Biosci. Biotechnol. Biochem., **66** (3), 571–575, 2002

JSBA

Erinacine Q, a New Erinacine from *Hericium erinaceum*, and its Biosynthetic Route to Erinacine C in the Basidiomycete

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Received September 17, 2001; Accepted November 6, 2001

Erinacines as cyathane-xylosides are known to have potent stimulating activity for nerve-growth-factor synthesis. Our search for new cyathane metabolites from a liquid culture of *Hericium erinaceum* YB4-6237 resulted in the isolation of a new erinacine named erinacine Q (1). NMR spectrometry and a chemical derivation from erinacine P (2) determined the compound to be a derivative in which the formyl group of erinacine P had been reduced to the hydroxymethyl group. To clarify the biosynthetic relationship between erinacine Q and the others, [1′-^{13}C]erinacine Q ([1′-^{13}C]-1) was chemically derived from [1′-^{13}C]erinacine P ([1′-^{13}C]-2) which had been prepared by feeding [1-^{13}C]-D-glucose to the basidiomycete. The biotransformation of labeled erinacine Q into [1′-^{13}C]erinacine C ([1′-^{13}C]-5) *via* [1′-^{13}C]erinacine P in this basidiomycete was demonstrated by NMR spectrometry.

Key words: erinacine Q; erinacines P and C; *Hericium erinaceum*; biosynthesis of erinacines; [1-^{13}C]-D-glucose

Erinacines[1–4)] and striatins,[5)] which are diterpene-xylosides possessing a cyathane skeleton, are currently attracting attention because of their unique biological activities. Erinacines have potent stimulating activity for nerve-growth-factor synthesis[1–4)] and agonistic activity towards the k opioid receptor.[6)] In particular, erinacine C (**5**) is known to the most potent stimulator of the erinacines for nerve-growth-factor synthesis.[1)] In addition, striatins have leishmanicidal activity.[7)] We have reported in a previous paper the isolation of new erinacine P (**2**) from the mycelia of *Hericium erinaceum* YB4-6237 and its *in vitro* biomimetic conversion into erinacine A (**3**) and B (**4**) (Fig. 1).[8)] Our search for new cyathane metabolites biosynthetically related to erinacines from this basidiomycete resulted in the isolation of a new cyathane-xyloside named erinacine Q (**1**) (Fig. 1) from the mycelial extract. From a biosynthetic point of view, **1** seems to be a precursor of **2** as a parental metabolite of **3**, **4** and **5**. We report here the isolation and structural elucidation of **1** from this basidiomycete, and its biotransformation into **5** *via* **2** by using [1′-^{13}C]erinacine Q ([1′-^{13}C]-**1**) and [1′-^{13}C]erinacine P ([1′-^{13}C]-**2**).

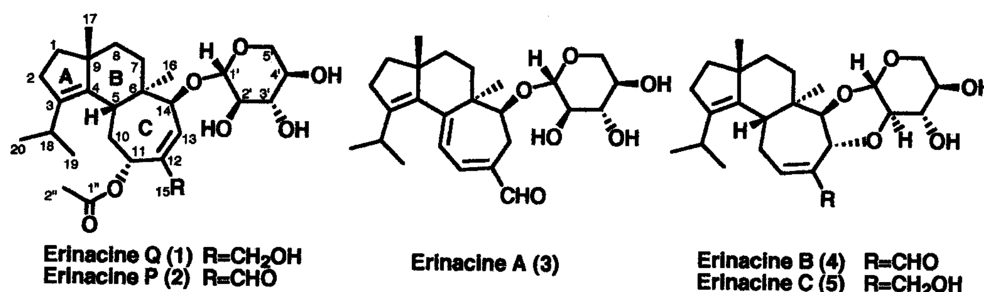

Fig. 1. Structures of Erinacines A, B, C, P and Q.

