JOC The Journal of Organic Chemistry

Note

pubs.acs.org/joc

Total Synthesis and Structural Revision of Hericerin

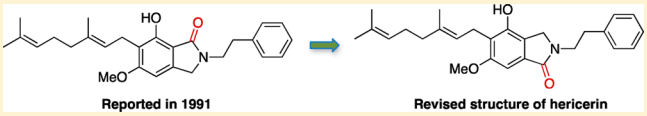
Shoji Kobayashi,*[,†] Tomoharu Inoue,[†] Ami Ando,[‡] Hidetsugu Tamanoi,[†] Ilhyong Ryu,[‡] and Araki Masuyama[†]

[†]Department of Applied Chemistry, Faculty of Engineering, Osaka Institute of Technology, 5-16-1 Ohmiya, Asahi-ku, Osaka 535-8585, Japan

[‡]Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai 599-8531, Japan

Supporting Information

ABSTRACT: The total synthesis of hericerin, a pollen growth inhibitor from *Hericium erinaceum*, was achieved. We found that the reported structure of hericerin should be revised to be the carbonyl regioisomer.



Hericerin is one of the members of the geranyl resorcylate family of natural products, isolated from the mushroom *Hericium erinaceum*.[1] The structure was determined by Tsuneda and co-workers in 1991 as **1** (Figure 1).[2] Hericerin shows

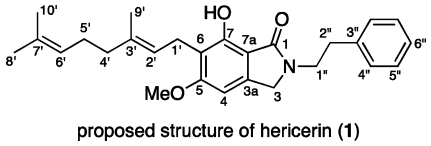


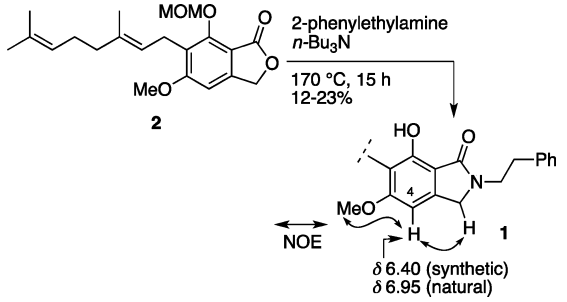
Figure 1. Proposed structure of hericerin.[2]

inhibitory activity against pine pollen germination and tea pollen growth and, therefore, is expected to be useful as a research tool for agrochemical discovery.

Recently, in the course of our studies on development of one-pot multifunctionalization reactions for an assembly of bioactive molecules, we discovered an efficient route to 6-bromo-5,7-dihydroxyphthalide 5-methyl ether, a key synthetic intermediate of the geranyl resorcylates, employing a $CuBr_2$-mediated multistep reaction.[3] This development was extended to the total synthesis of hericenone J and hericene A, both of which are members of the hericerin family.[3] Since our synthetic method was designed to cover a broad range of structures of geranylated resorcinols, we expanded the strategy to lactam-containing natural products. In this paper, we report the first total synthesis of hericerin, which revealed that the structure reported in 1991 was incorrect and should be revised to be the carbonyl regioisomer.

The geranylated lactone **2**[3,4] was subjected to direct lactamization in the presence of excess 2-phenylethylamine (20 equiv) under thermal conditions. The reaction, however, resulted in partial cleavage of the methoxymethyl (MOM) ether without forming the lactam, even after prolonged heating. When the reaction was carried out in the presence of *i*-Pr_2NEt at 135 °C, the acyclic amide intermediate was produced as the major product, together with a trace amount of lactam **1**. This indicated that higher temperature would be necessary to trigger lactamization. Eventually, heating with *n*-Bu_3N (bp 216 °C) at 170 °C for 15−22 h provided lactam **1** in 12−23% yield (Scheme 1).[5]

