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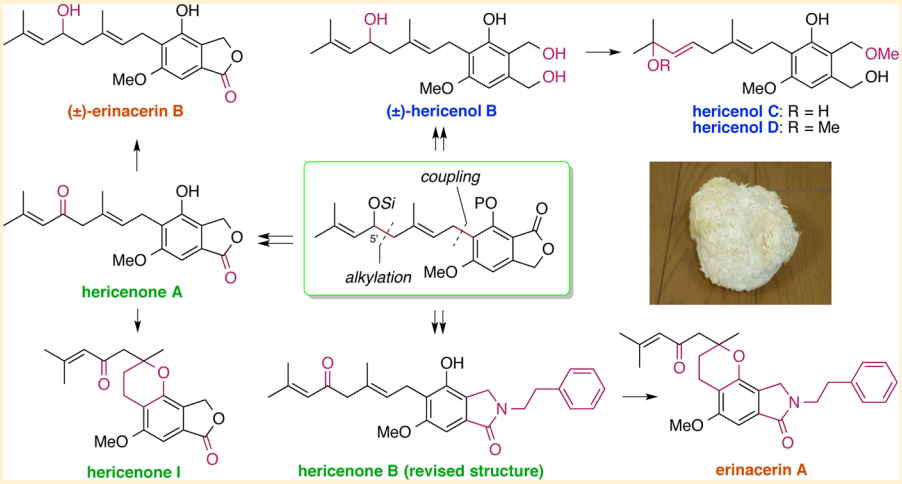
# Divergent Synthesis of Bioactive Resorcinols Isolated from the Fruiting Bodies of *Hericium erinaceum*: Total Syntheses of Hericenones A, B, and I, Hericenols B–D, and Erinacerins A and B

Shoji Kobayashi,* Hidetsugu Tamanoi, Yuichi Hasegawa, Yusuke Segawa, and Araki Masuyama

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

Supporting Information




**ABSTRACT:** Total syntheses of 5′- and 7′-oxidized geranyl resorcylates isolated from the fruiting bodies of *Hericium erinaceum* and the submerged cultures of a *Stereum* species were achieved. Our synthesis features derivatization of a suitably functionalized 5′-oxidized geranyl phthalide as a common intermediate, which was obtained by Stille coupling between the phthalide core and the side chain, into a series of natural products by divergent functional group manipulations. The crucial C5′-oxygen functionality was installed at the initial stage by alkylation by an α-cyano ethoxyethyl ether. From a common synthetic intermediate, eight total syntheses including hericenones A, B, and I, hericenols B–D, and erinacerins A and B were achieved (hericenol B and erinacerin B were synthesized as racemates). The structure of hericenone B established in the isolation paper was unambiguously revised as the carbonyl regioisomer at the lactam moiety.

## INTRODUCTION

An edible mushroom, *Hericium erinaceum*, called Yamabushitake in Japanese, has long been used in traditional Chinese medicine and is now widely available as a health food supplement, especially in East Asia and Europe. Various forms of *H. erinaceum*, including perishables, lyophilized solids, powders, and tablets, are available in stores. The increasing demand for this mushroom is mostly due to its effects on cognitive function, partially demonstrated by a double-blind placebo-controlled clinical trial with dozens of patients diagnosed with mild cognitive impairment.[1] According to Mori's report,[1] a group given *H. erinaceum* showed significantly increased scores on the cognitive function scale in comparison with the placebo group. Their study also showed no adverse effects of *H. erinaceum*. Consequently, *H. erinaceum* can be regarded as a useful food for the prevention of dementia without any adverse effects.

In 1990, Kawagishi et al. first isolated low-molecular-weight ingredients from the fruiting bodies of *H. erinaceum* and named them hericenones A and B.[2] Stimulated by their discovery, a number of structurally related molecules were isolated from natural sources, including the hericenones,[3] hericerin,[4] hericenes,[5] hericenols,[6] and erinacerins.[7] All of these molecules possess a geranyl side chain attached to a resorcinol framework as a common structure and exhibit a wide variety of biological activities, including antitumor,[2a] antibacterial,[6] stimulation of nerve-growth-factor (NGF) synthesis,[3a,b] suppression of endoplasmic reticulum (ER) stress,[3c] inhibition of collagen-induced platelet aggregation,[8] and plant growth regulation.[4a] Therefore, the members of the geranyl resorcylate family are considered to be key players that define the function of *H. erinaceum*. However, in spite of the discovery of these intriguing

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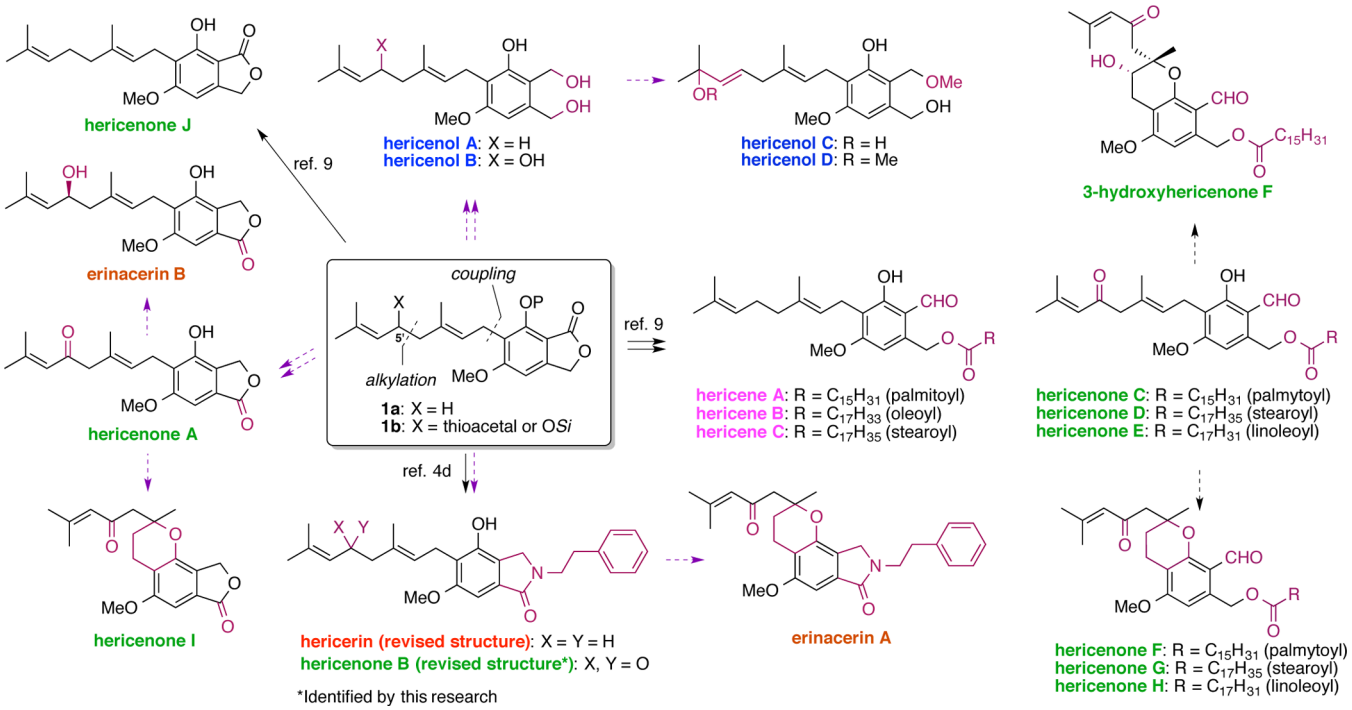


**Figure 1.** Structure relationships among naturally occurring geranyl resorcylates. The purple dashed arrows indicate achievements in this report.

biological activities, inclusive structure−activity relationships (SAR) for the broad range of geranyl resorcylates are still unknown. In addition, limited supplies and cumbersome purification procedures for the active ingredients from natural sources have impeded more detailed pharmacological and pharmacokinetic studies at the in vivo level. In this context, synthetic studies of this class of natural products have been explored for SAR studies and to supply materials for further research.[2b,4d,e,9,10]

In their pioneering work, Rao et al. first synthesized hericenone A by using a Diels−Alder reaction for the construction of the aromatic unit and subsequent elongation of the side chain.[2b] Importantly, their research resulted in the conclusion that the actual structure of hericenone A was the carbonyl regioisomer of the proposed structure. They also suggested from the NMR research that hericenone B had a structure similar to that of revised hericenone A, while confirmation by total synthesis had not been achieved. After 19 years, we reported the total syntheses of hericenone J, hericene A, and hericerin by a strategy composed of a one-pot multifunctionalization reaction and a Stille coupling (vide infra).[4d,9] Around the same time, Barrett et al. reported efficient total syntheses of hericenone J and hericenol A via regioselective palladium(0)-catalyzed decarboxylative geranyl migration and aromatization sequence as the key steps.[10] More recently, the Miranda group reported a short-step synthesis of hericerin using an ether−phenol rearrangement and $Pd(OAc)_2$-catalyzed carbonylative ring closure.[4e] However, previous reports except for Rao's achievement focused only on the synthesis of the geranyl-substituted resorcinols lacking an oxygen functionality on their side chains.

In this article, we report the divergent total syntheses of eight natural products, hericenones A, B, and I, hericenols B−D, and erinacerins A and B, all of which include an oxygen functionality on their side chains. Among these eight natural products, hericenol B and erinacerin B were synthesized as racemates. This study also implied that hericenols C and D are artifacts resulting from degradation of hericenol B. In addition, the total synthesis of hericenone B led to the revision of the structure of the natural product as the carbonyl regioisomer of the original assignment.

## RESULTS AND DISCUSSION

Figure 1 shows the structure relationships among naturally occurring geranyl resorcylates. The members are categorized on the basis of the substitution patterns of the resorcinol core. They contain a variety of functional groups, including alcohols, ethers, aldehydes, ketones, esters, lactones, and lactams, as well as a pentasubstituted benzene ring, which makes their syntheses more challenging despite their compact structures. The side chains can be categorized into two general groups, one containing an oxygen functionality at the C5′ or the C7′ position and one without. In our recent achievements, the C5′-deoxo series including hericenone J, hericene A, and hericerin were synthesized by using the geranyl phthalide **1a** as a common precursor.[4d,9] This intermediate was readily prepared by a Michael−Claisen condensation, a $CuBr_2$-mediated one-pot multifunctionalization, and a CsF-assisted Stille coupling as key reactions (Scheme 1).[9] However, synthesis of the C5′-oxidized series remained unexplored because it was anticipated that the regioselective oxidation of the geranyl-containing products at the late stage of the synthesis would be difficult due to the presence of multiple allylic carbons. Therefore, we planned to incorporate the oxygen functionality at the early stage to prepare C5′-oxidized natural products such as hericenones A−I, hericenol B, and erinacerins.