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Materials and Methods

General procedures. Optical rotation data were measured by a Horiba SEPA-300 digital polarimeter. ^{1}H- and ^{13}C-NMR spectra were recorded by a Jeol EX-400 spectrometer, and FABMS and HR-FABMS data were recorded by a JMS-700 mass spectrometer. Flash chromatography employed Wako FC-40 silica gel, and HPLC analysis was conducted with a Jasco PU-980 instrument equipped with a Jasco UV-970 detector.

Extraction and isolation. H. erinaceum YB4-6237 was reciprocally shake-cultured for 20 days at 25°C in 2000-ml Sakaguchi flasks, each containing 500 ml of a 5% D-glucose-0.5% peptone-1% Pharmamedia-0.5% NaCl medium. The fermentation broth (3 liter) was filtered to give mycelia (182 g by wet weight) and the culture filtrate. The mycelia were homogenized with acetone (900 ml), treated at 50°C for one hour and then filtered to give an aqueous acetone solution. This solution was concentrated under reduced pressure, and the resulting aqueous solution was extracted with *n*-hexane (450 ml) at pH 9, before the aqueous layer was extracted with EtOAc (450 ml). The EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a dark brownish residue (6.6 g). This residue was separated by silica gel flash chromatography, using mixtures of $CHCl_3$ and EtOH (40:1-5:1) as the eluent. The eluates were collected in test tubes (10 ml each) and analyzed by TLC. Known erinacines **4** (1313.5 mg, test tubes no. 46–63), **3** (254.2 mg, test tubes no. 64–72), **5** (98.0 mg, test tubes no. 76–81), and **2** (1633.3 mg, test tubes no. 82–115) were obtained, together with **1** as a new metabolite (147.1 mg, test tubes no. 130–133). The fraction containing **1** was further purified by silica gel flash chromatography with a mixture of $CHCl_3$-EtOH (40:1) to give **1** as a colorless amorphous solid (34.1 mg).

Erinacine Q (1): $[\alpha]_D^{25}$ −43.6° (*c* 0.20, $CHCl_3$). FABMS *m/z*: 517 $[M+Na]^+$, 495 $[M+H]^+$. HR-FABMS *m/z* $[M+Na]^+$: Calcd. for $C_{27}H_{42}O_8Na$: 517.2777, Found, 517.2773. ^{1}H-NMR (400 MHz, $CDCl_3$) δ (*J* in Hz): 0.77 (3H, s; Me-16), 0.94 (3H, d, 6.8; Me-19 or 20), 0.95 (3H, d, 6.8; Me-20 or 19), 1.03 (1H, br. d, *ca.* 13; H-7), 1.06 (3H, s; Me-17), 1.40 (1H, dm, *ca.* 13; H-8), 1.46 (1H, ddd, 12.8, 7.8 and 7.6; H-1), 1.49 (1H, ddd, 12.8, 12.8 and 4.2; H-8), 1.56 (1H, ddd, 12.8, 7.8 and 7.6; H-1), 1.95 (1H, br. d, 12.0 Hz; H-10), 2.10 (3H, s; Me-2″), 2.13 (1H, br. dd, *ca.* 13 and *ca.* 13; H-7), 2.26 (1H, ddd, *ca.* 12, *ca.* 12 and *ca.* 11; H-10), 2.26 (2H, *t*-like, *ca.* 8; H-2), 2.88 (1H, septet, 6.8; H-18), 3.03(1H, br. d, *ca.* 12; H-5), 3.30 (1H, dd, 12.0 and 8.0; H-5′), 3.52 (1H, dd, 7.6 and 6.2; H-2′), 3.57 (1H, dd, 7.8 and 7.6; H-3′), 3.70 (1H, ddd, 8.0, 7.8 and 4.4; H-4′), 3.73 (1H, d, 6.6; H-14), 4.01(1H, dd, 12.0 and 4.4; H-5′), 4.08 (2H, br. s; H-15), 4.47 (1H, d, 6.2; H-1′), 5.87 (1H, d, 6.6; H-13), and 5.98 (1H, br. d, 10.4; H-11). ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 16.5 (CH_3; C-16), 21.2 (CH_3; C-2″), 21.7 (CH_3; C-19 or 20), 21.8 (CH_3; C-20 or 19), 24.2 (CH_3; C-17), 26.7 (CH; C-18), 28.6 (CH_2; C-2), 33.4 (br., CH_2; C-7), 33.6 (br., CH_2; C-10), 36.6 (CH_2; C-8), 37.8 (CH_2; C-1), 40.5 (CH; C-5), 42.2 (C; C-6), 49.2 (C; C-9), 63.4 (CH_2; C-15), 64.6 (CH_2; C-5′), 69.5 (CH, C-4′), 72.3 (CH; C-2′), 73.9 (CH; C-11), 74.7 (CH; C-3′), 82.3 (CH; C-14), 103.9 (CH; C-1′), 125.7 (br., CH; C-13), 137.8(C; C-4), 140.0 (C; C-3), 143.8 (br., C; C-12), and 171.4 (C; C-1″).

