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Total Synthesis of Isohericerin, Isohericenone, and Erinacerin A: Development of a Copper-Catalyzed Methylboronation of Terminal Alkynes

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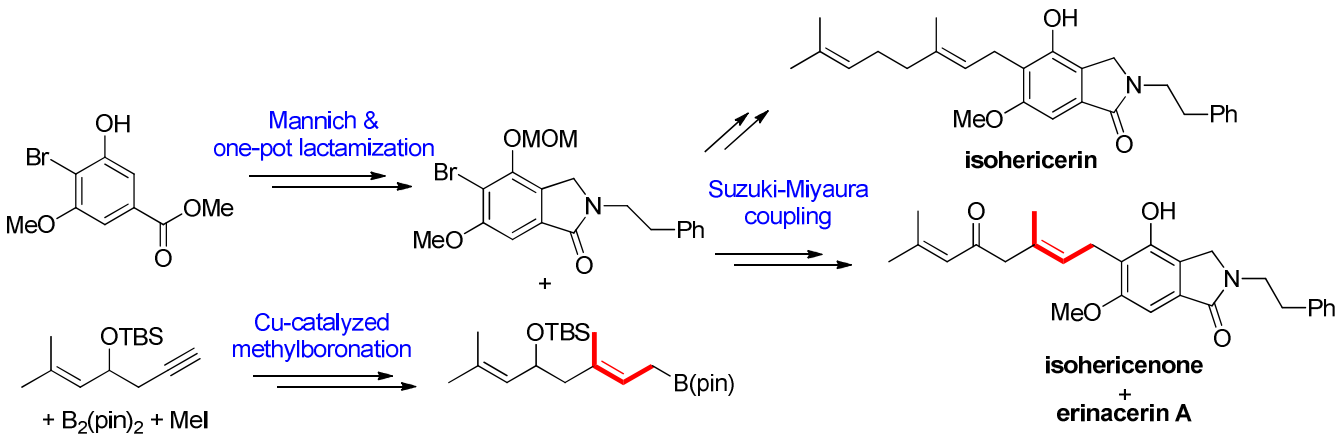


ABSTRACT:

Efficient and concise approaches for the synthesis of three bioactive natural products, isohericerin, isohericenone, and erinacerin A, are described in this paper. The key reactions employed include a Mannich reaction with commercially available hydroxybenzoate and subsequent one-pot lactamization to afford the common precursor isoindolinone in 3 steps and a Suzuki-Miyaura coupling reaction to connect geranyl side chains to the isoindolinone core. In addition, the mild and efficient synthesis of the C5'-oxidized geranyl side unit of isohericenone is enabled by developing a highly regioselective and efficient method for the Cu-catalyzed methylboronation of functionalized terminal alkynes.

INTRODUCTION

The edible mushroom *Hericium erinaceum* has been widely used in traditional Chinese medicine for the treatment of dyspepsia, gastric ulcer and enervation and has been reported to have various intriguing biological functions, including antioxidant, antihypertensive, anti-diabetic, antitumor, antibacterial, and plant growth regulation functions.[1] The biological effects of the diverse chemical components, including geranyl-containing resorcylates, sterols, and polysaccharides, isolated from the fruiting bodies of this mushroom have been examined to identify compounds of interest for medicinal chemistry. Recently, Lee and coworkers isolated several resorcinol compounds from *H. erinaceum* and evaluated their cytotoxic activities against various human cancer cell lines, such as A549, SKOV-3, SK-MEL-2 and HCT-15.[2] Among the isolated metabolites, isohericerin (**1**),[1g,3] isohericenone (**2**)[1h,4] and erinacerin A (**3**),[5] which consist of an isoindolinone framework bearing a geranyl side chain (Figure 1), exhibited significant inhibitory activity (i.e., IC_{50} values in the range of 1.9-7.7 μM) against the proliferation of SK-MEL-2 cells. Thus, these natural products are potential targets for anti-cancer drug discovery. To evaluate their biological activities in more detail, efficient and straightforward synthetic routes must be developed.