Scheme 1. Direct Lactamization of 2



Unexpectedly, the NMR data of synthetic **1** were not the same as those of the natural product. Among the chemical shifts observed, the signals assigned to the benzolactam moiety (C1−C7a), C1′, and C1″ were considerably different, whereas the signals assigned to the geranyl side chain (C2′−C10′) and the phenylethyl group (C2″−C6″) were nearly identical. This observation indicates that the major difference is ascribed to the structure of the benzolactam moiety. To determine the actual structure of the natural product, the H4 chemical shift of known compounds was surveyed. Figure 2 shows the structures of related compounds along with chemical shifts of the aromatic protons. These data clearly suggest that the chemical shift of the aromatic proton is largely dependent on the location of the carbonyl group. While the aromatic signal of hericenone J (**3**)[3,4,6] and Rama Rao's intermediate (**4**)[7] appears at 6.4−6.7 ppm, the corresponding signals of erinacerin A (**5**)[8] and hericenone A (**6**)[7] appear around 6.9 ppm. These analyses indicate that our synthetic compound with its aromatic proton at δ 6.40 possesses a structure related to the former compounds **3** and **4**, while the structure of the natural product is analogous

Received: April 9, 2012
Published: June 6, 2012

   dx.doi.org/10.1021/jo300719m | J. Org. Chem. 2012, 77, 5819−5822

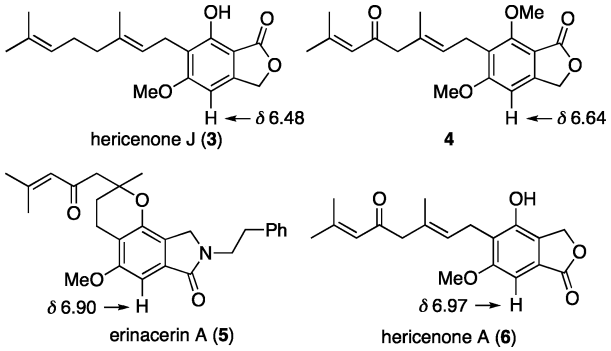


Figure 2. Structures and ^{1}H NMR data of related compounds.

to that of the latter molecules **5** and **6** based on the aromatic proton signal at δ 6.95. In the preceding research, Rama Rao pointed out the same regiochemical issues with respect to hericenone A and B.[7] They suggested that the structures of natural products should be revised as the carbonyl regioisomers on the basis of IR and PMR spectra. A part of their assertion was confirmed by the unambiguous total synthesis of hericenone A (**6**), whereas structure elucidation of hericenone B, which was the 5′-oxo analogue of hericerin, was left untouched. Of special interest is that their work ensures occurrence of both regioisomeric phthalides in nature. On the basis of the above information, we speculated that the actual structure of hericerin was the carbonyl regioisomer and undertook its synthesis to verify the hypothesis.

Thus, lactone **2** was reduced with $LiAlH_4$ to provide the 1,3-diol, which was selectively oxidized upon exposure to Ag_2CO_3 on Celite[9] to produce the desired lactone **8** accompanied by isomeric lactone **2** in 72% and 21% yields, respectively, for two steps (Scheme 2). This selectivity is explained by oxidation taking place more facilely at the less hindered lower alcohol rather than the upper one, which is then followed by rapid lactol formation and the second oxidation to afford **8**. Since direct lactamization of **8** under extreme thermal conditions resulted in a very poor yield of the lactam, we resorted to a stepwise method including amide formation and N-cyclization. Thus, lactone **8** was treated with 2-phenylethylamine in the presence of Me_3Al[10] to afford acyclic amide **9** in 87% yield.[11] Because direct intramolecular N-alkylation of **9** with *i*-PrMgCl and $ClP(O)(OEt)_2$[12] resulted in a low yield of **11** (27% yield),[13] we again employed a two-step method. Alcohol **9** was treated with excess MsCl and Et_3N to provide chloride **10**, which possibly arises from S_N2 displacement onto the mesylate or the O-cyclized imine intermediate.[14] Subsequent treatment with NaH in DMF induced rapid N-cyclization to provide lactam **11** in 83% yield. Finally, acid-catalyzed cleavage of the MOM ether provided our desired product **12**.