HPLC analysis of the erinacines. Erinacines A, B and C were analyzed by HPLC under the following conditions: column, Crestpack C18S (150×4.6 mm i.d., Jasco); solvent, 40:10 CH_3OH/H_2O; flow rate, 1.5 ml/min; detection, 210 nm. The retention times of erinacines A, B and C were 4.1, 6.1 and 6.7 min, respectively. Erinacines P and Q were analyzed by the similar conditions: column, Crestpack C18S (150 ×4.6 mm i.d., Jasco); solvent, 40:70 CH_3CN/H_2O; flow rate, 2.5 ml/min; detector, 210 nm. The retention times of erinacines P and Q were 18.9 and 13.1 min, respectively.

Preparation of erinacine Q (1) from erinacine P (2). To an ice-cooled solution of **2** (11.1 mg, 0.0225 mmol) in MeOH (1 ml) was added excess $NaBH_4$ (~10 mg). The reaction mixture was stirred at 0°C for 20 min before adding aqueous 20% acetone (2.5 ml) and then extracted tree times with EtOAc (12 ml). The organic solution obtained was separated, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a residue. This residue was separated by silica gel flash chromatography with a mixture of $CHCl_3$ and EtOH (20:1) to give a colorless amorphous solid {8.4 mg, $[\alpha]_D^{25}$ −39.8° (*c* 0.20, $CHCl_3$)}. This material showed the same ^{1}H- and ^{13}C-NMR spectra, and $[\alpha]_D$ value as those of **1** isolated from the basidiomycete.

Preparation of [1′-^{13}C]erinacine P ([1′-^{13}C]-2). H. erinaceum YB4-6237 was reciprocally shake-cultured at 25°C in a 500-ml Sakaguchi flask containing 100 ml of a 2% D-glucose-0.3% peptone-0.6% Pharmamedia-0.5% NaCl medium. [1-^{13}C]-D-Glucose (0.5 g, 99 atom% ^{13}C, Sigma-Aldrich) was added 5 days after inoculation, and the culture was continued for a further 9 days. The fermentation broth (100 ml) was filtered to give mycelia (5.4 g by wet weight) and a residue (150 mg) in a similar manner to that already described. The residue was separated by silica gel flash chromatography with mixtures of $CHCl_3$ and EtOH (40:1–20:1) to yield ^{13}C-labeled **2** (9.0 mg). The

intensity of the C-1′ signal of [1′-^{13}C]-**2** was strongly enriched in the ^{13}C-NMR spectrum (Fig. 2(e)).