With ready availability and step economy in mind, 3-methyl-2-butenal (**8**) and isoprene (**9**) were chosen as starting materials (Scheme 2). Our initial plan was to use a dithiane as the protecting group of the C5′-carbonyl and build up the side chain (**7**) via alkylation.[11] This approach emerged from Rao's


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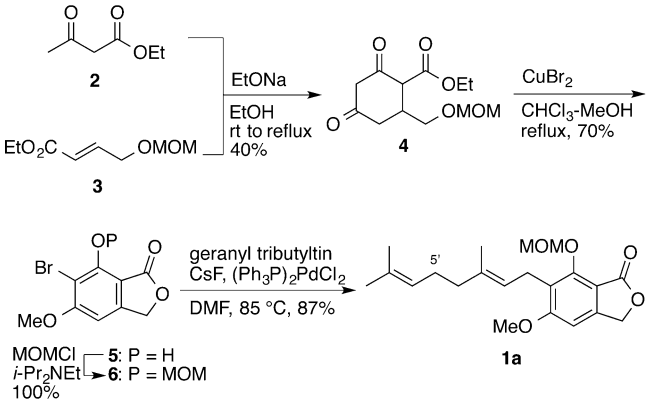
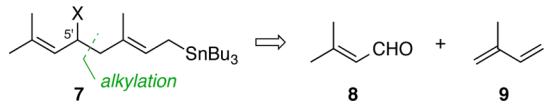
**Scheme 1. Previous Synthesis of the Geranyl Phthalide 1a**



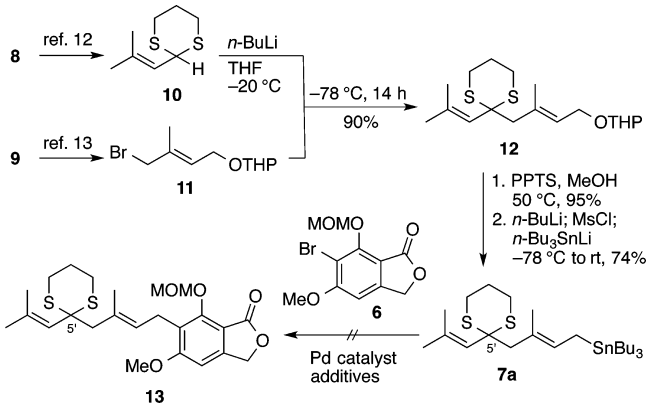

**Scheme 2. Retrosynthesis of the Side Chain**




total synthesis of hericenone A, in which the side chain was elaborated by the dithiane chemistry.[2b]

Thus, dithioacetal **10**[12] obtained by thioacetalization of **8** was lithiated by *n*-BuLi at −20 °C and then alkylated with allyl bromide **11**[13] prepared in three steps from **9** to provide the desired product **12** in 90% yield (Scheme 3). It was critical to

**Scheme 3. Dithiane-Based Strategy To Prepare the Common Intermediate 13**




keep the reaction temperature at −78 °C during alkylation to obtain a high yield. After deprotection, the resulting alcohol was converted into allylstannane **7a** by a one-pot method.[14] The Stille coupling[15] between **7a** and the phthalide core **6**[9] was problematic, however. Even under the optimized conditions established in coupling between **6** and geranyl tributyltin (cf. Scheme 1[9,16]), no coupling product **13** was detected. While the precise cause of this failure is as yet not known, it is speculated that the neighboring thioketal moiety reduces the activity of the catalyst possibly through intramolecular coordination between sulfur and the allylpalladium that was formed by transmetalation of the allylstannane. Since further screening of the coupling conditions was not fruitful and conversion of thioketal (e.g., **12**) to the corresponding ketal or ketone resulted in low yield,[17] the dithiane-based strategy was abandoned.

The alternate plan for the synthesis of the side chain was to use a cyanohydrin derivative as the alkylation precursor[18] and to protect the C5′-functional group as the silyl ether, a fluoride-removable protective group, as it was later found that the C5′-allylic alcohol was highly susceptible to acidic conditions (vide infra). Thus, the ethoxyethyl (EE)-protected cyanohydrin **14** was readily prepared from **8** in three conventional steps (Scheme 4). The benzoyl-protected allylic bromide **15** was synthesized from isoprene (**9**) via bromination and substitution according to the literature.[19,20] The key alkylation[18] was achieved by adding $LiN(TMS)_2$ to a mixture of **14** (1 equiv) and **15** (1 equiv). Remarkably, alkylation was complete within 30 min at −78 °C, providing the desired product **16** in quantitative yield. The EE group of **16** was removed by acidic methanol, and subsequent treatment with $Et_3N$ generated the corresponding ketone, which was reduced without isolation by $NaBH_4$ in the presence of $CeCl_3{\cdot}7H_2O$ (Lüche reduction) to afford the C5′-allylic alcohol. It should be noted that the ketone intermediate was unstable to basic treatment and a brief exposure to $Et_3N$ (preferably less than 10 min) was essential to suppress undesired elimination of benzoate, which resulted in the formation of a conjugated trienone. Next, TBS protection of the resultant alcohol provided the corresponding silyl ether, the benzoyl group of which was removed by DIBAL to provide allylic alcohol **17** in 55% overall yield from **15**. One-pot stannylation[14] of **17** afforded the requisite allylstannane **7b** in 90% yield. Although the total synthetic steps were increased in comparison to those with the dithiane-based strategy, several cleaner, high-yielding reactions allowed for gram-scale preparation of the side chain.

With the two coupling partners in hand, the divergent synthesis of the C5′-oxidized geranyl resorcylates began with the assembly of allylstannane **7b** and the MOM-protected aryl bromide **6**[9] under modified Stille coupling conditions.[16] In comparison to the dithiane substrate **7a**, **7b** was reactive to coupling conditions and the desired product **18a** was formed in moderate yield. It is noteworthy that the TBS ether was tolerated by the CsF-mediated coupling conditions. As the silyl protective group at C5′ was appropriate for subsequent transformations, further exploration was dedicated to optimization of the phenolic protective group. While various phthalides with different protective groups were screened, results for the coupling reaction could not be improved by protection with EE (4% yield), acetyl (0% yield), TBS (0% yield), or 2-(trimethylsilyl)ethoxymethyl (SEM) (42% yield). Accordingly, we carried the MOM-protected substrate **18a** forward.

Among the C5′-oxidized natural resorcinols, we selected hericenone A as the initial target. While the isolation and structure determination of hericenone A were first achieved in 1990, its structure was later revised by Rao et al. as the carbonyl regioisomer of the original structure.[2] Thus, the lactone moiety of **18a** was reduced by $LiAlH_4$ and then reoxidized with $Ag_2CO_3$ on Celite (Fetizon oxidation)[21] to provide the carbonyl-inverted lactone **20** as the major product (74% in two steps), accompanied by its isomer **18a** (23% in two steps). Further research indicated that the allylic ether portion of **20** was highly susceptible to acidic conditions. For instance, when **20** was exposed to MOM deprotection conditions with $Me_2BBr$ at −78 °C,[9,22] rapid formation of triene **22** resulted. Hence, the TBS group of **20** was first removed by TBAF and the resultant C5′-alcohol was oxidized with $PhI(OAc)_2$/2-azaadamantane *N*-oxyl (AZADO)[23] to provide the corresponding ketone **21**. As a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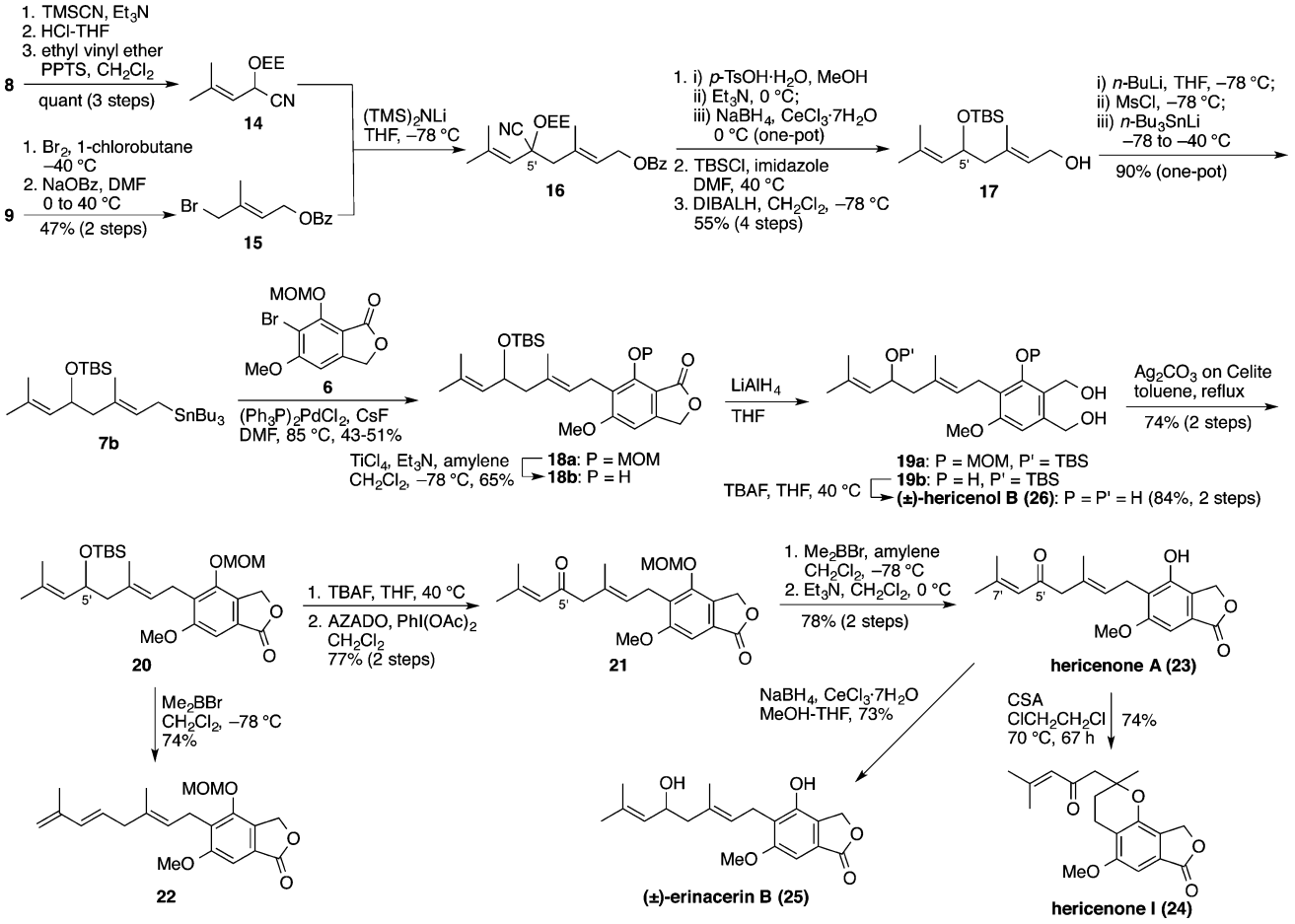
**Scheme 4. Total Syntheses of Hericenones A and I, (±)-Hericenol B, and (±)-Erinacerin B**




result of screening the oxidation conditions applied to such an electron-rich resorcinol, $PhI(OAc)_2$/AZADO was found to be superior to $PhI(OAc)_2$/TEMPO,[24] Dess–Martin periodinane,[25] and Swern conditions.[26] Removal of the MOM protective group in **21** with $Me_2BBr$ in the presence of excess amylene[27] gave a mixture of two products, including hericenone A (**23**) and its bromide-conjugated addition product at C7′. The mixture was subsequently treated with $Et_3N$ to induce $\beta$-elimination of the bromide to furnish hericenone A (**23**) in 78% overall yield from **21**. The spectral data for the synthetic product **23** were identical with those reported in previous papers.[2]

We next turned our attention to the synthesis of hericenone I,[3c] as it can be presumed that it was biosynthetically generated from hericenone A via acid-catalyzed cyclization. Thus, synthetic hericenone A (**23**) was treated with a couple of acids to induce cyclization. While **23** was inactive to PPTS in $CH_2Cl_2$, it gradually cyclized into hericenone I (**24**) upon treatment with CSA at 70 °C. The cyclization was almost complete after 3 days, and **24** was isolated in 74% yield. The spectral data for **24** were exactly the same as those for the natural product,[3c] which constituted the first total synthesis of hericenone I.

The structure of erinacerin B isolated by Kikuchi et al. in 2005[7] is a reduced form of hericenone A. Notably this compound was isolated as an optically active molecule with a positive specific optical rotation. This implies that biosynthetically erinacerin B is generated by enzymatic asymmetric oxidation of the parent C5′-deoxy molecule or enzymatic asymmetric reduction of hericenone A. Before addressing this intriguing issue, we undertook the racemic synthesis of erinacerin B. To promote selective 1,2-reduction, the synthetic hericenone A (**23**) was submitted to Lüche conditions. Reduction proceeded within 1 min, and (±)-erinacerin B (**25**) was isolated in 73% yield. While the NMR data for natural erinacerin B were measured in $CDCl_3$,[7] our synthetic sample was only slightly soluble in $CDCl_3$, which did not permit comparison of the $^{13}C$ NMR spectra in the same solvent. Furthermore, our research proved that **25** gradually degraded in $CDCl_3$. It can be presumed that the instability of **25** arises from the allylic alcohol structure of the side chain.