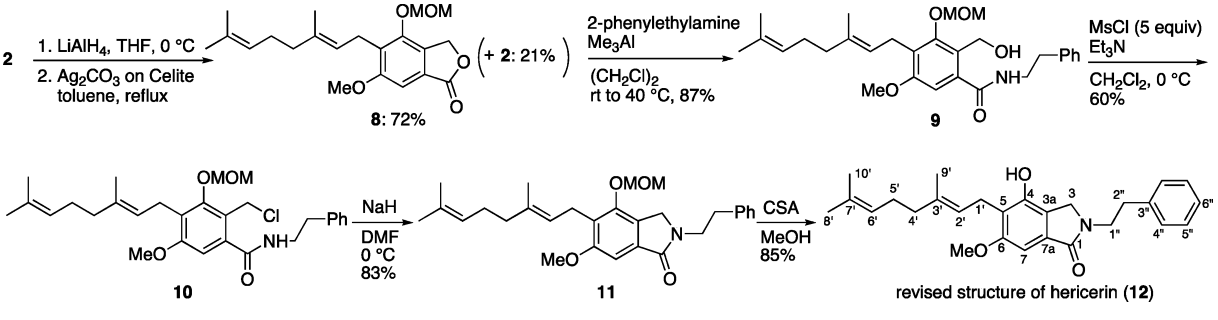
As expected, ^{1}H and ^{13}C NMR data of synthetic **12** were in accordance with those of the natural product, even though the original raw data were not available (Table S1, Supporting Information).[15] Nuclear Overhauser effect spectroscopy (NOESY) analysis of synthetic **12** revealed a correlation between H7 (δ 6.96) and C6-OMe (δ 3.84). In contrast, a cross peak between H7 (δ 6.96) and H3 (δ 4.15) was not observed. In the original paper, the authors reported that NOE effects were observed between the signals at δ 6.95 (H7) and δ 3.84 (OMe) and at δ 6.95 (H7) and δ 4.16 (H3). However, the supplemental spectra to support this observation were not provided.[2] It is possible that the authors' latter correlation could be attributed to noise signals. Very recently, Miyazawa and co-workers isolated compound **12** from the fruiting bodies of *Hericium erinaceum* and named it isohericerin.[16] The two sets of spectra are in good agreement. Accordingly, it is speculated that the two natural products isolated independently are the same.

In conclusion, we have achieved the first total synthesis of hericerin starting from the key synthetic intermediate **2** prepared in our previous paper. Our findings reveal that the actual structure of hericerin is **12**, which is the carbonyl regioisomer of **1**. From a biosynthetic standpoint, it is interesting that both series of carbonyl regioisomers are distributed in the same organism. We believe that the present investigation will be informative for researchers who are interested in the biosynthetic pathway of hericerin and its family.

EXPERIMENTAL SECTION

General Techniques. All reactions utilizing air- or moisture-sensitive reagents were performed under an atmosphere of argon. Commercially available dry solvents were used for DMF, CH_2Cl_2, THF, and MeOH. Triethylamine and 1,2-dichloroethane were distilled from CaH_2. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (60-F254) that were analyzed by fluorescence upon 254 nm irradiation or by staining with *p*-anisaldeyde/AcOH/H_2SO_4/EtOH, $12MoO_3{\cdot}H_3PO_4$/EtOH, or $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O/H_2SO_4$. The products were purified by flash chromatography on silica gel (spherical, neutral, 40−50 μm) and, if necessary, HPLC equipped with prepacked column using hexane/EtOAc as eluent. NMR spectra were recorded with a 500 MHz (^{1}H: 500 MHz, ^{13}C: 125 MHz), a 400 MHz (^{1}H: 400 MHz, ^{13}C: 100 MHz), or a 300 MHz (^{1}H: 300 MHz, ^{13}C: 75 MHz) spectrometer and referenced to the solvent peak at 7.26 ppm (^{1}H) and 77.16 ppm (^{13}C) for $CDCl_3$. Splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Infrared spectra were recorded with a FT/IR spectrometer and reported as wavenumber (cm^{-1}). Low- and high-resolution FAB mass spectra

Scheme 2. Total Synthesis of Hericerin



dx.doi.org/10.1021/jo300719m | J. Org. Chem. 2012, 77, 5819−5822

were recorded with a double-focusing magnetic sector mass spectrometer in positive ion mode.

