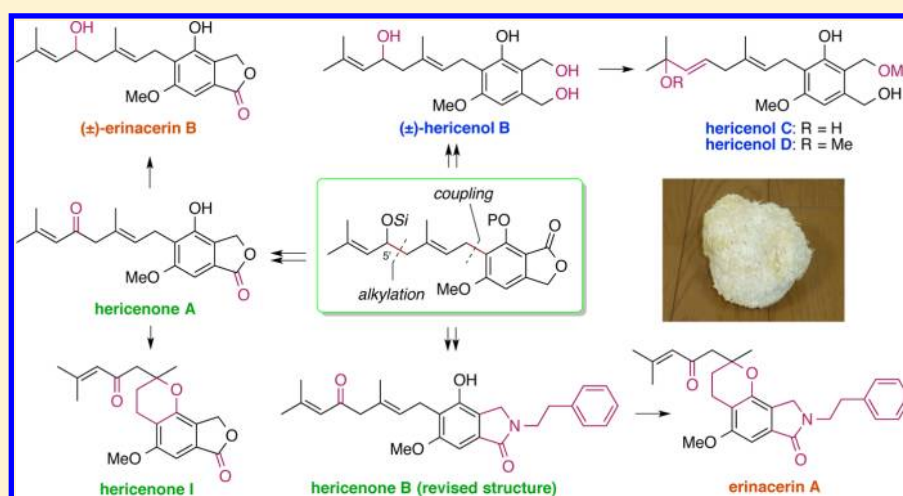


Divergent Synthesis of Bioactive Resorcinols Isolated from the Fruiting Bodies of *Hericium erinaceum*: Total Syntheses of Hericenones A, B, and I, Hericenols B–D, and Erinacerins A and B

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Supporting Information



ABSTRACT: Total syntheses of 5'- and 7'-oxidized geranyl resorcyates 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

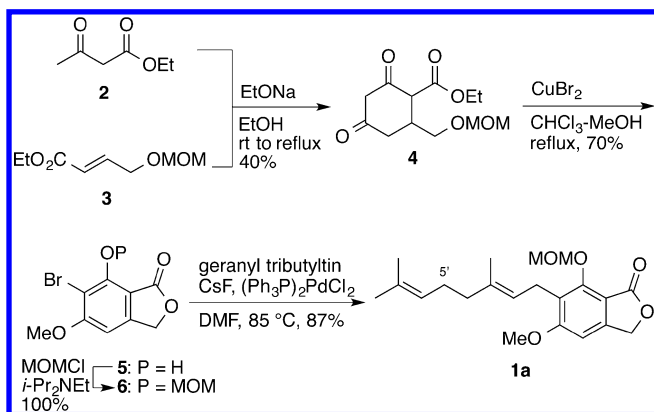
An edible mushroom, *Hericium erinaceum*, called Yamabushitake in Japanese, has long been used in traditional Chinese medicine and is now widely available as a health food supplement, especially in East Asia and Europe. Various forms of *H. erinaceum*, including perishables, lyophilized solids, powders, 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 hericenols,⁵ hericenones,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 resorcyate family are considered to be key players that define the function of *H. erinaceum*. However, in spite of the discovery of these intriguing

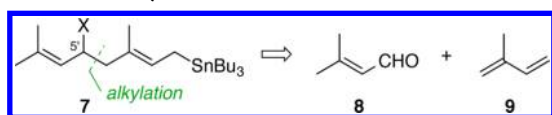
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Scheme 1. Previous Synthesis of the Geranyl Phthalide 1a



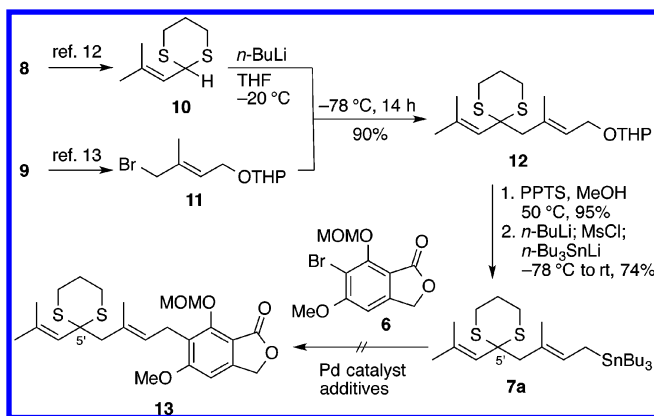
Scheme 2. Retrosynthesis of the Side Chain