Next, our research was directed to the synthesis of hericenol B derived from submerged cultures of a *Streum* species.[6] As the labile nature of (±)-erinacerin B (**25**) became apparent, we decided to synthesize (±)-hericenol B from the key intermediate **18a** instead of **25**. After extensive screening of deprotection conditions acceptable for such an acid-labile C5′-siloxy-containing substrate, the combination of $TiCl_4$ and $Et_3N$ in the presence of excess amylene proved the best. This combination reproducibly generated the deprotected phenol **18b** without affecting the C5′-allylic ether portion. The lactone moiety of **18b** was then reduced with $LiAlH_4$, and the TBS group of the resulting triol **19b** was removed by TBAF to provide (±)-hericenol B (**26**) in 84% isolated yield over two steps. The spectral data, except for the optical rotation values,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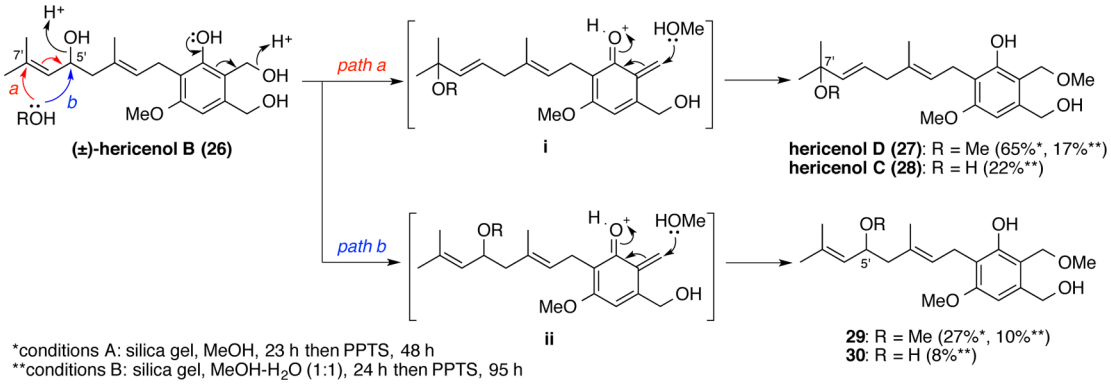
**Scheme 5. Total Syntheses of Hericenols C and D**

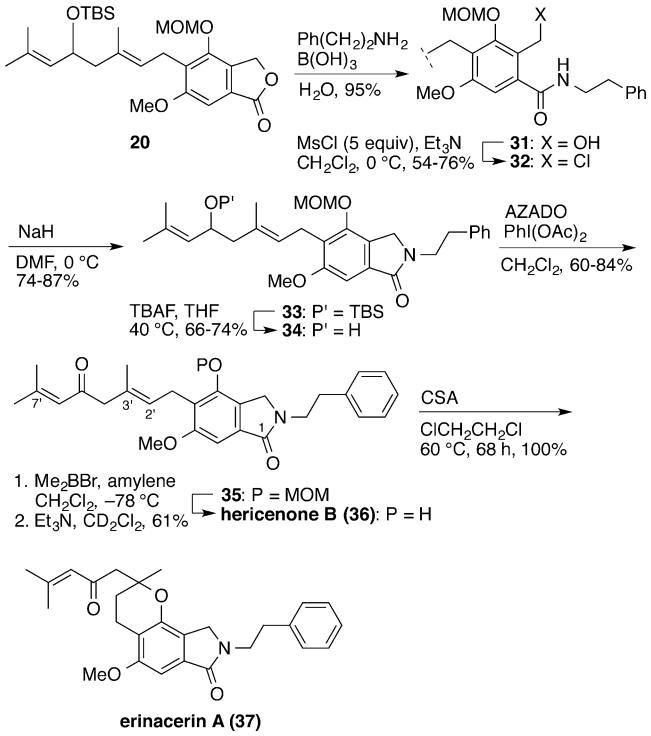



for the synthetic compound (**26**) and the natural product[6] were all identical.

We next focused on the synthesis of hericenols C and D,[6] since it can be supposed that they are derived biosynthetically from hericenol B via allylic and benzylic substitutions. In the course of our investigations on model substrates, we serendipitously observed that such substitution reactions were triggered by acid catalysts. Encouraged by our original findings, synthetic (±)-hericenol B (**26**) was treated with PPTS in MeOH after silica gel treatment[28] (Scheme 5). As expected, hericenol D was generated in 65% yield, accompanied by the formation of the C5′-methoxy substituted product **29** (27% yield). TLC analyses indicated that allylic substitution at the side chain moiety was rapid, while substitution at the benzylic position gradually occurred over hours to days. The rationale for the regioselective substitution at the upper benzyl alcohol lies in the formation of the *o*-quinone methide intermediates **i** and **ii** generated by acid-catalyzed dehydration of **26**. When the solvent was replaced by MeOH/$H_2O$ (1/1), a small amount of hericenol C (**28**) was formed (22% yield) along with hericenol D (**27**) (17% yield) and their regioisomers **30** (8% yield) and **29** (10% yield). Anke and Sterner et al. had performed repeated silica gel column chromatographic separations followed by preparative HPLC in the isolation of the hericenols.[6] The samples were eluted with a linear gradient of $H_2O$/MeOH.[6] Given these observations, it is possible that hericenols C and D might be artifacts resulting from degradation of hericenol B. However, it cannot completely be ruled out that these compounds actually occur in natural sources.

Next, we focused our attention on the synthesis of lactam-containing natural products such as hericenone B and erinacerin A. Recently, we achieved the first total synthesis of hericerin, a 5′-deoxo analogue of hericenone B, and confirmed that the actual structure of hericerin was the carbonyl regioisomer of the reported structure.[4d] Our data were later supported by Miranda's total synthesis, in which the structure of the synthetic sample was unambiguously established by X-ray crystallographic analysis.[4e] As the structure and the spectroscopic data for hericenone B are highly correlated with those of hericerin, we were convinced that natural hericenone B had an inverse carbonyl group as well. With this expectation in mind, the synthesis commenced with the carbonyl-inverted phthalide **20** (Scheme 6). Whereas either direct lactamization under thermal conditions[4d,29] or $Me_3Al$-mediated amidation[4d,30] resulted in mostly decomposition of the substrate, application of the transamidation conditions with boric acid developed by Nguyen et al.[31] provided amide **31** in 95% yield. It should be

**Scheme 6. Total Syntheses of Hericenone B and Erinacerin A**




mentioned that such a mild amidation has a great deal of potential for acid-sensitive substrates, as shown in this case. Next, a two-step cyclization sequence[4d,32] afforded the expected lactam **33**, which was subjected to deprotection and oxidation[23] to provide ketone **35**. As established earlier, final deprotection of the phenolic hydroxyl group was undertaken with $Me_2BBr$ in the presence of excess amylene to suppress undesired addition of HBr to the C2′−C3′ double bond. This careful procedure successfully furnished hericenone B (**36**) after treatment with $Et_3N$ in 61% yield. The $^1H$ and $^{13}C$ NMR data for the synthetic compound **36** were in accordance with those reported in the literature,[2a] which unambiguously revised the structure of hericenone B. Very recently, Lee and co-workers isolated the same product from the fruiting bodies of *H. erinaceum* and named it isohericenone.[33] Our data are also in good agreement with their spectral data. Accordingly, it is suggested that the two natural products isolated by different researchers are probably identical.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Erinacerin A, discovered in 2005,[7] can be regarded as a cyclized product of newly identified hericenone B (**36**). Therefore, we undertook an acid-catalyzed cyclization of **36**. TLC analysis indicated gradual generation of erinacerin A (**37**) over a few days. Isolation by chromatography provided **37** in almost quantitative yield. The spectral data for the synthetic sample (**37**) matched the previously published physical data.[7]

In summary, we have achieved total syntheses of eight natural products derived from *H. erinaceum* and a *Stereum* species. Our strategy was based on divergent assembly of a geranyl resorcylate library using the suitably protected C5′-oxygen incorporated geranyl phthalide **18a** as a common intermediate. This intermediate (**18a**) was efficiently prepared by a $CuBr_2$-mediated multifunctionalization reaction and a CsF-assisted Stille coupling reaction as key reactions. The C5′-oxygen functionality was installed by alkylation of a cyanohydrin ether, which was later protected as the TBS ether until final transformations. From a common synthetic intermediate, total syntheses of hericenones A (**23**), B (**36**), and I (**24**), hericenols B (**26**), C (**28**) and D (**27**), and erinacerins A (**37**) and B (**25**) were achieved. Among the eight natural products, hericenol B and erinacerin B were synthesized as racemates. The reported structure for hericenone B was unambiguously revised. Moreover, this study showed that hericenols C and D could be generated from hericenol B via allylic and benzylic substitutions. The present investigation not only provides a natural product library for SAR studies but also offers information to deduce the biosynthetic pathway of naturally occurring geranyl resorcylates. The syntheses of other members of this family are ongoing in our laboratory.

## 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 either open chromatography on silica gel (spherical, neutral, 70−230 μm) or flash chromatography on silica gel (spherical, neutral, 40−50 μm) and, if necessary, HPLC equipped with a prepacked column using hexane/EtOAc as eluent. NMR spectra were recorded with a 300 MHz ($^1$H, 300 MHz; $^{13}$C, 75 MHz) or a 400 MHz ($^1$H, 400 MHz; $^{13}$C, 100 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; sept, septet; m, multiplet. Infrared spectra were recorded with a FT/IR spectrometer and reported as wavenumbers ($cm^{-1}$). Low- and high-resolution FAB mass spectra were recorded with a double-focusing magnetic sector mass spectrometer in positive or negative ion mode. High-resolution ESI, APCI, and APPI mass spectra were recorded with an Orbitrap analyzer in positive or negative ion mode.

**(*E*)-2-((3-Methyl-4-(2-(2-methylprop-1-en-1-yl)-1,3-dithian-2-yl)but-2-en-1-yl)oxy)tetrahydro-2*H*-pyran (12).** To a solution of dithiane **10**[12] (1.22 g, 7.02 mmol) in THF (34 mL) was added *n*-BuLi (1.63 M in hexane, 4.30 mL, 7.02 mmol) at −20 °C. After it was stirred for 2 h at −20 °C, the reaction mixture was cooled to −78 °C followed by the addition of allyl bromide **11**[13] (874 mg, 3.51 mmol) in THF (20 mL). After it was stirred for 14 h at −78 °C, the reaction mixture was quenched with 1 M aqueous HCl. The resulting mixture was extracted with hexane (3×), and the combined organic layer was washed with brine, dried over anhydrous $Na_2SO_4$, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 15) to give the title compound **12** (1.09 g, 3.17 mmol, 90%) as a pale yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.52−5.47 (m, 2H), 4.64 (dd, 1H, *J* = 4.4, 3.2 Hz), 4.22 (dd, 1H, *J* = 12, 8.8 Hz), 4.09 (dd, 1H, *J* = 12, 7.2 Hz), 3.91−3.86 (m, 1H), 3.52−3.47 (m, 1H), 2.91−2.78 (m, 4H), 2.82 (s, 2H), 2.04−1.48 (m, 8H), 1.95 (d, 3H, *J* = 1.2 Hz), 1.77 (d, 3H, *J* = 1.2 Hz), 1.58 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 138.7, 135.6, 128.0, 127.0, 97.7, 63.4, 62.5, 52.8, 50.5, 30.9, 28.0, 27.7, 25.6, 25.5, 19.8, 19.5, 18.3; FT-IR (film on ZnSe) 2938, 1652, 1442, 1384, 1354, 1320, 1275, 1200, 1183, 1158, 1117 $cm^{-1}$; HRMS (ESI-pos) *m*/*z* calcd for $C_{18}H_{31}O_2S_2$ $[M + H]^+$ 343.1760, found 343.1756.