(*E*)-6-(3,7-Dimethylocta-2,6-dienyl)-7-hydroxy-5-methoxy-2-phenethylisoindolin-1-one (1). A mixture of phthalide **2** (59.0 mg, 0.164 mmol), phenylethylamine (413 μL, 3.28 mmol), and *n*-Bu_3N (1.39 mL, 5.84 mmol) was heated in a screw-capped test tube at 170 °C. After being stirred for 22 h, the reaction mixture was diluted with EtOAc, washed with 1 M aqueous HCl and brine, and dried over anhydrous $MgSO_4$. After concentration, the residue was purified by flash chromatography (*n*-hexane/EtOAc = 5) to give the title compound **1** (15.7 mg, 0.0374 mmol, 23%) as a pale yellow solid: mp 69−71 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1H, OH), 7.34−7.20 (m, 5H, Ph), 6.40 (s, 1H, H4), 5.20 (br t, 1H, *J* = 7.2 Hz, H2′), 5.06 (br t, 1H, *J* = 7.2 Hz, H6′), 4.12 (s, 2H, H3), 3.83 (s, 3H, OMe), 3.78 (t, 2H, *J* = 7.6 Hz, H1″), 3.34 (d, 2H, *J* = 6.8 Hz, H1′), 2.95 (t, 2H, *J* = 7.6 Hz, H2″), 2.05 (m, 2H, H5′), 1.95 (br t, 2H, *J* = 7.6 Hz, H4′), 1.77 (s, 3H, H9′), 1.64 (br s, 3H, H8′), 1.57 (s, 3H, H10′); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5 (C1), 162.4 (C5), 153.9 (C7), 140.2 (C3a), 138.9 (C3″), 135.5 (C3′), 131.3 (C7′), 128.8 (C4″, C5″), 126.7 (C6″), 124.6 (C6′), 122.0 (C2′), 116.0 (C6), 110.7 (C7a), 97.1 (C4), 56.1 (OMe), 51.4 (C3), 43.7 (C1″), 39.9 (C4′), 35.3 (C2″), 26.9 (C5′), 25.8 (C8′), 21.7 (C1′), 17.8 (C10′), 16.2 (C9′); FT-IR (ZnSe) 3326, 3062, 3028, 2963, 2938, 2856, 1666, 1498, 1456, 1438, 1417, 1375, 1336, 1250, 1236, 1198, 1170 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{34}NO_3$ $[M + H]^+$ 420.2539, found 420.2539.

(*E*)-5-(3,7-Dimethylocta-2,6-dienyl)-6-methoxy-4-(methoxymethoxy)isobenzofuran-1(3*H*)-one (8). To a solution of phthalide **2** (264 mg, 0.731 mmol) in THF (7.3 mL) was added $LiAlH_4$ (83.5 mg, 2.20 mmol) at 0 °C. The mixture was stirred at 0 °C for 1 h and quenched with water. Et_2O and saturated aqueous Rochelle salt solution were added, and the resulting mixture was stirred at room temperature for 1 h. The mixture was extracted with Et_2O (3×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give the corresponding diol[3] (269 mg), which was used for the next reaction without further purification.

To a solution of diol (266 mg) in toluene was added 50 wt % of Ag_2CO_3 on Celite (1.01 g, 1.83 mmol). The mixture was heated at reflux and stirred for 1 h. The precipitate was removed by filtration, and the filtrate was concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 5 → 3) to give phthalide **8** (189 mg, 0.525 mmol, 72%) as a pale yellow viscous oil and phthalide **2** (56.0 mg, 0.155 mmol, 21%) as a colorless solid. Data for **8**: mp 36−39 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (s, 1H, H7), 5.37 (s, 2H, MOM), 5.11 (br t, *J* = 5.7 Hz, H2′), 5.06 (s, 2H, H3), 5.04 (m, 1H, H6′), 3.89 (s, 3H, OMe), 3.53 (s, 3H, MOM), 3.44 (d, 2H, *J* = 6.9 Hz, H1′), 2.07−2.01 (m, 2H, H5′), 1.98−1.93 (m, 2H, H4′), 1.77 (br s, 3H, H9′), 1.63 (br s, 3H, H8′), 1.56 (br s, 3H, H10′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 159.7, 150.3, 136.1, 131.5, 129.2, 129.1, 125.3, 124.2, 121.3, 101.7, 97.2, 69.2, 56.8, 56.2, 39.8, 26.7, 25.8, 23.7, 17.8, 16.3; FT-IR (ZnSe) 2973, 2914, 2848, 1766, 1736, 1475, 1434, 1409, 1373, 1332, 1230, 1213, 1155, 1100, 1066, 1023 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{21}H_{29}O_5$ $[M + H]^+$ 361.2015, found 361.1993. Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.98; H, 7.83. Found: C, 69.81; H, 7.72.