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 $-20\text{ }^{\circ}\text{C}$ 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

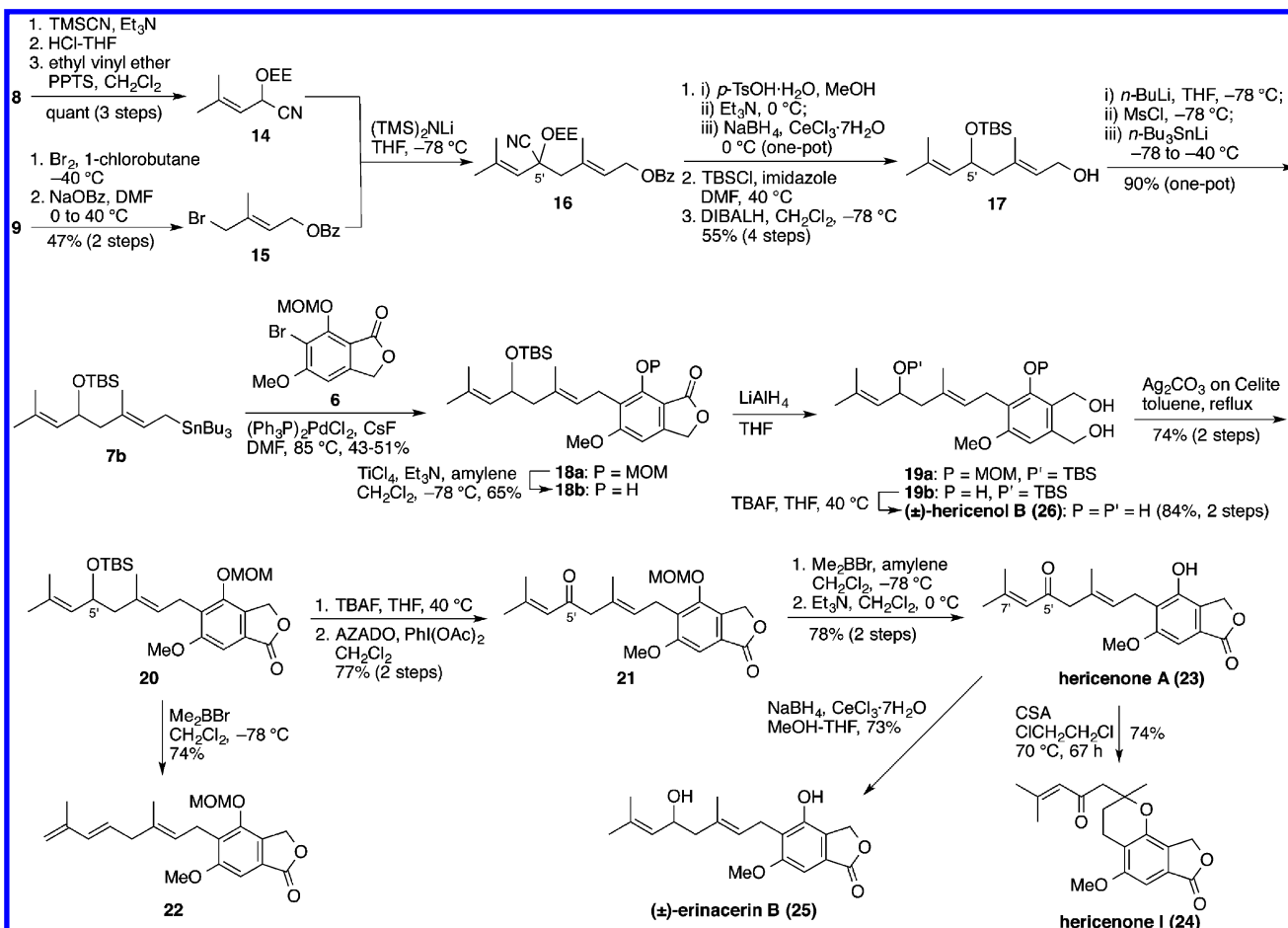


keep the reaction temperature at $-78\text{ }^{\circ}\text{C}$ during alkylation to obtain a high yield. After deprotection, the resulting alcohol was converted into allylstannane **7a** by a one-pot method.¹⁴ The Stille coupling¹⁵ between **7a** and the phthalide core **6**⁹ was problematic, however. 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 precursor¹⁸ 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 alkylation¹⁸ was achieved by adding $\text{LiN}(\text{TMS})_2$ to a mixture of **14** (1 equiv) and **15** (1 equiv). Remarkably, alkylation was complete within 30 min at $-78\text{ }^{\circ}\text{C}$, 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 $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (Luche 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 stannylation¹⁴ 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 resorcylics 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 $-78\text{ }^{\circ}\text{C}$,^{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 $\text{PhI}(\text{OAc})_2/2\text{-azaadamantane N-oxyl}$ (AZADO)²³ to provide the corresponding ketone **21**. As a

Scheme 4. Total Syntheses of Hericenones A and I, (\pm)-Hericenol B, and (\pm)-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 Me₂BBr in the presence of excess amylene²⁷ gave a mixture of two products, including hericenone A (**23**) and its bromide-conjugated addition product at C7'. The mixture was subsequently treated with Et₃N to induce β -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