**(*E*)-Tributyl(3-methyl-4-(2-(2-methylprop-1-en-1-yl)-1,3-dithian-2-yl)but-2-en-1-yl)stannane (7a).** To a solution of **12** (1.06 g, 3.09 mmol) in MeOH (31 mL) was added PPTS (156 mg, 0.621 mmol). The mixture was stirred for 1.5 h at room temperature and then warmed to 50 °C and stirred for 45 min. $Et_3N$ (866 μL, 6.21 mmol) was added, and the resulting mixture was concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 5) to give the corresponding alcohol (760 mg, 2.94 mmol, 95%) as a pale yellow oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.57 (td, 1H, *J* = 6.8, 1.2 Hz), 5.51 (br s, 1H), 4.18 (d, 2H, *J* = 6.4 Hz), 2.93−2.78 (m, 4H), 2.80 (s, 2H), 2.05−1.92 (m, 2H), 1.95 (d, 3H, *J* = 1.2 Hz), 1.78 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 138.6, 134.6, 129.6, 128.0, 59.3, 52.7, 50.3, 27.9, 27.7, 25.3, 19.4, 18.2; FT-IR (film on ZnSe) 3400, 2929, 2902, 1652, 1441, 1423, 1383, 1356, 1275, 1242, 1194, 1124, 1091 $cm^{-1}$; HRMS (FAB) *m*/*z* calcd for $C_{13}H_{23}OS_2$ $[M + H]^+$ 259.1190, found 259.1193. To a solution of the alcohol (424 mg, 1.64 mmol) in THF (3.3 mL) was added *n*-BuLi (1.54 M solution in hexane, 1.07 mL, 1.65 mmol) at −78 °C. After the mixture was stirred for 30 min, MsCl (130 μL, 1.64 mmol) was added. After the mixture was stirred for 75 min, *n*-$Bu_3SnLi$ in THF (10 mL) was added dropwise (*n*-$Bu_3SnLi$ was prepared as follows: to a solution of *i*-$Pr_2NH$ (700 μL, 5.00 mmol) in THF (5.5 mL) was added *n*-BuLi (1.53 M solution in hexane, 3.20 mL, 4.93 mmol) at 0 °C; after the mixture was stirred for 50 min at 0 °C, *n*-$Bu_3SnH$ (1.42 g, 4.89 mmol) in THF (4.5 mL) was added and the mixture was stirred for 40 min at 0 °C). After it was stirred for 2 h at −78 °C, the solution was warmed to room temperature and quenched after 3.5 h with $H_2O$. The resulting mixture was extracted with EtOAc (3×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (hexane/$Et_3N$ = 50 → hexane/EtOAc/$Et_3N$ = 100/1/2) to give allylstannane **7a** (649 mg, 1.22 mmol, 74%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 5.51 (br t, 1H, *J* = 6.6 Hz), 5.51 (br s, 1H), 2.93−2.72 (m, 6H), 2.04−1.85 (m, 2H), 1.95 (d, 3H, *J* = 1.2 Hz), 1.76 (d, 3H, *J* = 1.2 Hz), 1.65 (br s, 3H), 1.70−1.43 (m, 8H), 1.34−1.22 (m, 6H), 0.91−0.82 (m, 15H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 137.9, 129.7, 128.6, 124.6, 53.8, 50.6, 29.3, 27.9, 27.7, 27.5, 25.7, 19.4, 17.7, 13.8, 11.3, 9.7; FT-IR (film on ZnSe) 2952, 2926, 2871, 2852, 1647, 1464, 1156, 1442, 1422, 1375, 1355, 1292, 1274, 1243, 1194, 1118 $cm^{-1}$. Anal. Calcd for $C_{25}H_{48}S_2Sn$: C, 56.50; H, 9.10. Found: C, 56.53; H, 8.78.

**2-(1-Ethoxyethoxy)-4-methylpent-3-enenitrile (14).** To a solution of 3-methyl-2-butenal (**8**; 20.0 g, 238 mmol) in $CH_2Cl_2$ (119 mL) were added TMSCN (32.7 mL, 262 mmol) and $Et_3N$ (3.3 mL, 23.8 mmol) The mixture was stirred at room temperature for 7 h and concentrated. The resulting α-cyano TMS ether (48.6 g) was dissolved in THF (95 mL), to which was added 1 M aqueous HCl (24 mL). The mixture was stirred at room temperature for 30 min and extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give the corresponding cyanohydrin (43.0 g) as a yellow oil. To a solution of crude cyanohydrin (43.0 g) in $CH_2Cl_2$ (119 mL) were added ethyl vinyl ether (114 mL, 1.19 mol) and PPTS (5.85 g, 23.8 mmol). The solution was stirred at room temperature for 1.5 h, which was followed by the addition of $Et_3N$ (33.0 mL, 238 mmol). The resulting mixture was concentrated and purified by open chromatography (hexane/EtOAc = 10) to give the title compound **14** (44.5 g, quant) as a pale pink oil: $^1$H NMR (400 MHz, $CDCl_3$) δ 5.37−5.28 (m, 1H), 5.13 (d, 0.5H, *J* = 8.7 Hz), 5.03 (d, 0.5H, *J* = 9.0 Hz), 4.96 (q, 0.5H, *J* = 5.4 Hz), 4.88 (q, 0.5H, *J* = 5.4 Hz), 3.70−3.46 (m, 2H), 1.79 (d, 3H, *J* = 0.9 Hz), 1.74 (d, 3H, *J* = 1.5 Hz), 1.39 (d, 3H, *J* = 5.7 Hz), 1.36 (d,


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3H, $J$ = 5.4 Hz), 1.22 (t, 3H, $J$ = 7.2 Hz, EE), 1.21 (t, 3H, $J$ = 7.2 Hz, EE); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 141.5, 141.4, 118.9, 118.7, 118.2, 117.9, 98.8, 98.5, 60.8, 60.6, 59.9, 59.2, 25.7, 19.6, 18.5, 15.3, 15.1; FT-IR (film on ZnSe) 2979, 2937, 2918, 2237, 1675, 1445, 1387, 1379, 1342, 1310, 1200, 1141, 1082 cm$^{-1}$; HRMS (ESI-pos) $m/z$ calcd for $C_{10}H_{17}O_2NNa$ $[M + Na]^+$ 206.1152, found 206.1152.

**(*E*)-4-Bromo-3-methylbut-2-en-1-yl Benzoate (15).**[19] To a solution of isoprene (**9**; 31.1 mL, 309 mmol) in 1-chlorobutane (309 mL) was added bromine (24.7 g, 155 mmol) through a dropping funnel over 20 min at −40 °C. After it was stirred for 2.5 h at −40 °C, the reaction mixture was warmed to room temperature and the solution was poured into water. The organic layer was washed successively with aqueous $Na_2S_2O_3$ solution, aqueous saturated $NaHCO_3$ solution, and brine. The resulting organic layer was dried over anhydrous $MgSO_4$ and concentrated to give (*E*)-1,4-dibromo-2-methyl-2-butene (29.4 g) as a yellow oil. To a solution of the above product (27.9 g) in DMF (245 mL) was added sodium benzoate (19.4 g, 135 mmol) at 0 °C. The mixture was stirred for 3.5 h at room temperature and 0.5 h at 40 °C. An additional portion of sodium benzoate (1.79 g, 12.2 mmol) was added at 0 °C, and the stirring was continued for 1 h at 40 °C. The reaction mixture was quenched by the addition of water and extracted with EtOAc (3×). The combined organic layer was washed with water and brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by repeated flash chromatography (*n*-hexane → *n*-hexane/EtOAc = 60 → 30 → 10 then *n*-hexane/EtOAc = 500 → 300 → 100 → 30 → 10) to give the title compound **15** (18.5 g, 68.9 mmol, 47% for two steps) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07−8.03 (m, 2H), 7.59−7.54 (m, 1H), 7.47−7.41 (m, 2H), 5.86 (br t, 1H, $J$ = 6.0 Hz), 4.86 (br d, 2H, $J$ = 6.6 Hz), 3.98 (br s, 2H), 1.92 (br s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.5, 137.5, 133.2, 130.2, 129.8, 128.5, 124.4, 61.5, 39.6, 15.4; FT-IR (film on ZnSe) 3062, 3032, 2956, 1721, 1602, 1585, 1491, 1451, 1388, 1380, 1335, 1314, 1271, 1221, 1201, 1176, 1111 cm$^{-1}$; HRMS (FAB) $m/z$ calcd for $C_{12}H_{14}BrO_2$ $[M + H]^+$ 269.0177, found 269.0150.

**(*E*)-5-Cyano-5-(1-ethoxyethoxy)-3,7-dimethylocta-2,6-dien-1-yl Benzoate (16).** To a solution of $\alpha$-cyano ether **14** (12.6 g, 68.9 mmol) and allylic bromide **15** (18.5 g, 68.9 mmol) in THF (138 mL) was added $(TMS)_2NLi$ (1.0 M solution in THF, 82.7 mL, 82.7 mmol) at −78 °C. After it was stirred for 30 min at −78 °C, the reaction mixture was quenched with saturated aqueous $NH_4Cl$ solution. Most of the THF was removed by evaporation, and the residue was extracted with hexane (2×). The combined organic layer was washed with phosphate buffer (pH 3.9) and brine and dried over anhydrous $MgSO_4$. Concentration of the solution gave the alkylation product **16** (27.4 g) as a pale yellow oil, which was used for the next reaction without further purification. The analytical sample was obtained by flash chromatography (*n*-hexane/EtOAc = 20 → 10): $^1$H NMR (300 MHz, $CDCl_3$, 2/1 diastereomeric mixture) $\delta$ 8.05−8.01 (m, 2H), 7.56−7.50 (m, 1H), 7.44−7.38 (m, 2H), 5.72−5.65 (m, 1H), 5.30−5.28 (m, 0.33H), 5.14−5.11 (m, 0.67H), 5.02 (q, 0.67H, $J$ = 5.4 Hz), 4.96 (q, 0.33H, 5.4 Hz), 4.86 (d, 2H, $J$ = 6.9 Hz), 3.67−3.40 (m, 2H), 2.79−2.53 (m, 2H), 1.96−1.88 (m, 6H), 1.77−1.76 (m, 3H), 1.37 (d, 1H, $J$ = 5.1 Hz), 1.31 (d, 2H, $J$ = 5.4 Hz), 1.20 (t, 2H, $J$ = 6.9 Hz), 1.16 (t, 1H, $J$ = 6.9 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$, 2/1 diastereomeric mixture) $\delta$ 166.5, 140.9, 139.1, 135.5, 132.9, 130.4, 129.6, 128.4, 125.6, 125.5, 123.1, 121.6, 120.3, 119.5, 98.5, 97.2, 74.4, 73.4, 61.5, 61.4, 60.0, 50.7, 50.2, 27.3, 27.2, 21.1, 20.8, 19.0, 18.9, 18.5, 18.4, 15.2, 15.0; FT-IR (film on ZnSe) 3062, 2978, 2934, 2227, 1720, 1665, 1602, 1585, 1451, 1382, 1342, 1314, 1271, 1176 cm$^{-1}$; HRMS (FAB) $m/z$ calcd for $C_{22}H_{30}NO_4$ $[M + H]^+$ 372.2175, found 372.2183.