Isohericerin (**1**) was first synthesized by the Kobayashi group using tandem $CuBr_2$-mediated aromatization for the construction of the resorcinol aromatic unit and subsequent Stille coupling between the geranyl side chain and the isoindolinone moiety.[6] This approach required 12 synthetic steps and provided low isohericerin yields (~4%). Miranda and coworkers used a five-step isohericerin synthesis method utilizing Claisen rearrangement of the geranyl group and Pd-catalyzed carbonylative lactamization as key steps, which resulted in an isohericerin yield of 34%.[7] The use of toxic CO gas, however, is a problem in this synthesis method. By contrast, the only synthetic route for obtaining isohericenone (**2**) was reported by Kobayashi and coworkers.[4a] In their synthesis route, synthetic strategies similar to those developed for the synthesis of isohericerin[6] were used to form the main geranylated isoindolinone scaffold. However, because of the presence of allylic carbons, the oxygen functionality at the C5' position on the geranyl side chain presented a synthetic challenge. The synthesis of the C5'-oxidized geranyl unit required 10 steps, including alkylation of a cyanohydrin ether intermediate, which was prepared from the addition of cyanide to an aldehyde, and appropriate manipulation of protecting groups. Thus, the total isohericenone synthesis route consisted of a lengthy 21-step procedure. To address this issue, we developed a mild and efficient method for converting functionalized terminal alkynes into *cis*-branched methyl alkenyl boronates, which are potentially direct precursors of the *cis*-branched methyl alkenes composing the terpenoid units found in various biologically active molecules and natural products.

Cu-catalyzed alkylboronation of alkynes with a diboron and an alkyl halide has received attention as an effective method for synthesizing multisubstituted alkenyl boronates. Tortosa and coworkers described regioselective- and stereoselective synthesis of methyl alkenyl boronates using a three-component coupling reaction of alkynes, bis(pinacolato)diboron ($B_2(pin)_2$) and methyl iodide in the presence of a Cu catalyst and phosphine ligand.[8] However, this method is limited in substrate scope to aryl-substituted alkynes and 1,3-enynes; reactions with alkyl-substituted terminal alkynes were not efficient, and only alkynes bearing a propargylic ether group provided moderate methyl alkenyl

boronate yields. In addition, the need for relatively high catalyst loading (10 mol % of CuCl) and long reaction times remained unsolved. Subsequently, Ong, Cazin, and Kanai reported an *N*-heterocyclic carbene (NHC)-promoted Cu-catalyzed alkylboronation of internal alkynes with a diboron for efficiently and selectively synthesizing tetrasubstituted vinyl boronates.[9]

Herein, we described the highly regioselective- and stereoselective Cu-catalyzed methylboronation of alkyl-substituted terminal alkynes for the efficient synthesis of *cis*-branched methyl alkenyl boronates. Various readily available terminal alkynes, including those with ether, chloride, and ester groups, are selectively borylated in the presence of a copper catalyst and $B_2(pin)_2$ in situ to form a C-B bond and a C-Cu bond, which subsequently reacts with methyl iodide, affording good methyl alkenyl boronate yields. This methodology was successfully applied to construct the functionalized geranyl unit on isohericenone, enabling the efficient and concise total synthesis of isohericenone in 11 overall steps. In addition, we demonstrated the straightforward synthesis of isohericerin using a Mannich reaction to install the common isoindolinone core structure and a Suzuki-Miyaura coupling reaction between the isoindolinone unit and geranyl boronate. This synthesis was accomplished in 5 steps and improved the overall yield to 44%.