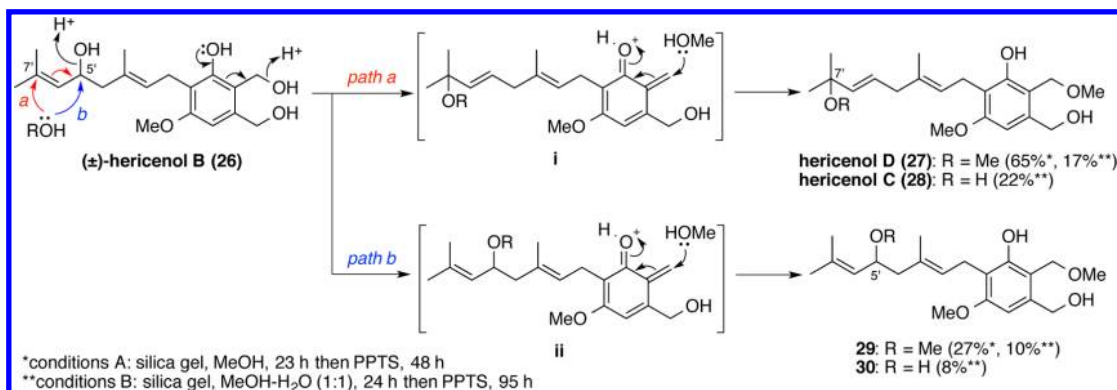
We next turned our attention to the synthesis of hericenone I,^{3c} as it can be presumed that it was biosynthetically generated from hericenone A via acid-catalyzed cyclization. Thus, synthetic hericenone A (**23**) was treated with a couple of acids to induce cyclization. While **23** was inactive to PPTS in CH₂Cl₂, 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 2005⁷ 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 Luche conditions. Reduction proceeded within 1 min, and (\pm)-erinacerin B (**25**) was isolated in 73% yield. While the NMR data for natural erinacerin B were measured in CDCl₃,⁷ our synthetic sample was only slightly soluble in CDCl₃, which did not permit comparison of the ¹³C NMR spectra in the same solvent. Furthermore, our research proved that **25** gradually degraded in CDCl₃. 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 (\pm)-erinacerin B (**25**) became apparent, we decided to synthesize (\pm)-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 TiCl₄ and Et₃N 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 LiAlH₄, and the TBS group of the resulting triol **19b** was removed by TBAF to provide (\pm)-hericenol B (**26**) in 84% isolated yield over two steps. The spectral data, except for the optical rotation values,