**(*E*)-5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-ol (17).** To a solution of crude **16** (27.4 g) in MeOH (138 mL) was added $TsOH·H_2O$ (1.31 g, 6.89 mmol). After it was stirred for 20 min at room temperature, the solution was cooled to 0 °C followed by the addition of $Et_3N$ (14.3 mL, 103 mmol). After the mixture was stirred for 10 min at 0 °C, a solution of $CeCl_3·7H_2O$ (51.3 g, 138 mmol) in MeOH (138 mL) and $NaBH_4$ (6.52 g, 172 mmol) were successively added. After it was stirred for 15 min at 0 °C, the reaction mixture was quenched with phosphate buffer (pH 7). Most of the MeOH was removed by evaporation, and the residue was treated with EtOAc. The precipitate was carefully removed by decantation and filtration through a pad of Celite. The combined filtrate was concentrated and extracted with EtOAc (5×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give the corresponding allylic alcohol (16.6 g) as a yellow oil, which was used for the next reaction without further purification. The analytical sample was obtained by flash chromatography (*n*-hexane/EtOAc = 5): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.02−7.97 (m, 2H), 7.52−7.45 (m, 1H), 7.40−7.33 (m, 2H), 5.51 (br t, 1H, $J$ = 6.9 Hz), 5.16−5.10 (m, 1H), 4.80 (br d, 2H, $J$ = 6.6 Hz), 4.51−4.43 (m, 1H), 2.27 (dd, 1H, $J$ = 14, 8.1 Hz), 2.15 (br dd, 1H, $J$ = 14, 5.7 Hz), 1.77 (br s, 3H), 1.65 (br s, 3H), 1.62 (br s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.5, 138.8, 134.7, 132.8, 130.3, 129.5, 128.2, 127.5, 121.6, 66.4, 61.6, 47.7, 25.6, 18.1, 16.8; FT-IR (film on ZnSe) 3422, 3061, 3031, 2972, 2931, 1720, 1602, 1585, 1451, 1377, 1340, 1315, 1273, 1176, 1111 cm$^{-1}$; HRMS (FAB) $m/z$ calcd for $C_{17}H_{23}O_3$ $[M + H]^+$ 275.1647, found 275.1639. To a solution of the crude alcohol (16.6 g) in DMF (61 mL) were added imidazole (12.4 g, 182 mmol) and TBSCl (10.9 g, 72.6 mmol). The mixture was stirred for 30 min at 40 °C and then cooled to 0 °C and diluted with *n*-hexane and water. The resulting mixture was extracted with *n*-hexane (2×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give the corresponding TBS ether (23.9 g) as a pale yellow oil, which was used for the next reaction without further purification. The analytical sample was obtained by flash chromatography (*n*-hexane/EtOAc = 50): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 8.07−8.03 (m, 2H), 7.57−7.51 (m, 1H), 7.45−7.39 (m, 2H), 5.50 (br t, 1H, $J$ = 7.2 Hz), 5.11 (dqq, 2H, $J$ = 8.7, 1.5, 1.2 Hz), 4.83 (d, 1H, $J$ = 6.9 Hz), 4.82 (d, 1H, $J$ = 7.2 Hz), 4.47 (ddd, 1H, $J$ = 8.7, 7.5, 5.4 Hz), 2.27 (dd, 1H, $J$ = 13, 7.5 Hz), 2.10 (dd, 1H, $J$ = 13, 5.4 Hz), 1.79 (br s, 3H), 1.66 (d, 3H, $J$ = 1.2 Hz), 1.60 (d, 3H, $J$ = 1.5 Hz), 0.85 (s, 9H), 0.01 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 166.7, 139.4, 132.9, 131.3, 130.6, 129.7, 129.3, 128.3, 121.2, 68.8, 61.9, 48.6, 25.9, 25.7, 18.3, 17.5, −4.2, −4.8; FT-IR (film on ZnSe) 3063, 3033, 2929, 2856, 1721, 1674, 1603, 1586, 1472, 1461, 1451, 1376, 1361, 1332, 1314, 1270, 1176, 1107 cm$^{-1}$; HRMS (ESI-pos) $m/z$ calcd for $C_{23}H_{36}O_3NaSi$ $[M + Na]^+$ 411.2326, found 411.2325. To a solution of the crude TBS ether (23.9 g) in $CH_2Cl_2$ (121 mL) was added DIBALH (1.0 M in *n*-hexane, 133 mL, 133 mmol) at −78 °C. The mixture was stirred for 1 h at −78 °C and quenched with aqueous Rochelle salt solution. The resulting mixture was diluted with *n*-hexane and stirred vigorously at room temperature for 14 h. The organic layer was separated, and the aqueous phase was extracted with EtOAc (4×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by repeated open chromatography (*n*-hexane → *n*-hexane/EtOAc = 50 → 20 → 10 → 5 then *n*-hexane → *n*-hexane/EtOAc = 100 → 50 → 30 → 20 → 10 → 5) to give allylic alcohol **17** (10.8 g, 37.8 mmol, 55% for four steps) as a pale yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.39 (br t, 1H, $J$ = 6.9 Hz), 5.08 (dsept, 1H, $J$ = 8.4, 1.5 Hz), 4.42 (ddd, 1H, $J$ = 8.4, 7.8, 5.4 Hz), 4.10 (br d, 2H, $J$ = 6.9 Hz), 2.19 (dd, 1H, $J$ = 13, 7.8 Hz), 2.03 (dd, 1H, $J$ = 13, 5.4 Hz), 1.67 (br s, 3H), 1.65 (d, 3H, $J$ = 1.5 Hz), 1.58 (d, 3H, $J$ = 1.5 Hz), 0.83 (s, 9H), −0.02 (s, 3H), −0.04 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 136.5, 131.2, 129.4, 126.4, 69.0, 59.4, 48.6, 25.9, 25.7, 18.3, 17.1, −4.2, −4.8; FT-IR (film on ZnSe) 3352, 2956, 2929, 2857, 1673, 1473, 1463, 1444, 1376, 1361, 1254, 1074 cm$^{-1}$; HRMS (ESI-pos) $m/z$ calcd for $C_{16}H_{32}O_2NaSi$ $[M + Na]^+$ 307.2064, found 307.2059.

**(*E*)-*tert*-Butyl((2,6-dimethyl-8-(tributylstannyl)octa-2,6-dien-4-yl)oxy)dimethylsilane (7b).** To a solution of alcohol **17** (3.95 g, 13.9 mmol) in THF (46 mL) was added *n*-BuLi (1.60 M solution in hexane, 8.67 mL, 13.9 mmol) at −78 °C. After the mixture was stirred for 35 min, MsCl (1.10 mL, 13.9 mmol) was added. After this mixture was stirred for 35 min, *n*-$Bu_3SnLi$ in THF was added (*n*-$Bu_3SnLi$ was prepared as follows: to a solution of *i*-$Pr_2NH$ (6.24 mL, 44.4 mmol) in THF (26 mL) was added *n*-BuLi (1.60 M solution in hexane, 26.0 mL, 41.6 mmol) at 0 °C; after the mixture was stirred for 25 min at 0 °C, *n*-$Bu_3SnH$ (12.1 g, 41.6 mmol) in THF (15 mL) was added and the mixture was stirred for 30 min at 0 °C). After it was stirred for 2 h at


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−78 °C, the solution was gradually warmed to −40 °C over 3.5 h and quenched with phosphate buffer (pH 7). The resulting mixture was extracted with *n*-hexane (3×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by repeated open chromatography (hexane/$Et_3N$ = 100) to give allylstannane **7b** (6.92 g, 12.4 mmol, 90%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 5.30 (br t, 1H, $J$ = 8.4 Hz), 5.10 (dsept, 1H, $J$ = 9.0, 1.2 Hz), 4.39 (dt, 1H, $J$ = 9.0, 6.3 Hz), 2.20 (dd, 1H, $J$ = 13, 6.6 Hz), 2.03 (dd, 1H, $J$ = 13, 6.3 Hz), 1.67 (d, 3H, $J$ = 1.2 Hz), 1.60 (d, 3H, $J$ = 1.2 Hz), 1.57 (br s, 3H), 1.71−1.42 (m, 8H), 1.35−1.23 (m, 6H), 0.91−0.80 (m, 15H), 0.86 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 131.0, 129.8, 126.1, 125.9, 69.5, 49.1, 29.4, 27.5, 26.1, 25.9, 18.4, 16.7, 13.9, 10.8, 9.5, −4.1, −4.6; FT-IR (film on ZnSe) 2956, 2927, 2856, 1676, 1463, 1376, 1360, 1254, 1119, 1073 cm$^{-1}$; HRMS (APPI-pos) $m/z$ calcd for $C_{28}H_{58}ONaSiSn$ $[M + Na]^+$ 581.3171, found 581.3178.

**(*E*)-6-(5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl)-5-methoxy-7-(methoxymethoxy)isobenzofuran-1(3*H*)-one (18a).** In a 20 mL two-necked round-bottom flask were placed aryl bromide **6** (170 mg, 0.560 mmol), allylstannane **7b** (624 mg, 1.12 mmol), $(Ph_3P)_2PdCl_2$ (39.9 mg, 0.0569 mmol), and CsF (169 mg, 1.11 mmol). DMF (2.8 mL) was added, and the mixture was heated to 85 °C and stirred for 24 h. The precipitate that formed was removed by filtration through a pad of Celite, and the filtrate was extracted with EtOAc (3×) and water. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 3) to give the coupling product **18a** (141 mg, 0.287 mmol, 51%) as a colorless solid: mp 83−85 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.64 (s, 1H), 5.36 (s, 2H), 5.20 (br t, 1H, $J$ = 7.2 Hz), 5.16 (s, 2H), 5.04 (br d, 1H, $J$ = 8.4 Hz), 4.42−4.34 (m, 1H), 3.88 (s, 3H), 3.57 (s, 3H), 3.43 (d, 1H, $J$ = 7.2 Hz), 3.42 (d, 1H, $J$ = 6.6 Hz), 2.13 (dd, 1H, $J$ = 13, 7.5 Hz), 1.97 (dd, 1H, $J$ = 13, 5.7 Hz), 1.78 (br s, 3H), 1.59 (d, 3H, $J$ = 1.2 Hz), 1.54 (d, 3H, $J$ = 1.2 Hz), 0.80 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 169.3, 164.2, 155.0, 148.6, 132.5, 130.8, 129.5, 124.7, 124.5, 109.2, 101.1, 99.0, 69.0, 68.7, 57.9, 56.2, 48.9, 25.9, 25.7, 23.1, 18.24, 18.18, 17.1, −4.3, −4.9; FT-IR (film on ZnSe) 3100, 2929, 2856, 1739, 1606, 1471, 1431, 1404, 1366, 1336, 1303, 1292, 1251, 1233, 1206, 1158, 1126 cm$^{-1}$; HRMS (ESI-pos) $m/z$ calcd for $C_{27}H_{42}O_6NaSi$ $[M + Na]^+$ 513.2643, found 513.2638.

**(*E*)-5-(5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)isobenzofuran-1(3*H*)-one (20).** To a solution of lactone **18a** (399 mg, 0.608 mmol) in THF (6.1 mL) was added $LiAlH_4$ (70.2 mg, 1.85 mmol) at 0 °C. After it was stirred for 5 min at 0 °C, the reaction mixture was quenched by the slow addition of water, EtOAc, and aqueous Rochelle salt solution. The resulting mixture was stirred at room temperature for 1 h and then extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated to give diol **19a** (384 mg) as a pale yellow oil. To a solution of crude diol **19a** (384 mg) in toluene (7.7 mL) was added $Ag_2CO_3$ on Celite (ca. 50 wt %, 1.08 g, ca. 1.94 mmol). The suspension was heated at reflux and stirred for 3 h. The precipitate was removed by filtration through a pad of Celite and washed with EtOAc, and the filtrate was concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 3) to give phthalide **20** (220 mg, 0.448 mmol, 74% for two steps) as a pale yellow viscous oil and phthalide **18a** (69.9 mg, 0.143 mmol, 23%) as a pale yellow solid. Data for **20**: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.12 (s, 1H), 5.36 (s, 2H), 5.15 (br t, 1H, $J$ = 7.2 Hz), 5.05 (s, 2H), 5.01 (br d, 1H, $J$ = 7.2 Hz), 4.38 (td, 1H, $J$ = 7.8, 5.7 Hz), 3.87 (s, 3H), 3.53 (s, 3H), 3.43 (d, 2H, $J$ = 7.2 Hz), 2.14 (dd, 1H, $J$ = 13, 7.5 Hz), 1.97 (dd, 1H, $J$ = 13, 5.1 Hz), 1.78 (d, 3H, $J$ = 1.2 Hz), 1.60 (d, 3H, $J$ = 1.2 Hz), 1.54 (d, 3H, $J$ = 1.2 Hz), 0.80 (s, 9H), −0.05 (s, 3H), −0.07 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.6, 159.7, 150.5, 133.0, 130.9, 129.6, 129.2, 129.1, 125.5, 124.2, 101.8, 97.3, 69.3, 68.9, 57.0, 56.3, 49.0, 26.1, 26.0, 25.8, 23.9, 18.3, 17.2, −4.2, −4.8; FT-IR (film on ZnSe) 2929, 2856, 1766, 1675, 1618, 1471, 1433, 1399, 1361, 1331, 1254, 1231, 1205, 1155 cm$^{-1}$; HRMS (FAB) $m/z$ calcd for $C_{26}H_{39}O_6Si$ $[M - CH_3]^+$ 475.2516, found 475.2509.