Preparation of [1′-^{13}C]erinacine Q ([1′-^{13}C]-1) from [1′-^{13}C]erinacine P ([1′-^{13}C]-2). The preparation of [1′-^{13}C]-**1** from [1′-^{13}C]-**2** (3.3 mg) was carried out in a similar manner to that already described to yield [1′-^{13}C]-**1** as a colorless amorphous solid (2.6 mg). Its ^{1}H- and ^{13}C-NMR data were in good agreement with those for **1**. The ^{13}C-NMR spectrum of [1′-^{13}C]-**1** is shown in Fig. 2(b).

Feeding experiments of [1′-^{13}C]erinacine Q ([1′-^{13}C]-1) to H. erinaceum YB4-6237. The basidiomycete was reciprocally shake-cultured at 25°C in a 100-ml Sakaguchi flask containing 30 ml of a 2% D-glucose-0.2% peptone-0.4% Pharmamedia-0.2% NaCl medium. [1′-^{13}C]-**1** (2.0 mg) was added 10 days after inoculation, and the culture was continued for a further 7 days. The fermentation broth (20 ml) was filtered to give mycelia (700 mg by wet weight) and a residue (20 mg) in a similar manner to that already described. This residue was separated by silica gel flash chromatography with mixtures of $CHCl_3$ and EtOH (40:1–20:1) to yield erinacine P (0.7 mg) as a colorless amorphous solid. Its ^{1}H- and ^{13}C-NMR data were in good agreement with those for [1′-^{13}C]-**2**. The ^{13}C-NMR spectrum is shown in Fig. 2(c).

Feeding experiments of [1′-^{13}C]erinacine P ([1′-^{13}C]-2) to H. erinaceum YB4-6237. The basidiomycete was reciprocally shake-cultured at 25°C in a 500-ml Sakaguchi flask containing 100 ml of a 2% D-glucose-0.2% peptone-0.4% Pharmamedia-0.2% NaCl medium. [1′-^{13}C]-**2** (4.0 mg), which had been prepared by feeding [1-^{13}C]-D-glucose to the basidiomycete, was added 13 days after inoculation, and the culture was continued for a further 16 days. The fermentation broth (100 ml) was filtrated to give mycelia (1.9 g by wet weight) and a residue (230 mg) by a similar manner to that already described. This residue was separated by silica gel flash chromatography with mixtures of $CHCl_3$ and EtOH (40:1–20:1) to yield erinacine C as a colorless amorphous solid (1.3 mg) and [1′-^{13}C]-**2** (1.6 mg). The ^{1}H- and ^{13}C-NMR data (Fig. 2(f)) for the solid were in good agreement with those quoted in the literature.[1)]

Results and Discussion

To elucidate the biosynthetic pathway to erinacines in *H. erinaceum* YB4-6237, we carefully analyzed the mycelial extract to find a new erinacine. A reciprocally shaken culture in 2000-ml Sakaguchi flasks, each containing 500 ml of a medium (5% D-glucose-0.5% peptone-1% Pharmamedia-0.5% NaCl) was chose as one of the most effective media for producing erinacines with this basidiomycete. The EtOAc extract (6.6 g) obtained from the mycelia was separated by silica gel flash chromatography with mixtures of $CHCl_3$ and EtOH (40:1-5:1) as the eluent and gave a new erinacine named erinacine Q (**1**).

The molecular formula of **1** was determined as $C_{27}H_{42}O_8$ from its HR-FABMS data. Its ^{1}H- and ^{13}C-NMR spectra showed similar signals to those of **2**.[8)] The former differed from the latter by the presence of a hydroxymethyl group [δ_H 4.08, (2H, br. s)] instead of a formyl group. The characteristic methine proton at C-11 in **1** appeared at δ 5.98 and was coupled to the methylene protons of C-10 in the H-H COSY spectrum. Its also had a correlation peak with the carbonyl carbon (δ_C 171.4) of the acetyl group in HMBC measument. The olefinic proton at δ 5.87 was coupled to an oxymethine proton of C-14 at δ 3.73. The stereochemistry at C-11 and C-14 was determined by difNOE experiments; clear NOEs were observed between H5/H11 and H14/H16. Thus, **1** has the same C-ring structure as that of **2**, but without the functional group at C-15. The absolute stereostructure of **1** was unambiguously confirmed by the chemical transformation of **2** to **1**. The specific rotation of the primary alcohol derivative from **2** (−39.8°) was good agreement with that of **1** (−43.6°). The stereo-structure of **1** was thus elucidated to be shown in Fig. 1.