Scheme 5. Total Syntheses of Hericenols C and D

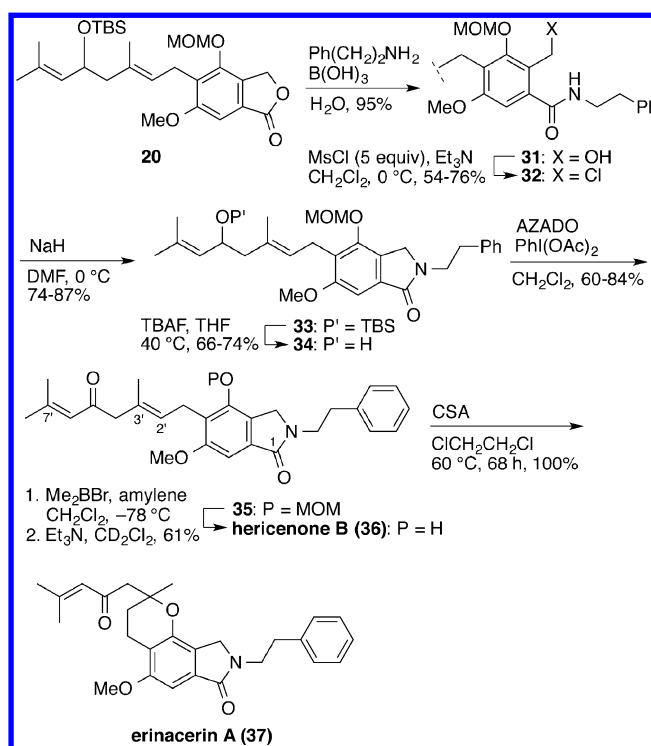


for the synthetic compound (26) and the natural product⁶ were all identical.

We next focused on the synthesis of hercenols C and D,⁶ since it can be supposed that they are derived biosynthetically from hercenol 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 (\pm) -hercenol B (26) was treated with PPTS in MeOH after silica gel treatment²⁸ (Scheme 5). As expected, hercenol 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/H₂O (1/1), a small amount of hercenol C (28) was formed (22% yield) along with hercenol 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 hercenols.⁶ The samples were eluted with a linear gradient of H₂O/MeOH.⁶ Given these observations, it is possible that hercenols C and D might be artifacts resulting from degradation of hercenol 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 hercenone B and erinacerin A. Recently, we achieved the first total synthesis of hericerin, a 5'-deoxy analogue of hercenone 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 hercenone B are highly correlated with those of hericerin, we were convinced that natural hercenone 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 Me₃Al-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 Hercenone 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 oxidation²³ to provide ketone 35. As established earlier, final deprotection of the phenolic hydroxyl group was undertaken with Me₂BBr in the presence of excess amylene to suppress undesired addition of HBr to the C2'-C3' double bond. This careful procedure successfully furnished hercenone B (36) after treatment with Et₃N in 61% yield. The ¹H and ¹³C NMR data for the synthetic compound 36 were in accordance with those reported in the literature,^{2a} which unambiguously revised the structure of hercenone B. Very recently, Lee and co-workers isolated the same product from the fruiting bodies of *H. erinaceum* and named it isohercenone.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.

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 resorcyate library using the suitably protected C5'-oxygen incorporated geranyl phthalide 18a as a common intermediate. This intermediate (18a) was efficiently prepared by a CuBr₂-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 resorcyates. 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, CH₂Cl₂, THF, and MeOH. Triethylamine and 1,2-dichloroethane were distilled from CaH₂. 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*-anisaldehyde/AcOH/H₂SO₄/EtOH, 12MoO₃·H₃PO₄/EtOH, or (NH₄)₆Mo₇O₂₄·4H₂O/H₂SO₄. 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 (¹H, 300 MHz; ¹³C, 75 MHz) or a 400 MHz (¹H, 400 MHz; ¹³C, 100 MHz) spectrometer and referenced to the solvent peak at 7.26 ppm (¹H) and 77.16 ppm (¹³C) for CDCl₃. 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-2H-pyran (12). To a solution of dithiane 10¹² (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 11¹³ (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 Na₂SO₄, 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: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₈H₃₁O₂S₂ [*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. Et₃N (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: ¹H NMR (400 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₁₃H₂₃OS₂ [*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*-Bu₃SnLi in THF (10 mL) was added dropwise (*n*-Bu₃SnLi was prepared as follows: to a solution of *i*-Pr₂NH (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*-Bu₃SnH (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 H₂O. The resulting mixture was extracted with EtOAc (3×), and the combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated. The residue was purified by flash chromatography (hexane/Et₃N = 50 → hexane/EtOAc/Et₃N = 100/1/2) to give allylstannane 7a (649 mg, 1.22 mmol, 74%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) 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); ¹³C NMR (75 MHz, CDCl₃) 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 C₂₅H₄₈S₂Sn: C, 56.50; H, 9.10. Found: C, 56.53; H, 8.78.