**(*E*)-5-(3,7-Dimethyl-5-oxoocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)isobenzofuran-1(3*H*)-one (21).** To a solution of TBS ether **20** (52.2 mg, 0.106 mmol) in THF (2.1 mL) was added TBAF (1 M solution in THF, 638 μL, 0.638 mmol). The mixture was stirred for 7 h at 40 °C and directly subjected to flash chromatography (*n*-hexane/EtOAc = 1) to give the corresponding alcohol (49.0 mg) as a colorless viscous oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.12 (s, 1H), 5.35 (s, 2H), 5.23 (br t, 1H, $J$ = 6.9 Hz), 5.10 (dsept, 1H, $J$ = 8.7, 1.2 Hz), 5.06 (s, 2H), 4.41 (td, 1H, $J$ = 8.1, 5.4 Hz), 3.87 (s, 3H), 3.52 (s, 3H), 3.50 (dd, 1H, $J$ = 14, 7.2 Hz), 3.43 (dd, 1H, $J$ = 14, 6.9 Hz), 2.19−2.04 (m, 2H), 1.81 (br s, 3H), 1.67 (d, 3H, $J$ = 1.2 Hz), 1.65 (d, 3H, $J$ = 1.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 171.3, 159.7, 150.4, 135.0, 132.7, 129.0, 128.5, 127.5, 125.7, 125.6, 101.8, 97.2, 69.2, 65.9, 56.9, 56.3, 48.2, 25.8, 23.8, 18.3, 16.4; FT-IR (film on ZnSe) 3510, 2965, 2931, 1766, 1618, 1469, 1434, 1401, 1332, 1231, 1210, 1154, 1112 cm$^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{21}H_{28}O_6Cl$ $[M + Cl]^-$ 411.1580, found 411.1594. To a solution of the above alcohol (49.0 mg) in $CH_2Cl_2$ (1 mL) were added $PhI(OAc)_2$ (206 mg, 0.638 mmol) and 2-azaadamantane *N*-oxyl (1.6 mg, 0.011 mmol). The mixture was stirred for 3 h at room temperature followed by the addition of $PhI(OAc)_2$ (103 mg, 0.319 mmol). After 40 min, the solution was diluted with $CH_2Cl_2$ (2 mL) and quenched successively with saturated aqueous $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution. After it was stirred for 1.2 h, the mixture was extracted with EtOAc (3×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (hexane/EtOAc = 3) to give ketone **21** (30.8 mg, 0.0823 mmol, 77% for two steps) as a pale yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.12 (s, 1H), 6.05 (sept, 1H, $J$ = 1.2 Hz), 5.36 (s, 2H), 5.24 (br t, 1H, $J$ = 7.2 Hz), 5.06 (s, 2H), 3.87 (s, 3H), 3.52 (s, 3H), 3.50 (d, 2H, $J$ = 7.6 Hz), 3.01 (s, 2H), 2.11 (d, 3H, $J$ = 1.2 Hz), 1.83 (d, 3H, $J$ = 0.9 Hz), 1.78 (br s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 199.2, 171.4, 159.7, 155.9, 150.4, 130.7, 129.0, 128.4, 126.2, 125.6, 122.9, 101.7, 97.2, 69.2, 56.9, 56.2, 55.4, 27.8, 23.9, 20.8, 16.7; FT-IR (film on ZnSe) 2938, 2913, 2845, 1766, 1686, 1618, 1469, 1434, 1401, 1382, 1356, 1332, 1231, 1209, 1154, 1112 cm$^{-1}$; HRMS (ESI-pos) $m/z$ calcd for $C_{21}H_{27}O_6$ $[M + H]^+$ 375.1802, found 375.1794.

**(*E*)-5-(3,7-Dimethyl-5-oxoocta-2,6-dien-1-yl)-4-hydroxy-6-methoxyisobenzofuran-1(3*H*)-one (Hericenone A, 23).** To a solution of ketone **21** (18.6 mg, 49.7 μmol) in $CH_2Cl_2$ (1 mL) were added successively amylene (149 μL, 1.40 mmol) and $Me_2BBr$ (0.5 M solution in $CH_2Cl_2$, 149 μL, 74.5 μmol) at −78 °C. After 1 h at −78 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (3×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue (20.4 mg) was dissolved in $CH_2Cl_2$ (1 mL) and treated with $Et_3N$ (41.3 μL, 298 μmol) for 1 h at 0 °C. The resulting mixture was directly subjected to flash chromatography (*n*-hexane/EtOAc = 3 → 2) to give hericenone A (**23**; 12.8 mg, 38.7 μmol, 78%) as a colorless solid: mp 134−136 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.96 (s, 1H), 6.09 (sept, 1H, $J$ = 1.2 Hz), 5.30 (br t, 1H, $J$ = 7.2 Hz), 5.24 (s, 2H), 3.86 (s, 3H), 3.58 (d, 2H, $J$ = 7.2 Hz), 3.18 (s, 2H), 2.17 (d, 3H, $J$ = 1.2 Hz), 1.90 (d, 3H, $J$ = 1.2 Hz), 1.81 (br s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 199.2, 172.0, 159.3, 157.7, 150.7, 133.8, 128.3, 125.9, 125.2, 123.2, 121.4, 98.6, 68.4, 56.3, 54.5, 28.0, 23.5, 21.2, 17.3; FT-IR (film on ZnSe) 3248, 2940, 2842, 1765, 1666, 1595, 1470, 1381, 1348, 1330, 1265, 1237, 1206 cm$^{-1}$; HRMS (FAB) $m/z$ calcd for $C_{19}H_{23}O_5$ $[M + H]^+$ 331.1545, found 331.1551.

**5-Methoxy-2-methyl-2-(4-methyl-2-oxopent-3-en-1-yl)-3,4-dihydro-2*H*-furo[3,4-*h*]chromen-7(9*H*)-one (Hericenone I, 24).** To a solution of hericenone A (**23**; 7.4 mg, 22 μmol) in $ClCH_2CH_2Cl$ (1 mL) was added CSA (10.5 mg, 45.2 μmol). The mixture was stirred for 67 h at 70 °C and directly subjected to flash chromatography (*n*-hexane/EtOAc = 3) to give hericenone I (**24**; 5.5 mg, 17 μmol, 74%) as a colorless viscous oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.89 (s, 1H), 6.05 (sept, 1H, $J$ = 1.2 Hz), 5.18 (d, 1H, $J$ = 15 Hz), 5.11 (d, 1H, $J$ = 15 Hz), 3.87 (s, 3H), 2.78 (d, 1H, $J$ = 14 Hz), 2.71 (dd, 2H, $J$ = 6.9,


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6.6 Hz), 2.65 (d, 1H, $J$ = 14 Hz), 2.15 (d, 3H, $J$ = 1.2 Hz), 2.05 (dt, 1H, $J$ = 14, 6.6 Hz), 1.94 (dt, 1H, $J$ = 14, 6.9 Hz), 1.88 (d, 3H, $J$ = 1.2 Hz), 1.42 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 197.9, 171.9, 159.4, 156.4, 148.5, 128.1, 125.1, 125.0, 116.8, 97.0, 76.6, 68.1, 56.1, 52.3, 30.4, 28.0, 24.8, 21.0, 17.7; FT-IR (film on ZnSe) 2977, 2939, 2882, 2844, 1766, 1681, 1618, 1474, 1439, 1380, 1342, 1308, 1240, 1204, 1157, 1101 cm$^{-1}$; HRMS (FAB) $m/z$ calcd for $C_{19}H_{23}O_5$ $[M + H]^+$ 331.1545, found 331.1551.

**(*E*)-4-Hydroxy-5-(5-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl)-6-methoxyisobenzofuran-1(3*H*)-one ((±)-Erinacerin B, 25).** To a solution of **23** (12.8 mg, 0.0387 mmol) in MeOH (1 mL) and THF (0.3 mL) was added $CeCl_3{\cdot}7H_2O$ (43.3 mg, 0.116 mmol). After 5 min, $NaBH_4$ (4.9 mg, 0.13 mmol) was added and the mixture was stirred at room temperature for 10 min. The reaction mixture was concentrated to ca. 0.5 mL and directly subjected to flash chromatography ($n$-hexane/EtOAc = 3 → 1) to give (±)-erinacerin B (**25**; 9.4 mg, 0.0283 mmol, 73%) as a colorless solid: mp 134−135 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) $\delta$ 9.90 (s, 1H), 6.87 (s, 1H), 5.23 (s, 2H), 5.09 (br t, 1H, $J$ = 6.9 Hz), 4.97 (br d, 1H, $J$ = 8.6 Hz), 4.31 (br d, 1H, $J$ = 4.6 Hz), 4.26−4.17 (m, 1H), 3.40−3.25 (m, 2H), 3.33 (s, 3H), 2.07 (dd, 1H, $J$ = 13, 6.6 Hz), 1.88 (dd, 1H, $J$ = 13, 6.9 Hz), 1.73 (s, 3H), 1.53 (s, 3H), 1.48 (s, 3H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) $\delta$ 170.9, 159.1, 149.4, 132.1, 130.9, 129.6, 126.7, 123.7, 123.5, 123.0, 97.4, 68.2, 65.9, 56.0, 48.1, 25.3, 22.5, 17.8, 16.6; FT-IR (film on ZnSe) 1183, 2927, 1723, 1624, 1594, 1471, 1457, 1437, 1355, 1328, 1313, 1237, 1225, 1168 cm$^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{19}H_{23}O_5$ $[M - H]^-$ 331.1551, found 331.1561.

**(*E*)-6-(5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl)-7-hydroxy-5-methoxyisobenzofuran-1(3*H*)-one (18b).** To a solution of MOM ether **18a** (103 mg, 0.209 mmol) and amylene (666 μL, 6.27 mmol) in $CH_2Cl_2$ (7 mL) were added $Et_3N$ (175 μL, 1.26 mmol) and $TiCl_4$ (1.0 M solution in $CH_2Cl_2$, 418 μL, 0.418 mmol) in this order at −78 °C. After it was stirred for 6 min at −78 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (2×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography ($n$-hexane/EtOAc = 8) to give phenol **18b** (60.8 mg, 0.136 mmol, 65%) as a colorless viscous oil: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.70 (s, 1H), 6.47 (s, 1H), 5.22 (s, 2H), 5.20 (br t, 1H, $J$ = 7.2 Hz), 5.04 (dsept, 1H, $J$ = 8.7, 1.2 Hz), 4.37 (td, 1H, $J$ = 7.8, 5.7 Hz), 3.88 (s, 3H), 3.33 (d, 2H, $J$ = 7.2 Hz), 2.14 (dd, 1H, $J$ = 13, 7.5 Hz), 1.97 (dd, 1H, $J$ = 13, 5.4 Hz), 1.78 (d, 3H, $J$ = 0.9 Hz), 1.60 (d, 3H, $J$ = 1.2 Hz), 1.54 (d, 3H, $J$ = 1.2 Hz), 0.79 (s, 9H), −0.05 (s, 3H), −0.07; $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 173.0, 164.9, 154.6, 146.0, 132.6, 130.7, 129.6, 124.2, 116.9, 104.3, 96.1, 70.5, 68.9, 56.2, 48.9, 25.9, 25.7, 21.8, 18.3, 18.2, 17.0, −4.3, −4.9; FT-IR (film on ZnSe) 3424, 2955, 2929, 2855, 1732, 1632, 1616, 1499, 1469, 1375, 1345, 1317, 1289, 1253, 1204, 1173, 1127, 1077 cm$^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{25}H_{37}O_5Si$ $[M - H]^-$ 445.2416, found 445.2431.

**(*E*)-(3-Hydroxy-4-(5-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)-5-methoxy-1,2-phenylene)dimethanol (Hericenol B, 26).** To a solution of lactone **18b** (46.3 mg, 0.104 mmol) in THF (3.5 mL) was added $LiAlH_4$ (11.8 mg, 0.311 mmol) at 0 °C. The mixture was stirred at room temperature for 3 h and quenched by the addition of water (0.4 mL), $Et_2O$ (5 mL), and 1 M aqueous HCl (0.4 mL) in that order at 0 °C. The resulting mixture was extracted with $Et_2O$ (3×). The combined organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine, dried over anhydrous $MgSO_4$, and concentrated to give diol **19b** (52.2 mg) as a pale yellow oil. To a solution of the crude diol **19b** (52.2 mg) in THF (3.5 mL) was added TBAF (1.0 M solution in THF, 520 μL, 0.520 mmol). The mixture was stirred for 6 h at 40 °C and concentrated to ca. 1 mL. The solution was directly subjected to flash chromatography ($n$-hexane/EtOAc = 1 → EtOAc → EtOAc/MeCN = 5) to give (±)-hericenol B (**26**; 29.3 mg, 0.0871 mmol, 84% for two steps) as an amber viscous oil and the recovery of **19b** (4.2 mg, 0.0093 mmol, 9%). Data for (±)-hericenol B (**26**): $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.45 (br s, 1H), 6.43 (s, 1H), 5.30 (t, 1H, $J$ = 7.2 Hz), 5.11 (d, 1H, $J$ = 8.7 Hz), 4.81 (s, 2H), 4.57 (s, 2H), 4.43 (td, 1H, $J$ = 8.7, 4.5 Hz), 3.80 (s, 3H), 3.41 (d, 2H, $J$ = 7.2 Hz), 2.15 (dd, 1H, $J$ = 14, 4.8 Hz), 2.08 (dd, 1H, $J$ = 13, 8.4 Hz), 1.82 (s, 3H), 1.70 (br s, 3H), 1.68 (br s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 157.5, 155.6, 137.2, 135.2, 132.6, 127.4, 127.0, 117.6, 116.7, 103.8, 65.8, 64.0, 58.8, 55.8, 48.2, 25.9, 22.5, 18.3, 16.3; FT-IR (film on ZnSe) 3319, 2968, 2930, 1617, 1585, 1508, 1426, 1375, 1319, 1220, 1167, 1114, 1008 cm$^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{19}H_{27}O_5$ $[M - H]^-$ 335.1864, found 335.1873.