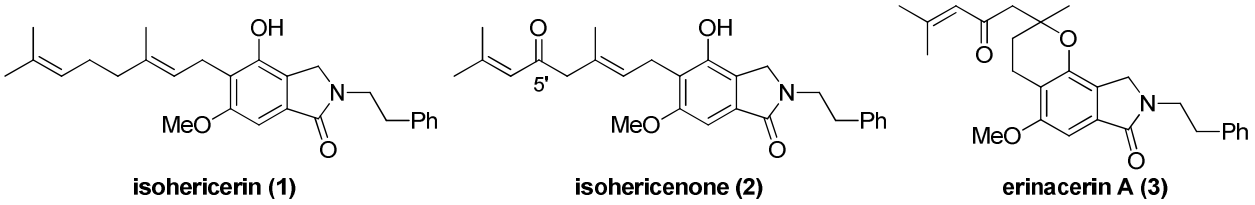


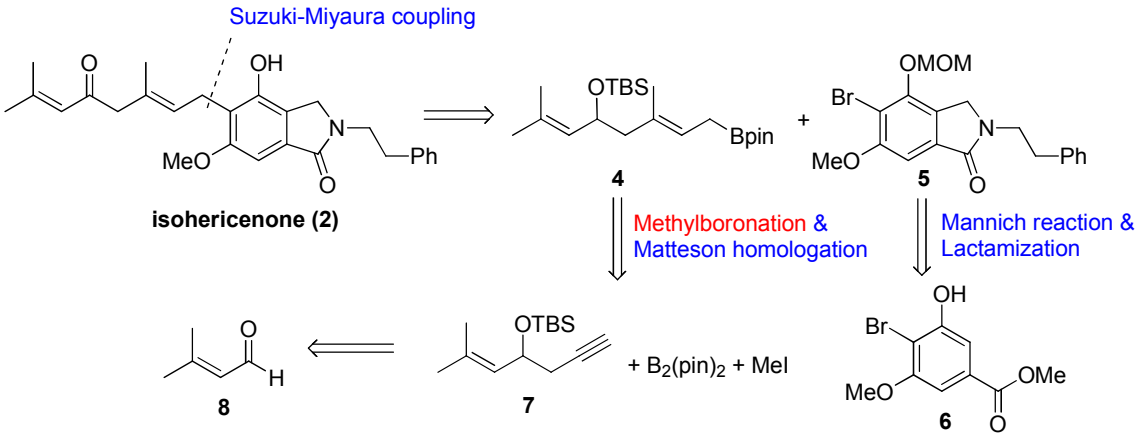
Figure 1. Structures of isohericerin (**1**), isohericenone (**2**), and erinacerin A (**3**).

RESULTS AND DISCUSSION

Our retrosynthetic analysis of **2** began with palladium-catalyzed coupling to connect the geranyl side chain **4** and isoindolinone **5** (Scheme 1). Allylic boronate **4** would be derived from alkyne **7** *via* the Cu-catalyzed methylboronation of **7** with diboron and methyliodide to form a methyl alkenyl boronate, followed by a Matteson homologation. Compound **7** would be obtained *via* the 1,2-addition of

propargylzinc bromide to commercially available aldehyde **8**. The aromatic scaffold **5** would be accessed using a Mannich reaction with benzoate **6** and a sequential one-step lactamization. The common aromatic unit **5** would be coupled with geranyl boronate **11** (Scheme 2) to achieve the total synthesis of isohericerin (**1**).