2-(1-Ethoxyethoxy)-4-methylpent-3-enitrile (14). To a solution of 3-methyl-2-butenal (8; 20.0 g, 238 mmol) in CH₂Cl₂ (119 mL) were added TMSCN (32.7 mL, 262 mmol) and Et₃N (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 MgSO₄, and concentrated to give the corresponding cyanohydrin (43.0 g) as a yellow oil. To a solution of crude cyanohydrin (43.0 g) in CH₂Cl₂ (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 Et₃N (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: ¹H NMR (400 MHz, CDCl₃) 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,

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) δ 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 $\text{C}_{10}\text{H}_{17}\text{O}_2\text{NNa}$ [$\text{M} + \text{Na}$] $^+$ 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 $\text{Na}_2\text{S}_2\text{O}_3$ 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 \times). 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 \rightarrow *n*-hexane/EtOAc = 60 \rightarrow 30 \rightarrow 10 then *n*-hexane/EtOAc = 500 \rightarrow 300 \rightarrow 100 \rightarrow 30 \rightarrow 10) to give the title compound 15 (18.5 g, 68.9 mmol, 47% for two steps) as a colorless oil: ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{12}\text{H}_{14}\text{BrO}_2$ [$\text{M} + \text{H}$] $^+$ 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 α -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) $_2\text{NLi}$ (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 \times). 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 \rightarrow 10): ^1H NMR (300 MHz, CDCl_3 , 2/1 diastereomeric mixture) δ 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) δ 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 $\text{C}_{22}\text{H}_{30}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$ 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 $\text{TsOH}\cdot\text{H}_2\text{O}$ (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 $\text{CeCl}_3\cdot 7\text{H}_2\text{O}$ (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 \times). 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): ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{17}\text{H}_{23}\text{O}_3$ [$\text{M} + \text{H}$] $^+$ 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 \times), 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): ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{23}\text{H}_{36}\text{O}_3\text{NaSi}$ [$\text{M} + \text{Na}$] $^+$ 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 \times). 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 \rightarrow *n*-hexane/EtOAc = 50 \rightarrow 20 \rightarrow 10 \rightarrow 5 then *n*-hexane \rightarrow *n*-hexane/EtOAc = 100 \rightarrow 50 \rightarrow 30 \rightarrow 20 \rightarrow 10 \rightarrow 5) to give allylic alcohol 17 (10.8 g, 37.8 mmol, 55% for four steps) as a pale yellow oil: ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{16}\text{H}_{32}\text{O}_2\text{NaSi}$ [$\text{M} + \text{Na}$] $^+$ 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 $_3\text{SnLi}$ in THF was added (*n*-Bu $_3\text{SnLi}$ was prepared as follows: to a solution of *i*-Pr $_2\text{NH}$ (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 $_3\text{SnH}$ (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

–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 MgSO₄, and concentrated. The residue was purified by repeated open chromatography (hexane/Et₃N = 100) to give allylstannane **7b** (6.92 g, 12.4 mmol, 90%) as a colorless oil: ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₂₈H₅₈ONaSiSn [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(3H)-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), (Ph₃P)₂PdCl₂ (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 MgSO₄, 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; ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₂₇H₄₂O₆NaSi [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(3H)-one (20). To a solution of lactone **18a** (399 mg, 0.608 mmol) in THF (6.1 mL) was added LiAlH₄ (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 MgSO₄, 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 Ag₂CO₃ 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**: ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₂₆H₃₉O₆Si [M – CH₃]⁺ 475.2516, found 475.2509.

(E)-5-(3,7-Dimethyl-5-oxoocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)isobenzofuran-1(3H)-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: ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₂₁H₂₈O₆Cl [M + Cl][–] 411.1580, found 411.1594. To a solution of the above alcohol (49.0 mg) in CH₂Cl₂ (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 CH₂Cl₂ (2 mL) and quenched successively with saturated aqueous NaHCO₃ solution and saturated aqueous Na₂S₂O₃ 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 MgSO₄, 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: ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₂₁H₂₇O₆ [M + H]⁺ 375.1802, found 375.1794.