**3-(Hydroxymethyl)-5-methoxy-6-((2*E*,5*E*)-7-methoxy-3,7-dimethylocta-2,5-dien-1-yl)-2-(methoxymethyl)phenol (Hericenol D, 27) and (*E*)-3-(Hydroxymethyl)-5-methoxy-6-(5-methoxy-3,7-dimethylocta-2,6-dien-1-yl)-2-(methoxymethyl)-phenol (29).** To a solution of (±)-hericenol B (**26**; 7.2 mg, 0.021 mmol) in MeOH (1 mL) was added silica gel (103 mg, spherical, neutral, 63−210 μm). The suspension was stirred at room temperature for 23 h. Then, PPTS (5.3 mg, 0.021 mmol) was added and the resulting mixture was stirred for 48 h. The reaction mixture was directly subjected to flash chromatography ($n$-hexane/EtOAc = 1) to give hericenol D (**27**) (0.7 mg) and a 2.3:1 mixture of **27** and **29** (6.2 mg). Calculated yields of **27** and **29** were 65% and 27%, respectively. The mixture was purified by normal-phase HPLC using $n$-hexane/EtOAc as eluent for data analyses. Data for hericenol D (**27**): colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.34 (s, 1H), 6.46 (s, 1H), 5.51 (dt, 1H, $J$ = 15.6, 6.3 Hz), 5.41 (d, 1H, $J$ = 15.6 Hz), 5.27 (br t, 1H, $J$ = 7.2 Hz), 4.73 (s, 2H), 4.60 (s, 2H), 3.81 (s, 3H), 3.44 (s, 3H), 3.40 (d, 2H, $J$ = 7.2 Hz), 3.13 (s, 3H), 2.71 (d, 2H, $J$ = 6.3 Hz), 1.77 (br s, 3H), 1.24 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 157.8, 155.7, 137.8, 136.8, 135.1, 128.6, 123.4, 116.5, 114.3, 103.7, 75.0, 68.7, 64.4, 58.2, 55.8, 50.4, 43.0, 26.0, 22.4, 16.2; FT-IR (film on ZnSe) 3350, 2928, 2855, 1618, 1586, 1508, 1464, 1426, 1378, 1362, 1319, 1287, 1257, 1220, 1188, 1167, 1117, 1076 cm$^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{21}H_{31}O_5$ $[M - H]^-$ 363.2177, found 363.2193. Data for **29**: colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 6.96 (s, 1H), 6.48 (s, 1H), 5.24 (br t, 1H, $J$ = 7.2 Hz), 4.95 (dsept, 1H, $J$ = 9.0, 1.2 Hz), 4.70 (s, 2H), 4.60 (s, 2H), 4.00 (dt, 1H, $J$ = 9.0, 6.9 Hz), 3.81 (s, 3H), 3.42 (s, 3H) 3.40 (d, 2H, $J$ = 7.2 Hz), 3.22 (s, 3H), 2.31 (br dd, 2H, $J$ = 13, 6.6 Hz), 2.07 (br dd, 2H, $J$ = 13, 6.6 Hz), 1.80 (d, 3H, $J$ = 1.5 Hz), 1.72 (d, 3H, $J$ = 1.2 Hz), 1.65 (d, 3H, $J$ = 1.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 157.7, 155.7, 138.8, 136.4, 134.2, 125.9, 124.8, 116.0, 115.2, 104.0, 75.9, 67.7, 64.5, 58.0, 55.81, 55.76, 46.0, 26.0, 22.6, 18.4, 16.7; FT-IR (film on ZnSe) 3382, 2962, 2928, 2859, 1617, 1585, 1508, 1465, 1148, 1424, 1375, 1261 cm$^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{21}H_{32}O_5Cl$ $[M + Cl]^-$ 399.1944, found 399.1955.

**2-((2*E*,5*E*)-7-Hydroxy-3,7-dimethylocta-2,5-dien-1-yl)-5-(hydroxymethyl)-3-methoxy-6-(methoxymethyl)phenol (Hericenol C, 28).** To a solution of (±)-hericenol B (**26**; 8.2 mg, 0.024 mmol) in MeOH (0.7 mL) and water (0.7 mL) was added silica gel (100 mg, spherical, neutral, 63−210 μm). The suspension was stirred at room temperature for 24 h. Then, PPTS (17.2 mg, 0.068 mmol) was added and the resulting mixture was stirred at room temperature for 95 h. The reaction mixture was directly subjected to flash chromatography ($n$-hexane/EtOAc = 1.5 → 1 → 0.5) to give a 1.6:1 mixture of hericenol D (**27**) and its isomer **29** (2.4 mg) and a 2.8:1 mixture of hericenol C (**28**) and its isomer **30** (2.6 mg). Calculated yields of **27**−**30** were 17%, 22%, 10% and 8%, respectively. The mixtures were purified by normal-phase HPLC using $n$-hexane/EtOAc as eluent for data analyses. Data for hericenol C (**28**): colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.32 (s, 1H), 6.46 (s, 1H), 5.66−5.54 (m, 2H), 5.25 (br t, 1H, $J$ = 6.9 Hz), 4.73 (s, 2H), 4.60 (s, 2H), 3.82 (s, 3H), 3.44 (s, 3H), 3.39 (br d, 2H, $J$ = 6.9 Hz), 2.68 (br d, 2H, $J$ = 5.1 Hz), 1.76 (s, 3H), 1.30 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 157.8, 155.7, 139.5, 137.9, 135.4, 125.3, 123.3, 116.4, 114.3, 103.7, 70.9, 68.7, 64.4, 58.2, 55.8, 42.6, 29.93, 29.86, 22.4, 16.2; FT-IR (film on ZnSe) 3369, 2967, 2925, 2855, 1618, 1586, 1507, 1465, 1424, 1378, 1319, 1289, 1221, 1190, 1116 cm$^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{20}H_{29}O_5$ $[M - H]^-$ 349.2020, found 349.2035. Data for **30**: colorless oil; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 7.61 (s, 1H), 6.44 (s, 1H), 5.32 (br t, 1H, $J$ = 6.6 Hz), 5.12 (br d, 1H, $J$ = 8.7 Hz), 4.74 (s, 2H), 4.60 (s, 2H), 4.42 (td, 1H, $J$ = 8.4, 5.1 Hz), 3.81 (s, 3H), 3.44 (s, 3H) 3.40 (d, 2H, $J$ = 7.2 Hz), 2.18−2.05 (m, 2H), 1.83 (br s, 3H), 1.70 (d, 3H, $J$ = 0.9 Hz), 1.68 (d, 3H, $J$ = 1.2 Hz); FT-IR (film on ZnSe) 3372, 2929,


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2857, 1618, 1585, 1508, 1464, 1448, 1426, 1380, 1319, 1290, 1219, 1190, 1167, 1116 $cm^{-1}$. HRMS (ESI-neg) $m/z$ calcd for $C_{20}H_{29}O_5$ $[M - H]^-$ 349.2020, found 349.2031.

**(*E*)-4-(5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl)-2-(hydroxymethyl)-5-methoxy-3-(methoxymethoxy)-*N*-phenethylbenzamide (31).** A mixture of lactone **20** (50.0 mg, 0.102 mmol), 2-phenylethylamine (258 μL, 2.04 mmol), $B(OH)_3$ (12.6 mg, 0.204 mmol), and water (36.7 μL, 2.04 mmol) was stirred at room temperature for 114 h. The reaction mixture was directly subjected to flash chromatography (*n*-hexane/EtOAc = 2) to give amide **31** (59.4 mg, 0.0971 mmol, 95%) as a pale yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.51 (t, 1H, *J* = 5.7 Hz), 7.38−7.19 (m, 5H), 7.01 (s, 1H), 5.11 (br t, 1H, *J* = 6.6 Hz), 5.05 (br d, 1H, *J* = 8.7 Hz), 4.97 (d, 1H, *J* = 6.5 Hz), 4.95 (d, 1H, *J* = 6.5 Hz), 4.54 (dd, 1H, *J* = 12, 6.0 Hz), 4.49 (dd, 1H, *J* = 12, 6.3 Hz), 4.39 (ddd, 1H, *J* = 8.7, 7.2, 5.7 Hz), 3.88 (br t, 1H, *J* = 6.3 Hz), 3.82 (s, 3H), 3.73 (td, 2H, *J* = 7.5, 5.7 Hz), 3.62 (s, 3H), 3.35 (dd, 1H, *J* = 14, 6.6 Hz), 3.29 (dd, 1H, *J* = 14, 6.3 Hz), 2.96 (t, 2H, *J* = 7.5 Hz), 2.15 (dd, 1H, *J* = 13, 6.9 Hz), 1.98 (dd, 1H, *J* = 13, 5.7 Hz), 1.76 (br s, 3H), 1.61 (d, 3H, *J* = 1.2 Hz), 1.55 (d, 3H, *J* = 1.2 Hz), 0.83 (s, 9H), −0.03 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.8, 158.2, 156.2, 139.1, 136.5, 132.5, 131.0, 129.5, 128.9, 128.7, 126.6, 126.2, 124.8, 124.6, 107.7, 100.5, 69.0, 57.7, 56.9, 55.9, 48.8, 41.5, 35.7, 26.0, 25.7, 23.9, 18.3, 18.2, 17.2, −4.2, −4.8; FT-IR (film on ZnSe) 3300, 3086, 3063, 3027, 2930, 2856, 1638, 1598, 1500, 1397, 1361, 1330, 1305, 1254, 1221, 1201, 1159 $cm^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{35}H_{53}O_6NClSi$ $[M + Cl]^-$ 646.3336, found 646.3354.

**(*E*)-4-(5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl)-2-(chloromethyl)-5-methoxy-3-(methoxymethoxy)-*N*-phenethylbenzamide (32).** To a solution of alcohol **31** (30.0 mg, 49.0 μmol) in $CH_2Cl_2$ (5.9 mL) were added $Et_3N$ (82.1 μL, 588 μmol) and MsCl (19.4 μL, 245 μmol) at 0 °C. The mixture was stirred for 50 min at 0 °C and quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (3×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 4) to give chloride **32** (23.6 mg, 37.4 μmol, 76%) as a pale yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H), 6.71 (s, 1H), 6.23 (t, 1H, *J* = 5.7 Hz), 5.10 (br t, 1H, *J* = 6.6 Hz), 5.04 (br d, 1H, *J* = 8.4 Hz), 5.02 (d, 1H, *J* = 5.4 Hz), 4.95 (d, 1H, *J* = 5.4 Hz), 4.81 (s, 2H), 4.39 (dt, 1H, *J* = 8.4, 6.9 Hz), 3.78 (s, 3H), 3.76 (td, 2H, *J* = 6.9, 5.7 Hz), 3.62 (s, 3H), 3.37 (dd, 1H, *J* = 14, 7.6 Hz), 3.30 (dd, 1H, *J* = 14, 6.2 Hz), 2.97 (t, 2H, *J* = 6.9 Hz), 2.15 (dd, 1H, *J* = 13, 6.9 Hz), 1.75 (br s, 3H), 1.62 (d, 3H, *J* = 1.2 Hz), 1.55 (d, 3H, *J* = 1.2 Hz), 0.83 (s, 9H), −0.03 (s, 6H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.8, 159.1, 155.8, 138.8, 136.6, 132.7, 131.0, 129.5, 128.9, 128.8, 126.7, 126.4, 124.8, 121.1, 106.6, 100.8, 69.0, 57.7, 55.8, 48.8, 41.2, 39.7, 35.5, 26.01, 25.96, 25.7, 23.9, 18.3, 18.2, 17.2, −4.2, −4.8; FT-IR (film on ZnSe) 3297, 3062, 3027, 2928, 2855, 1641, 1597, 1573, 1533, 1497, 1463, 1455, 1395, 1361, 1333, 1303, 1255, 1217, 1160 $cm^{-1}$; HRMS (ESI-neg) $m/z$ calcd for $C_{35}H_{52}O_5NCl_2Si$ $[M + Cl]^-$ 664.2997, found 664.3026.