While a trace amount of **4** was detected by the HPLC analysis, considerable amounts of **1** (*ca.* 150 mg/liter) and **2** (*ca.* 120 mg/liter) were detected 11 days after inoculating the YB4-6237 strain; the former then decreased rapidly to less than 30 mg/liter. The twenty-day culture of this strain gave large amounts of **2** and **4** (*ca.* 540 mg and *ca.* 440 mg from one liter of culture). In addition, our group has recently reported that **2** was chemically converted into **4** and then to **3** under mild chemical conditions.[8)] These findings suggest that **1** was a putative biosynthetic precursor of **2** as a parental metabolite of other important erinacines.

In order to clarify the biosynthetic relationship between **1** and other erinacines in this basidiomycete, we examined the incorporation of [1′-^{13}C]-**1** into **2**, and of [1′-^{13}C]-**2** into **4** and/or **5**. Details of the preparation of both [1′-^{13}C]-labeled erinacines can be found in the Materials and Methods section. In the ^{1}H-NMR spectrum of [1′-^{13}C]-**2**, the NMR signals were similar to those of **2**,[8)] apart from the occurrence of satellite signals of H-11, 13, 15, 16, 17, 19, 20, 1′ and 2″ due to mutual coupling with directly connected corresponding ^{13}C atoms. The absolute ^{13}C abundance at C-1′ was estimated to be *ca.* 20% from the ratio of the area of the satellite signals (δ_H 4.20 and 4.60) to that of the main signal (H-1′, δ 4.40). The absolute ^{13}C abundance at C-1′ of [1′-^{13}C]-**2** was estimated to be *ca.* 21% from the area of the satellite signals (δ 4.31 and 4.71) to that of the main signal

(H-1′, δ 4.51). Since each absolute ^{13}C abundance at C-1′ in addition to each intensity of the C-1′ signal of [1′-^{13}C]-**1** and [1′-^{13}C]-**2** was sufficiently enriched in their ^{13}C-NMR spectra (Figs. 2(b) and 2(e)), we used these ^{13}C-labeled substrates for the feeding experiments.

In view of the need to avoid any dilution of the ^{13}C-labeled substrate when feeding with endogenous erinacines, feeding experiments with [1′-^{13}C]-**1** (erinacine Q) were carried out in a reciprocally shaken culture in small 100-ml Sakaguchi flasks containing 30 ml of a diluted 2% glucose-0.2% peptone-0.4% Pharmamedia-0.2% NaCl medium, which resulted in low production of 2–3 mg of endogenous **2** in the medium (100 ml) by an HPLC analysis. When **2** was first detected in the mycelia 10 days after inoculation, [1′-^{13}C]-**1** was immediately added to the culture, and incubation was continued for a further 7 days. The EtOAc extract obtained from the mycelia was separated in a similar manner to that already described to yield **2**. Its ^{13}C-NMR spectrum (Fig. 2(c)) showed that the C-1′ position had been clearly labeled with the ^{13}C atom. The absolute ^{13}C abundance at C-1′ was obtained as *ca.* 12% by the ^{1}H-NMR analysis. These observations indicate that feeding erinacine Q had been easily metabolized with the endogenous one to erinacine P in the basidiomycete.