(E)-5-(3,7-Dimethyl-5-oxoocta-2,6-dien-1-yl)-4-hydroxy-6-methoxyisobenzofuran-1(3H)-one (Hericenone A, 23). To a solution of ketone **21** (18.6 mg, 49.7 μmol) in CH₂Cl₂ (1 mL) were added successively amylene (149 μL, 1.40 mmol) and Me₃BBR (0.5 M solution in CH₂Cl₂, 149 μL, 74.5 μmol) at –78 °C. After 1 h at –78 °C, the reaction was quenched with saturated aqueous NaHCO₃ solution. The resulting mixture was extracted with EtOAc (3×), and the combined organic layer was washed with brine, dried over anhydrous MgSO₄, and concentrated. The residue (20.4 mg) was dissolved in CH₂Cl₂ (1 mL) and treated with Et₃N (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; ¹H NMR (300 MHz, CDCl₃) δ 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); ¹³C NMR (75 MHz, CDCl₃) δ 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 C₁₉H₂₃O₅ [M + H]⁺ 331.1545, found 331.1551.

5-Methoxy-2-methyl-2-(4-methyl-2-oxopent-3-en-1-yl)-3,4-dihydro-2H-furo[3,4-*h*]chromen-7(9H)-one (Hericenone I, 24). To a solution of hericenone A (**23**; 7.4 mg, 22 μmol) in ClCH₂CH₂Cl (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: ¹H NMR (300 MHz, CDCl₃) δ 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,

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) δ 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 $\text{C}_{19}\text{H}_{23}\text{O}_5$ $[\text{M} + \text{H}]^+$ 331.1545, found 331.1551.

(E)-4-Hydroxy-5-(5-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl)-6-methoxyisobenzofuran-1(3H)-one ((\pm)-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 $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$ (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 \rightarrow 1) to give (\pm)-erinacerin B (25; 9.4 mg, 0.0283 mmol, 73%) as a colorless solid: mp 134–135 $^\circ\text{C}$; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 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, $\text{DMSO}-d_6$) δ 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 $\text{C}_{19}\text{H}_{23}\text{O}_5$ $[\text{M} - \text{H}]^-$ 331.1551, found 331.1561.

(E)-6-(5-(tert-Butyldimethylsilyloxy)-3,7-dimethylocta-2,6-dien-1-yl)-7-hydroxy-5-methoxyisobenzofuran-1(3H)-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 $^\circ\text{C}$. After it was stirred for 6 min at -78 $^\circ\text{C}$, the reaction mixture was quenched with saturated aqueous NaHCO_3 solution. The resulting mixture was extracted with EtOAc (2 \times), 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: ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{25}\text{H}_{37}\text{O}_5\text{Si}$ $[\text{M} - \text{H}]^-$ 445.2416, found 445.2431.

(E)-3-Hydroxy-4-(5-hydroxy-3,7-dimethylocta-2,6-dien-1-yl)-5-methoxy-1,2-phenylenedimethanol (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 $^\circ\text{C}$. 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 $^\circ\text{C}$. The resulting mixture was extracted with Et_2O (3 \times). 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 $^\circ\text{C}$ and concentrated to ca. 1 mL. The solution was directly subjected to flash chromatography (n -hexane/EtOAc = 1 \rightarrow EtOAc \rightarrow EtOAc/MeCN = 5) to give (\pm)-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 (\pm)-hericenol B (26): ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{19}\text{H}_{27}\text{O}_5$ $[\text{M} - \text{H}]^-$ 335.1864, found 335.1873.

3-(Hydroxymethyl)-5-methoxy-6-((2E,5E)-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 (\pm)-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; ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{21}\text{H}_{31}\text{O}_5$ $[\text{M} - \text{H}]^-$ 363.2177, found 363.2193. Data for 29: colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{21}\text{H}_{33}\text{O}_5\text{Cl}$ $[\text{M} + \text{Cl}]^-$ 399.1944, found 399.1955.