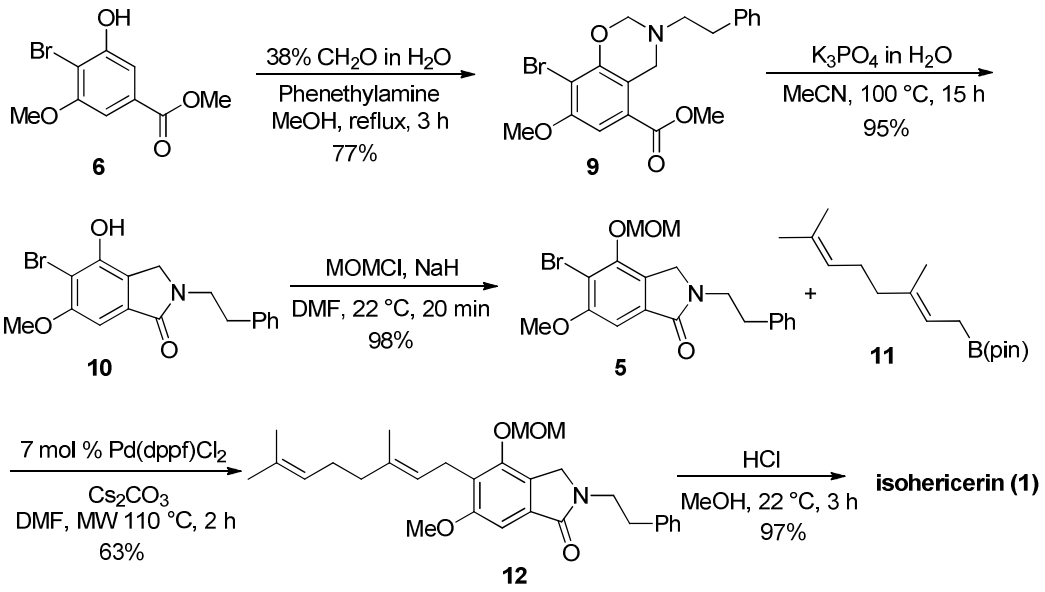
Scheme 1. Retrosynthetic analysis of isohericenone.



Scheme 2 depicts a synthetic approach to the common core isoindolinone **5** and total synthesis of isohericerin (**1**). Under modified Mannich reaction conditions, [10] commercially available hydroxybenzoate **6** was aminomethylated using phenethylamine and formaldehyde and simultaneously cyclized to afford an oxazine **9** in 77% yield. Synthesizing lactam moiety **10** from oxazine **9** is expected to require two steps; a ring opening of **9** under acidic conditions and intramolecular lactamization under basic conditions. However, upon treatment of an aqueous potassium phosphate solution when refluxing acetonitrile, oxazine **9** was transformed into the desired lactam **10** in a highly efficient single-step reaction (95% yield). Protection of the phenol group with methoxymethyl chloride then resulted in a MOM-protected **5** in 98% yield. With the core aromatic structure **5** in hand, we focused our efforts on accomplishing isohericerin synthesis by forming the carbon-carbon bond between the geranyl side chain and isoindolinone **5** using a Suzuki-Miyaura coupling reaction. Although palladium-catalyzed coupling reactions with aryl-, alkenyl-, and alkyl boron species have been intensively developed, couplings with allyl boron compounds are still challenging.[11] After screening various catalytic palladium systems,[12] we

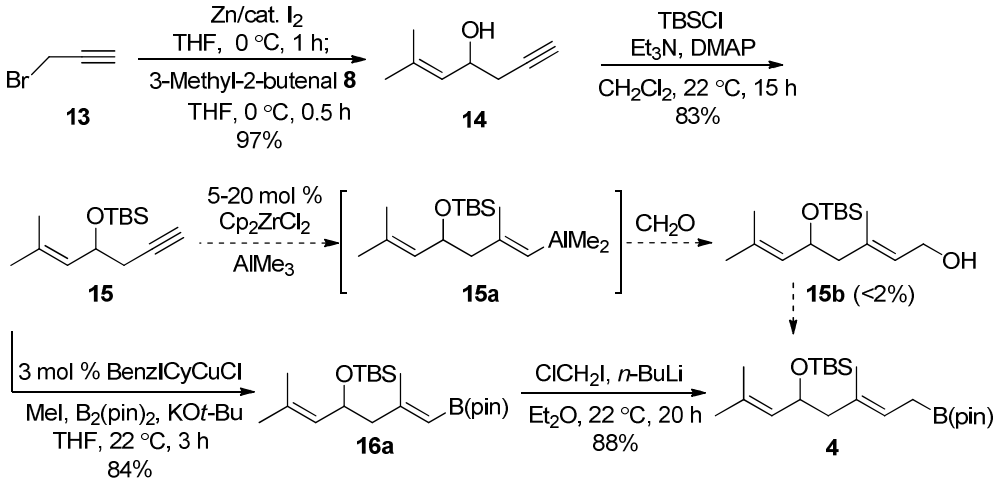
found that using $Pd(dppf)Cl_2$ as a catalyst with cesium carbonate under microwave irradiation promoted the C-C bond coupling reaction of **5** with geranyl boronate **11**.[13] The obtained product (**12**) was treated with hydrochloric acid in methanol to provide the final product (**1**) with an overall yield of 44% when using the 5 linear synthetic steps.