**(*E*)-5-(5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (33).** To a solution of chloride **32** (6.1 mg, 9.7 μmol) in DMF (1 mL) was added NaH (60% dispersion in mineral oil, ca. 10 mg) at 0 °C. The mixture was stirred for 25 min at 0 °C and quenched with water. The resulting mixture was extracted EtOAc (3×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 2) to give lactam **33** (5.0 mg, 8.4 μmol, 87%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.32−7.18 (m, 5H), 7.12 (s, 1H), 5.15 (br t, 1H, *J* = 6.5 Hz), 5.04 (dsept, 1H, *J* = 8.7, 1.2 Hz), 4.99 (s, 2H), 4.37 (ddd, 1H, *J* = 8.7, 7.5, 5.7 Hz), 4.23 (s, 2H), 3.86 (s, 3H), 3.85 (t, 2H, *J* = 7.2 Hz), 3.47 (s, 3H), 3.41 (dd, 1H, *J* = 14, 6.6 Hz), 3.35 (dd, 2H, *J* = 14, 6.6 Hz), 2.98 (t, 2H, *J* = 7.2 Hz), 2.14 (dd, 1H, *J* = 13, 7.5 Hz), 1.97 (dd, 1H, *J* = 13, 5.7 Hz), 1.77 (d, 3H, *J* = 1.2 Hz), 1.59 (d, 3H, *J* = 1.2 Hz), 1.53 (d, 3H *J* = 1.2 Hz), 0.81 (s, 9H), −0.05 (s, 3H), −0.06 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.4, 159.0, 150.9, 139.0, 132.6, 132.2, 130.8, 129.5, 128.9, 128.7, 126.6, 126.2, 124.9, 124.2, 100.9, 97.8, 68.9, 56.9, 56.1, 49.5, 48.9, 44.3, 35.1, 26.0, 25.9, 25.7, 23.7, 18.3, 18.2, 17.1, −4.3. −4.8; FT-IR (film on ZnSe) 3062, 3027, 2955, 2928, 2856, 1691, 1620, 1597, 1497, 1469, 1434, 1414, 1375, 1360, 1318, 1249, 1218, 1156 $cm^{-1}$; HRMS (ESI-pos) $m/z$ calcd for $C_{35}H_{52}O_5NSi$ $[M + H]^+$ 594.3609, found 594.3597.

**(*E*)-5-(5-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (34).** To a solution of TBS ether **33** (5.0 mg, 8.4 μmol) in THF (1 mL) was added TBAF (1 M solution in THF, 168 μL, 168 μmol). The mixture was stirred for 20 h at 40 °C and directly subjected to flash chromatography (*n*-hexane/EtOAc = 1) to give alcohol **34** (3.0 mg, 6.3 μmol, 74%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.32−7.19 (m, 5H), 7.13 (s, 1H), 5.25 (br t, 1H, *J* = 6.9 Hz), 5.11 (dsept, 1H, *J* = 8.4, 1.5 Hz), 5.01 (d, 1H, *J* = 6.6 Hz), 4.99 (d, 1H, *J* = 6.6 Hz), 4.41 (td, 1H, *J* = 8.4, 4.8 Hz), 4.23 (s, 2H), 3.87 (s, 3H), 3.85 (t, 2H, *J* = 7.6 Hz), 3.47 (s, 3H), 3.43 (d, 2H, *J* = 6.9 Hz), 2.98 (t, 2H, *J* = 7.6 Hz), 2.14 (dd, 1H, *J* = 14, 4.8 Hz), 2.07 (dd, 1H, *J* = 14, 8.4 Hz), 1.81 (br s, 3H), 1.68 (d, 3H, *J* = 1.5 Hz), 1.67 (d, 3H, *J* = 1.5 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 168.3, 159.0, 150.8, 139.0, 135.0, 132.9, 132.0, 128.88, 128.86, 128.7, 127.5, 126.6, 125.6, 124.2, 101.0, 97.8, 65.8, 57.0, 56.2, 49.5, 48.3, 44.3, 35.1, 25.9, 23.7, 18.3, 16.4; FT-IR (film on ZnSe) 3398, 3062, 3025, 2928, 2855, 1678, 1620, 1598, 1497, 1434, 1417, 1375, 1362, 1318, 1249, 1218 $cm^{-1}$; HRMS (ESI-pos) $m/z$ calcd for $C_{29}H_{38}O_5N$ $[M + H]^+$ 480.2744, found 480.2735.

**(*E*)-5-(3,7-Dimethyl-5-oxoocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (35).** To a solution of alcohol **34** (19.8 mg, 41.3 μmol) in $CH_2Cl_2$ (1 mL) were added $PhI(OAc)_2$ (66.5 mg, 207 μmol) and 2-azaadamantane *N*-oxyl (0.4 mg, 2 μmol). After the mixture was stirred for 7 h at room temperature, $PhI(OAc)_2$ (26.6 mg, 82.6 μmol) and 2-azaadamantane *N*-oxyl (1.0 mg, 6.6 μmol) were added. The resulting mixture was stirred for 30 min and diluted with $CH_2Cl_2$ (2 mL). The solution was quenched successively with saturated aqueous $NaHCO_3$ solution and saturated aqueous $Na_2S_2O_3$ solution. The resulting mixture was stirred for 30 min and extracted with EtOAc (3×). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 1) to give ketone **35** (16.6 mg, 34.8 μmol, 84%) as a pale yellow oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.32−7.18 (m, 5H), 7.13 (s, 1H), 6.06 (br s, 1H), 5.26 (br t, 1H, *J* = 6.5 Hz), 5.00 (s, 2H), 4.24 (s, 2H), 3.87 (s, 3H), 3.85 (t, 2H, *J* = 7.2 Hz), 3.47 (s, 3H), 3.46 (d, 2H, *J* = 6.5 Hz), 3.01 (s, 2H), 2.98 (t, 2H, *J* = 7.2 Hz), 2.12 (d, 3H, *J* = 0.9 Hz), 1.83 (d, 3H, *J* = 1.5 Hz), 1.78 (br s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 199.4, 168.4, 159.1, 155.7, 150.9, 139.0, 132.8, 130.1, 128.9, 128.7, 127.1, 126.6, 125.6, 124.3, 122.9, 101.0, 97.9, 56.9, 56.2, 55.5, 49.6, 44.3, 35.1, 27.8, 23.8, 20.8, 16.6; FT-IR (film on ZnSe) 3062, 3026, 2932, 2858, 1687, 1683, 1619, 1469, 1455, 1435, 1415, 1382, 1358, 1318, 1247, 1220, 1189, 1154, 1115 $cm^{-1}$; HRMS (FAB) $m/z$ calcd for $C_{29}H_{36}NO_5$ $[M + H]^+$ 478.2593, found 478.2551.

**(*E*)-4-Hydroxy-5-(5-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)-6-methoxy-2-phenethylisoindolin-1-one (Hericenone B, 36).** To a solution of ketone **35** (13.6 mg, 28.5 μmol) in $CH_2Cl_2$ (2 mL) were added amylene (90.8 μL, 0.86 mmol) and $Me_2BBr$ (0.5 M solution in $CH_2Cl_2$, 85 μL, 43 μmol) at −78 °C. After the mixture was stirred for 1 h at −78 °C, additional $Me_2BBr$ (0.5 M solution in $CH_2Cl_2$, 29 μL, 15 μmol) was added. After it was stirred for 2 h at −78 °C, the reaction mixture was quenched with saturated aqueous $NaHCO_3$ solution. The resulting mixture was extracted with EtOAc (3×), and the combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by flash chromatography (*n*-hexane/EtOAc = 1) to give an 1.1:1 inseparable mixture of hericenone B (**36**) and its bromide-conjugated addition product at C7′ (10.3 mg). The mixture was dissolved in $CH_2Cl_2$ (1 mL) and treated with $Et_3N$ (19.8 μL, 143 μmol) for 1 h at 0 °C. The resulting solution was directly subjected to flash chromatography (*n*-hexane/EtOAc = 1) to give the product (8.3 mg). The $^1$H NMR indicated that the ratio of **36** and its bromide-conjugated addition product was 1.8:1. The mixture was again dissolved in $CD_2Cl_2$ (0.75 mL) and treated with $Et_3N$ (15.9 μL, 115


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μmol) at room temperature. The reaction was monitored by $^1$H NMR, which indicated that most of the bromide was consumed after 5 h. The solution was subjected to flash chromatography (*n*-hexane/EtOAc = 1) to give hericenone B (**36**; 7.5 mg, 17 μmol, 61%) as a colorless oil. The sample was further purified by normal-phase HPLC using *n*-hexane/EtOAc as eluent for data analysis: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.31−7.17 (m, 5H), 6.96 (s, 1H), 6.61 (br s, 1H), 6.07 (br s, 1H), 5.30 (br t, 1H, *J* = 7.2 Hz), 4.20 (s, 2H), 3.84 (s, 3H), 3.84 (t, 2H, *J* = 7.5 Hz), 3.56 (d, 2H, *J* = 7.2 Hz), 3.14 (s, 2H), 2.97 (t, 2H, *J* = 7.5 Hz), 2.16 (d, 3H, *J* = 0.9 Hz), 1.88 (d, 3H, *J* = 0.9 Hz), 1.81 (br s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 199.0, 169.0, 158.5, 157.0, 150.9, 138.9, 133.3, 132.4, 128.8, 128.7, 126.6, 126.5, 123.1, 122.2, 118.3, 97.8, 56.3, 54.7, 48.4, 44.3, 35.0, 27.9, 23.2, 21.1, 17.2; $^{13}$C NMR (75 MHz, $CDCl_3$) δ 202.1, 171.1, 160.5, 157.7, 151.3, 140.1, 132.3, 130.6, 129.8, 129.8, 128.6, 127.6, 123.8, 122.3, 121.9, 97.6, 56.3, 56.2, 49.8, 45.4, 35.6, 27.7, 23.8, 20.8, 16.6; FT-IR (film on ZnSe) 3189, 3086, 3063, 3027, 2935, 2861, 1686, 1656, 1622, 1471, 1438, 1365, 1335, 1220, 1192, 1161 cm$^{-1}$; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{32}NO_4$ $[M + H]^+$ 434.2331, found 434.2326.

**5-Methoxy-2-methyl-2-(4-methyl-2-oxopent-3-en-1-yl)-8-phenethyl-3,4,8,9-tetrahydropyrano[2,3-*e*]isoindol-7(2*H*)-one (Erinacerin A, 37).** To a solution of hericenone B (**36**; 4.0 mg, 9.2 μmol) in $ClCH_2CH_2Cl$ (1 mL) was added CSA (4.3 mg, 18 μmol). The mixture was stirred for 68 h at 60 °C and directly subjected to flash chromatography (*n*-hexane/EtOAc = 2) to give erinacerin A (**37**; 4.0 mg, 9.2 μmol, 100%) as a colorless oil: $^1$H NMR (300 MHz, $CDCl_3$) δ 7.33−7.19 (m, 5H), 6.90 (s, 1H), 6.04 (sept, 1H, *J* = 1.2 Hz), 4.17 (d, 1H, *J* = 17 Hz), 4.11 (d, 1H, *J* = 17 Hz), 3.87 (s, 3H), 3.84 (t, 1H, *J* = 7.5 Hz), 3.83 (t, 1H, *J* = 7.5 Hz), 2.98 (t, 2H, *J* = 7.5 Hz), 2.76 (d, 1H, *J* = 14 Hz), 2.69 (t, 1H, *J* = 6.9 Hz), 2.68 (t, 1H, *J* = 6.9 Hz), 2.63 (d, 1H, *J* = 14 Hz), 2.14 (d, 3H, *J* = 1.2 Hz), 2.02 (dt, 1H, *J* = 14, 6.6 Hz), 1.90 (dt, 1H, *J* = 14, 6.9 Hz), 1.84 (d, 3H, *J* = 1.2 Hz), 1.40 (s, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 198.2, 169.0, 158.6, 155.8, 148.7, 138.9, 132.4, 128.8, 128.7, 126.6, 125.2, 122.0, 113.6, 96.3, 76.0, 56.0, 52.4, 48.1, 44.3, 35.0, 30.7, 28.0, 24.9, 20.9, 17.5; FT-IR (film on ZnSe) 3062, 3026, 2931, 2855, 1688, 1613, 1473, 1436, 1410, 1366, 1319, 1254, 1194, 1155, 1109, 1093 cm$^{-1}$; HRMS (FAB) *m*/*z* calcd for $C_{27}H_{32}NO_4$ $[M + H]^+$ 434.2331, found 434.2330.

## ■ ASSOCIATED CONTENT

### Supporting Information

Figures and tables giving $^1$H and $^{13}$C NMR spectra for all new synthetic compounds, as well as comparisons of the NMR data for synthetic compounds and natural products. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION

### Corresponding Author

*E-mail for S.K.: shoji.kobayashi@oit.ac.jp.

### Notes

The authors declare no competing financial interest.

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