2-((2E,5E)-7-Hydroxy-3,7-dimethylocta-2,5-dien-1-yl)-5-(hydroxymethyl)-3-methoxy-6-(methoxymethyl)phenol (Hericenol C, 28). To a solution of (\pm)-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 \rightarrow 1 \rightarrow 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; ^1H NMR (300 MHz, CDCl_3) δ 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) δ 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 $\text{C}_{20}\text{H}_{29}\text{O}_5$ $[\text{M} - \text{H}]^-$ 349.2020, found 349.2035. Data for 30: colorless oil; ^1H NMR (300 MHz, CDCl_3) δ 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,

2857, 1618, 1585, 1508, 1464, 1448, 1426, 1380, 1319, 1290, 1219, 1190, 1167, 1116 cm^{-1} . HRMS (ESI-neg) m/z calcd for $\text{C}_{20}\text{H}_{29}\text{O}_5$ [$\text{M} - \text{H}$] $^-$ 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), $\text{B}(\text{OH})_3$ (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: ^1H 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 $\text{C}_{35}\text{H}_{53}\text{O}_6\text{NClSi}$ [$\text{M} + \text{Cl}$] $^-$ 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 $^\circ\text{C}$. The mixture was stirred for 50 min at 0 $^\circ\text{C}$ and quenched with saturated aqueous NaHCO_3 solution. The resulting mixture was extracted with EtOAc (3 \times), 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: ^1H 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 $\text{C}_{35}\text{H}_{52}\text{O}_5\text{NCl}_2\text{Si}$ [$\text{M} + \text{Cl}$] $^-$ 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 $^\circ\text{C}$. The mixture was stirred for 25 min at 0 $^\circ\text{C}$ and quenched with water. The resulting mixture was extracted EtOAc (3 \times), 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: ^1H 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 $\text{C}_{35}\text{H}_{52}\text{O}_5\text{NSi}$ [$\text{M} + \text{H}$] $^+$ 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 $^\circ\text{C}$ 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: ^1H 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 $\text{C}_{29}\text{H}_{38}\text{O}_5\text{N}$ [$\text{M} + \text{H}$] $^+$ 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 $\text{PhI}(\text{OAc})_2$ (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, $\text{PhI}(\text{OAc})_2$ (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 $\text{Na}_2\text{S}_2\text{O}_3$ solution. The resulting mixture was stirred for 30 min and extracted with EtOAc (3 \times). 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: ^1H 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 $\text{C}_{29}\text{H}_{36}\text{NO}_5$ [$\text{M} + \text{H}$] $^+$ 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 $^\circ\text{C}$. After the mixture was stirred for 1 h at –78 $^\circ\text{C}$, 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 $^\circ\text{C}$, the reaction mixture was quenched with saturated aqueous NaHCO_3 solution. The resulting mixture was extracted with EtOAc (3 \times), 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 $^\circ\text{C}$. The resulting solution was directly subjected to flash chromatography (n -hexane/EtOAc = 1) to give the product (8.3 mg). The ^1H 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

μmol) at room temperature. The reaction was monitored by ^1H 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: ^1H 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 $\text{C}_{27}\text{H}_{32}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 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 $\text{ClCH}_2\text{CH}_2\text{Cl}$ (1 mL) was added CSA (4.3 mg, 18 μmol). The mixture was stirred for 68 h at 60 $^\circ\text{C}$ 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: ^1H 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 $\text{C}_{27}\text{H}_{32}\text{NO}_4$ $[\text{M} + \text{H}]^+$ 434.2331, found 434.2330.

■ ASSOCIATED CONTENT

■ Supporting Information

Figures and tables giving ^1H 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>.

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Notes

The authors declare no competing financial interest.

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NBS in AcOH at 100 °C for 1 h. However, a non-negligible amount of the regioisomer could not be separated from **15** by silica gel chromatography. Therefore, we resorted to the two-step method shown in Scheme 4.

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(28) To explore the convertibility of hericenol B to hericenol D upon exposure to silica gel, synthetic hericenol B (**26**) was first treated with silica gel in MeOH. TLC analysis indicated the appearance of hericenol D (**27**) after the mixture was stirred for 22 h at ambient temperature. However, the change was subtle and most of the hericenol B remained (as judged from TLC). Therefore, PPTS was subsequently added to enforce conversion.

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