Scheme 2. Total synthesis of isohericerin (**1**)



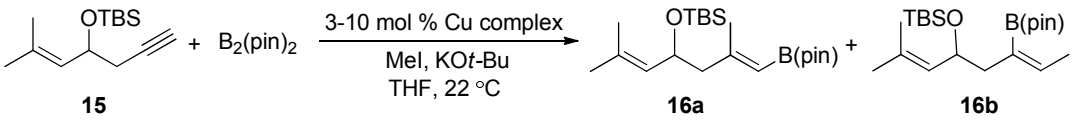
Next, we began synthesizing C5'-oxidized geranyl side chain **4**, as shown in Scheme 3. Propargylzinc bromide derived from the reaction of **13** with zinc was added to aldehyde **8** to provide allylic alcohol **14** with a yield of 97%; the product was subsequently protected with *tert*-butyldimethylsilyl chloride. To prepare functionalized geranyl boronate **4** from alkyne **15**, we initially planned to use trimethylaluminum in the zirconium-catalyzed carboalumination of alkyne **15** to generate alkenyl aluminum intermediate **15a**, which would then directly react with formaldehyde to provide allylic alcohol **15b**.[14] However, alkyne **15** bearing a TBS-protected allylic alcohol group decomposed in the presence of a catalytic amount of zirconium salt and aluminum reagent, and the desired product was not obtained (<2% of **15b**). As an alternative strategy, we investigated an efficient and mild method for preparing *cis*-methyl alkenyl boronate **16a** from the terminal alkyne using a selective copper-catalyzed methylboronation with bis(pinacolato)diboron and methyl iodide.

Scheme 3. Synthesis of geranyl boronate **4**



Under the basic conditions previously reported by the Tortosa group,[8] alkyne **15** was treated with $B_2(pin)_2$, methyl iodide and sodium *tert*-butoxide in the presence of 10 mol % of CuCl and Xantphos ligand to generate methyl alkenyl boronate **16a**. Pleasingly, as illustrated in entry 1 of Table 1, the anticipated product **16a** was provided with >98% *E*-selectivity; however, low yield (33%) and moderate regioselectivity of the boron addition (85:15 **16a**:**16b**) were observed. Thus, we examined the abilities of various NHC-copper complexes[15] to promote the efficient and regioselective addition of boron and methyl groups to the terminal alkyne (Table 1). In the presence of ^{NQ}IMesCuCl (Figure 2), which has shown good activity and regioselectivity for the methylboration of dialkyl-substituted internal alkynes,[9a] the reaction of **15** proceeded to complete conversion within 3 hours, affording the desired product (**16a**) with a yield of 86% (entry 2). When IPrCuCl was used, the catalytic reaction was not efficient or regioselective (32% yield and 67:33 **16a**:**16b**, entry 3). As shown in entries 4-7 of Table 1, the BenzICyCuCl complex is the optimum copper catalyst for the methylboronation of **15**. Although only 3 mol % of BenzICyCuCl was used, the reaction proceeded to complete conversion in 3 h with high efficiency and regioselectivity (entry 8). Therefore, under the optimal reaction conditions, the desired *cis*-methyl alkenyl boronate **16a** was synthesized with a yield of 84% after purification. Subsequently, treating alkeny boronate **16a** with chloroiodomethane and *n*-butyllithium provided allylic boronate **4** with a yield of 88%, as shown in Scheme 3.[16]