(*E*)-4-(3,7-Dimethylocta-2,6-dienyl)-2-(hydroxymethyl)-5-methoxy-3-(methoxymethoxy)-*N*-phenethylbenzamide (9). To a solution of 2-phenylethylamine (70.5 μL, 0.560 mmol) in $(CH_2Cl)_2$ (1.0 mL) was added Me_3Al (1.4 M solution in hexane, 104 μL, 0.146 mmol). The mixture was stirred at room temperature for 0.5 h followed by the addition of phthalide **8** (40.4 mg, 0.112 mmol) in $(CH_2Cl)_2$ (1.3 mL). The resulting mixture was stirred at 40 °C for 7.5 h and quenched by the addition of water at 0 °C. The resulting mixture was extracted with EtOAc (2×) and the combined organic layer was washed with 1 M aqueous HCl, brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 2) to give amide **9** (47.0 mg, 0.0976 mmol, 87%) as a pale yellow viscous oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (br t, *J* = 5.4 Hz, NH), 7.34−7.20 (m, 5H, Ph), 7.03 (s, 1H, H7), 5.10−5.00 (m, 2H, H2′, H6′), 4.96 (s, 2H, MOM), 4.53 (s, 2H, H3), 3.84 (s, 3H, OMe), 3.74 (dt, 2H, *J* = 7.2, 5.4 Hz, H1″), 3.62 (s, 3H, MOM), 3.34 (d, 2H, *J* = 6.6 Hz, H1′), 2.97 (t, 2H, *J* = 7.2 Hz, H2″), 2.08−2.00 (m, 2H, H5′), 1.98−1.93 (m, 2H, H4′), 1.74 (br s, 3H, H9′), 1.64 (br s, 3H, H8′), 1.57 (s, 3H, H10′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 158.3, 156.1, 139.1, 136.5, 135.7, 131.5, 128.9, 128.6, 126.5, 126.3, 124.5, 124.3, 122.0, 107.7, 100.4, 57.6, 56.8, 55.9, 41.5, 39.7, 35.7, 26.7, 25.8, 23.8, 17.8, 16.3; FT-IR (ZnSe) 3290, 3062, 3027, 2933, 1634, 1597, 1553, 1498, 1455, 1397, 1331, 1304, 1223, 1202, 1158, 1111, 1065 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{39}NO_5Na$ $[M + Na]^+$ 504.2726, found 504.2688.

(*E*)-2-(Chloromethyl)-4-(3,7-dimethylocta-2,6-dienyl)-5-methoxy-3-(methoxymethoxy)-*N*-phenethylbenzamide (10). To a solution of alcohol **9** (4.0 mg, 8.3 μmol) in CH_2Cl_2 (1.0 mL) were added Et_3N (13.9 μL, 99.7 μmol) and MsCl (3.3 μL, 41 μmol) at 0 °C. The mixture was stirred at 0 °C for 2 h and quenched by the addition of saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (2×), and the combined organic layer was washed with saturated aqueous NH_4Cl solution, brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 3) to give chloride **10** (2.5 mg, 5.0 μmol, 60%) as a colorless solid: mp 98−100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.19 (m, 5H, Ph), 6.72 (s, 1H, H6), 6.22 (br t, 1H, *J* = 6.0 Hz, NH), 5.10−5.01 (m, 2H, H2′, H6′), 5.02 (s, 2H, MOM), 4.82 (s, 2H, H7), 3.80 (s, 3H, OMe), 3.77 (td, 2H, *J* = 6.9, 6.0 Hz, H1″), 3.62 (s, 3H, MOM), 3.35 (d, 2H, *J* = 6.3 Hz, H1′), 2.98 (t, 2H, *J* = 6.9 Hz, H2″), 2.07−2.00 (m, 2H, H5′), 1.98−1.92 (m, 2H, H4′), 1.73 (br s, 3H, H9′), 1.63 (br s, 3H, H8′), 1.57 (br s, 3H, H10′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 159.2, 155.8, 138.8, 136.6, 135.9, 131.5, 128.9, 128.8, 126.7, 126.6, 124.3, 122.1, 121.1, 106.7, 100.8, 57.8, 55.9, 41.2, 39.8, 39.7, 35.5, 26.7, 25.8, 23.9, 17.8, 16.3; FT-IR (ZnSe) 3287, 3064, 3028, 2965, 2927, 2856, 1629, 1595, 1576, 1540, 1462, 1434, 1395, 1340, 1261, 1219, 1186, 1168, 1112 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{39}ClNO_4$ $[M + H]^+$ 500.2568, found 500.2548.

