[22,23] and including *Fusarium solani*, had ability to produce 2-alkanones by successive oxidation and decarboxylation mainly from the corresponding one-carbon-atom-longer fatty acids. This may show that the fungi, which have ability to degrade alkano-δ-lactones or 5-hydroxy alkanoic acids to 4-hydroxy-2-alkanones, were not exclusively δ-lactone-producing fungi, and that they are widespread in nature. Conversely, the δ-lactone-producing organisms could be found in wide varieties of filamentous fungi, if searched extensively. In addition to *Fusarium solani* that has already been described, we now have four strains of massoialactone-producing fungi, including the two strains of *Trichoderma viride* reported in the preceding paper. Another two strains of genus *Aureobasidium* will be described in a forthcoming paper.

Yagi *et al.* also investigated the 2-alkanone-forming enzyme system by using a cell homogenate prepared from the spores of *Penicillium decumbens* IFO 7091, a highly 2-alkanone-accumulative strain from a fatty acid.[24] They showed that the catalytic unit was specificically located in the wall-membrane fraction, and that the cooperative unit which could be replaced with Ca^{2+} was in the cytosol fraction. We discovered that strain IFO 7091 had the ability to form 4-hydroxy-2-nonanone from decano-δ-lactone. Both the 4-hydroxy-2-alkanones and the 2-alkanones derived from 5-hydroxy alkanoic acids and alkanoic acids, respectively, could be formed in the culture of *P. decumbens* IFO 7091 by the same enzyme system, this system probably being the same or very similar to that of *Fusarium solani* PM-1. However, *P. decumbens* IFO 7091 was demonstrated to be a non-producing organism of δ-lactones as well as *P. decumbens* NRRL 742, which has been reported by Halim *et al.* to produce 3-octanone, 3-hydroxy-1-octene, and some other sesquiterpenes in a potato-dextrose broth.[25] The difference between the two catabolic systems of the lactone in organisms, one with a biosynthetic system for the lactone, and the other without the system, need to be discussed, although we have no more data to support this contention. The degradation mechanisms for (*R*)- and (*S*)-massoialactone are suggested to be different, and clarification of this difference will be helpful.

A lactone is considered to be a compound of pentaketides, which are condensation products of acetate moieties.[26] On the other hand, massoialactone is suggested here to have been continuously degraded by modified β-oxidation, thereby releasing acetyl units which could be used as both carbon and energy sources by strain PM-1. Accordingly, the formation and degradation of massoialactone is considered to provide a conceptional cycle. This concept of acetate moieties is comparative to that of normal fatty acids, the storage compounds in both energy and carbon sources. However, massoialactone is probably unreasonable to refer to as a storage compound, because the accumulated amounts in the cells were very low. The significance of the cyclic production of massoialactone for producing organisms remains to be clarified. We have been searching for a reasonable answer to the ecological role of massoialactone, and intend to discuss this in a subsequent paper. The biosynthetic process, and the control mechanism for the production and degradation of the secondary metabolites are certainly potential topics of strong interest in the future.

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