Feeding experiments with [1′-^{13}C]-**2** (erinacine P) were carried out in a similar manner to that used for [1′-^{13}C]-**1**. [1′-^{13}C]-**2** was added to the culture 13 days after inoculation, and incubation was continued for a further 16 days. Throughout these 16 days, trace amounts of **3** and **4** were detected in the mycelia by an HPLC analysis, and **5** was markedly accumulated. **5** and [1′-^{13}C]-**2** were respectively separated from the EtOAc extract which had been obtained from the mycelia. In the ^{13}C-NMR spectrum of **5** (Fig. 2(f)), the C-1′ position was clearly labeled with ^{13}C atom in comparison with that of non-labeled **5** (Fig. 2(g)). This observation indicates that erinacine P had been metabolized to erinacine C. The absolute ^{13}C abundance at C-1′ could not estimated by ^{1}H-NMR analysis, because satellite signals (δ 4.38 and 4.78) of the H-1′ signal (δ 4.58) overlapped the H-15 signals (δ 4.03 and 4.33) and H-13 signal (δ 4.81). ^{13}C-labeled **5**, however, was not diluted at all with endogenous **5**, because only a trace amount of **5** was detected by the HPLC analysis in the culture medium not containing ^{13}C-labeled **2**.

The α,β-unsaturated aldehyde moiety would be essential for a biosynthetic precursor of erinacines B and C. Since the most likely explanation is that the C-ring, which was common to erinacines B and C, would be formed by 1,4-conjugated addition to the β-position (C-13) of the α,β-unsaturated aldehyde with the 2′-hydroxy group of the xylosyl moiety, with subsequent elimination of the acetate.[8] In fact, erinacine C was biotransformed from erinacine P which

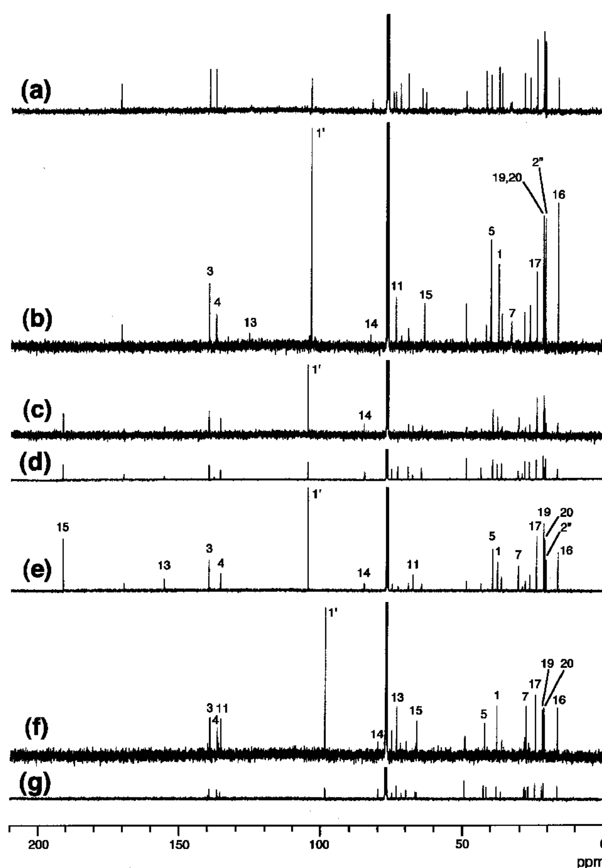

Fig. 2. ^{13}C-NMR (100 MHz, $CDCl_3$) Spectra of Erinacine Q with Natural ^{13}C Isotopic Abundance (a), of [1′-^{13}C]Erinacine Q as a Feeding Substrate (b), of [1′-^{13}C]Erinacine P from *H. erinaceum* Fed with [1′-^{13}C]Erinacine Q (c), of Erinacine P with Natural ^{13}C Isotopic Abundance (d), of [1′-^{13}C]Erinacine P as a Feeding Substrate (e), of [1′-^{13}C]Erinacine C from *H. erinaceum* Fed with [1′-^{13}C]Erinacine P (f), and of Erinacine C with Natural ^{13}C Isotopic Abundance (g).