(*E*)-5-(3,7-Dimethylocta-2,6-dienyl)-6-methoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (11). To a solution of chloride **10** (4.4 mg, 8.8 μmol) in DMF (1.0 mL) was added NaH (60% dispersion in mineral oil, 8.0 mg, 0.20 mmol) at 0 °C. The mixture was stirred at 0 °C for 20 min and quenched by the addition of water. The resulting mixture was extracted with Et_2O (2×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (*n*-hexane/EtOAc = 1) to give lactam **11** (3.4 mg, 7.3 μmol, 83%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H, Ph), 7.15 (s, 1H, H7), 5.12 (br t, 1H, *J* = 7.2 Hz, H2′), 5.04 (m, 1H, H6′), 4.99 (s, 2H, MOM), 4.24 (s, 2H, H3), 3.88 (s, 3H, OMe), 3.85 (t, 2H, *J* = 7.5 Hz, H1″), 3.47 (s, 3H, MOM), 3.40 (d, 2H, *J* = 6.9 Hz, H1′), 2.98 (t, 2H, *J* = 7.5 Hz, H2″), 2.07−2.00 (m, 2H, H4′), 1.98−1.92 (m, 2H, H5′), 1.76 (br s, 3H, H9′), 1.63 (br s, 3H, H8′), 1.56 (s, 3H, H10′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 159.1, 150.9, 139.0, 135.5, 132.6, 131.5, 128.9, 128.7, 126.6, 126.5, 124.44, 124.36, 122.2, 101.1, 98.0, 56.9, 56.2, 49.5, 44.3, 39.8, 35.1, 26.8, 25.8, 23.6, 17.8, 16.3; FT-IR (ZnSe) 3086, 3061, 3027, 2914, 2852, 1687, 1620, 1602, 1497, 1468, 1436, 1416, 1375, 1317, 1247, 1153, 1117 cm^{-1}; HRMS (FAB) *m*/*z* calcd for $C_{29}H_{38}NO_4$ $[M + H]^+$ 464.2801, found 464.2823.

(*E*)-5-(3,7-Dimethylocta-2,6-dienyl)-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one (Hericerin, 12). To a solution of lactam **11** (4.3 mg, 9.3 μmol) in MeOH (1 mL) was added CSA (5.0 mg, 0.022 mmol). The mixture was stirred at room temperature for 70 h and quenched by the addition of Et_3N (1 mL). The reaction mixture was concentrated and the residue was purified by flash column chromatography (*n*-hexane/EtOAc = 2) to give the title compound **12** (3.3 mg, 7.9 μmol, 85%) as a colorless solid: mp 143−146 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29−7.19 (m, 5H, Ph), 6.96 (s, 1H, H7), 6.13 (br s, 1H, OH), 5.23 (br t, 1H, *J* = 6.9 Hz, H2′), 5.02 (m, 1H, H6′), 4.15 (s, 2H, H3), 3.85 (br t, 2H, *J* = 7.3 Hz, H1″), 3.84 (s, 3H, OMe), 3.49 (d, 2H, *J* = 6.9 Hz, H1′), 2.97 (t, 2H, *J* = 7.3 Hz, H2″), 2.09 (br s, 2H, H4′, H5′), 1.80 (s, 3H, H9′), 1.66 (s, 3H, H8′), 1.58 (s, 3H, H10′); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1 (C1), 158.6 (C6), 150.7 (C4), 139.5 (C3′), 138.9 (C3″), 132.4 (C7′), 132.3 (C7a), 128.8