The heights of the C-14 signals from the ^{13}C-labeled erinacines were each adjusted to be the same with corresponding natural ^{13}C isotopic abundance.

had such an α,β-unsaturated aldehyde moiety. Therefore, it seems that erinacine C may be derived from erinacine P *via* erinacine B. A trace amount of erinacine B was detected by the HPLC analysis (t_R 6.1 min), but was not sufficient for an NMR analysis. In order to clarify the biosynthetic relationship between erinacines P and B in this basidiomycete, bioconversion experiments of [1′-^{13}C]-erinacine P into erinacine B by using a medium which results in a marked accumulation of erinacine B will be needed.

Feeding experiments with [1′-^{13}C]-erinacine Q and [1′-^{13}C]-erinacine P clearly demonstrated that erinacine Q was converted *via* erinacine P into erinacine C in *Hericium erinaceum* YB4-6237. Erinacines Q and P may be the common biosynthetic intermediates of cyathane xylosides in this basidiomycete, and others such as erinacines A, B, C and H in *H. erinaceum*,[1–4,8] erinacines E, F and G in *H. romosum*,[6,10,11] and striatals and striatins in *Cyathus* spp.[5,9–11] and

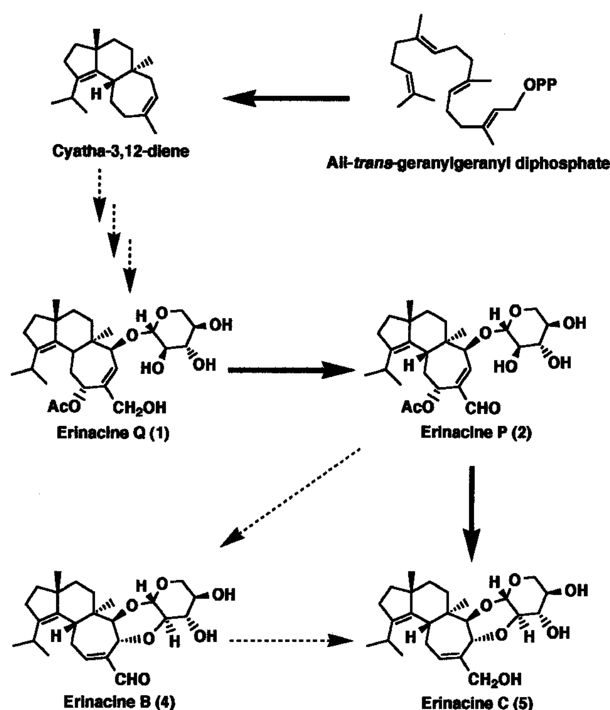

Fig. 3. Biosynthetic Route from Erinacine Q to Erinacine C *via* Erinacine P, and Possible Biosynthetic Pathway of GGDP to Erinacine C in *H. erinaceum* YB4-6237.

Gerronema fibula.[10,11] The biosynthetic hydrocarbon intermediate in the early stage of erinacine biosynthesis in *H. erinaceum* YB4-6237 has recently been investigated by our group, and isolation and structural determination of (−)-cyatha-3,12-diene and its formation from all-*trans*-geranylgeranyl diphosphate in a cell-free system have been reported.[12] Erinacines and the biosynthetic intermediates obtained from *H. erinaceum* YB4-6237 are biosynthetically arranged in Fig. 3.[8,12] We are now searching for putative hydroxylated-cyathadiene intermediates in the biosynthesis of erinacine aglycon from erinacine-producing *H. erinaceum* YB4-6237.

Acknowledgments

We thank Messrs. Eiichi Kimura and Takashi Shigihara at Edible Fungi Institute of Kinox Co. Ltd. for providing *H. erinaceum* YB4-6237. This work was partially supported by the Ministry of Education, Culture, Sports, Science and Technology of Japan though grant-aid for scientific research (no. 12556015).

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