dx.doi.org/10.1021/jo300719m | *J. Org. Chem.* 2012, 77, 5819−5822

(C4″), 128.7 (C5″), 126.6 (C6″), 123.8 (C6′), 121.34 (C2′ or C3a), 121.26 (C2′ or C3a), 118.6 (C5), 97.7 (C7), 56.2 (OMe), 48.3 (C3), 44.4 (C1″), 39.8 (C4′), 35.0 (C2″), 26.4 (C5′), 25.8 (C8′), 22.9 (C1′), 17.8 (C10′), 16.3 (C9′); FT-IR (ZnSe) 3146, 3029, 2966, 2927, 2856, 1647, 1589, 1471, 1455, 1436, 1422, 1368, 1336, 1310, 1264, 1229, 1193, 1165, 1119, 1089, 1066 cm^{-1}; HRMS (FAB) m/z calcd for $C_{27}H_{34}NO_3$ $[M + H]^+$ 420.2539, found 420.2535. Anal. Calcd for $C_{27}H_{33}NO_3$: C, 77.29; H, 7.93; N, 3.34. Found: C, 77.26; H, 7.81; N, 3.40.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new synthetic compounds as well as HMQC, HMBC, and NOESY spectra for **1** and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: koba@chem.oit.ac.jp.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research (C) (Nos. 22550115 and 24550124) from the JSPS.

■ REFERENCES

(1) Ma, B.-J.; Shen, J.-W.; Yu, H.-Y.; Ruan, Y.; Wu, T.-T.; Zhao, X. *Mycology* **2010**, *1*, 92−98.

(2) Kimura, Y.; Nishibe, M.; Nakajima, H.; Hamasaki, T.; Shimada, A.; Tuneda, A.; Shigematsu, N. *Agric. Biol. Chem.* **1991**, *55*, 2673−2674.

(3) Kobayashi, S.; Ando, A.; Kuroda, H.; Ejima, S.; Masuyama, A.; Ryu, I. *Tetrahedron* **2011**, *67*, 9087−9092.

(4) Cordes, J.; Calo, F.; Anderson, K.; Pfaffeneder, T.; Laclef, S.; White, A. J. P.; Barrett, A. G. M. *J. Org. Chem.* **2012**, *77*, 652−657.

(5) Although the mechanism for the spontaneous cleavage of the MOM ether bond is unclear, it appears that the harsh reaction conditions induced degradation of its functionality. In fact, the deprotected lactone (hericenone J) was obtained in 35% yield under these conditions and did not undergo further lactamization.

(6) Ueda, K.; Tsujimori, M.; Kodani, S.; Chiba, A.; Kubo, M.; Masuno, K.; Sekiya, A.; Nagai, K.; Kawagishi, H. *Bioorg. Med. Chem. Lett.* **2008**, *16*, 9467−9470.

(7) Rao, A. V. R.; Reddy, R. G. *Tetrahedron Lett.* **1992**, *33*, 4061−4064.

(8) Yaoita, Y.; Danbara, K.; Kikuchi, M. *Chem. Pharm. Bull.* **2005**, *53*, 1202−1203.

(9) (a) Fetizon, M.; Golfier, M. *C. R. Acad. Sci., Ser. C* **1968**, *267*, 900. (b) McKillop, A.; Young, D. W. *Synthesis* **1979**, 401−422.

(10) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171−4172. (b) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517−3520.

(11) The corresponding MOM-deprotected amide was obtained in 7% yield.

(12) (a) Tsuritani, T.; Kii, S.; Akao, A.; Sano, K.; Nonoyama, N.; Mase, T.; Yasuda, N. *Synlett* **2006**, 801−803. (b) Tsuritani, T.; Mizuno, H.; Nonoyama, N.; Kii, S.; Akao, A.; Sato, K.; Yasuda, N.; Mase, T. *Org. Process Res. Dev.* **2009**, *13*, 1407−1412.

(13) It is likely that phosphorylation was disturbed by the presence of the chelating MOM group. Addition of a cosolvent such as HMPA did not affect the result.

(14) When an equimolar amount of MsCl was employed, alcohol **9** was not fully consumed, likely due to hydrolysis of the O-cyclized imine intermediate after workup.

(15) We observed that the chemical shift of the phenolic OH varied according to the concentration of **12** in $CDCl_3$. For instance, when the ^1H NMR spectrum was recorded at 7 μM, the OH signal appeared at δ 5.84, whereas it shifted to δ 6.13 at 24 μM and δ 6.36 at 48 μM.

(16) (a) Miyazawa, M.; Takahashi, T.; Horibe, I.; Ishikawa, R. *Tetrahedron* **2012**, *68*, 2007−2010. (b) Miyazawa, M.; Takahashi, T.; Horibe, I.; Ishikawa, R. *Tetrahedron* **2012**, *68*, 3786.