Table 1. Optimization of the Cu-catalyzed methylboronation of alkyne **15**[a]



entry	Cu complex	Cu (mol %)	base	time (h)	conv (%)[b]	**16a**:**16b**[b]	yield of **16a** (%)[b]
1	Xantphos+CuCl	10	NaO*t*-Bu	12	39	85:15	33
2	^{NQ}IMesCuCl	10	KO*t*-Bu	3	>98	86:14	86
3	IPrCuCl	10	KO*t*-Bu	3	48	67:33	32
4	SIMesCuCl	10	KO*t*-Bu	3	>98	88:12	88
5	IMesCuCl	10	KO*t*-Bu	3	>98	93:7	93
6	ICyCuCl	10	KO*t*-Bu	3	>98	92:8	92
7	BenzICyCuCl	5	KO*t*-Bu	3	>98	94:6	94
8	BenzICyCuCl	3	KO*t*-Bu	3	>98	92:8	92

[a]Reactions run at 0.12 mmol scale with respect to **15**. Conditions: 1.0 equiv. of alkyne **15**, 3.0 equiv. of MeI, 1.3 equiv. of $B_2(pin)_2$, 1.5 equiv. of base and THF (0.2 M) under N_2. [b]Determined by ^{1}H NMR spectrum analysis using 1,3,5-trimethoxybenzene as an internal standard.

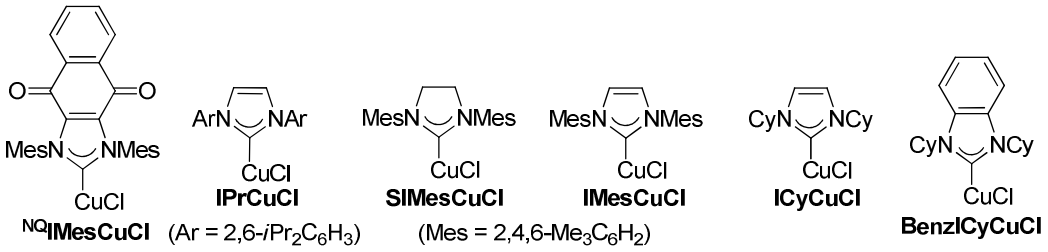
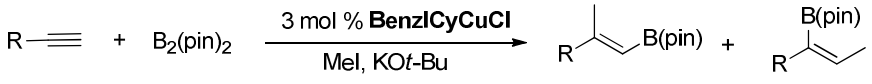


Figure 2. Various NHC-Cu complexes studied for methylboronation.

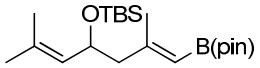
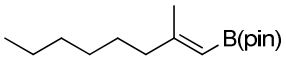
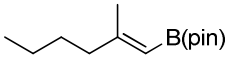
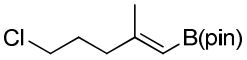
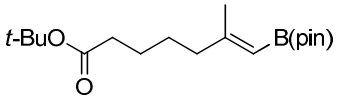
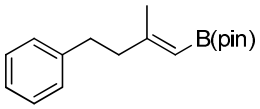
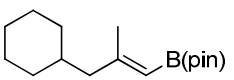
With the optimized reaction conditions for the Cu-catalyzed methylboronation of alkynes in hand, we examined a wide range of readily available terminal alkynes, as depicted in Table 2. All reactions were performed in THF at ambient temperature in the presence of 3 mol % of the BenzICyCuCl catalyst (Figure 2), providing various *cis*-methyl alkenyl boronates with good yields (77~86%) and high stereo- and regioselectivities. First, normal alkyl-substituted alkynes were employed

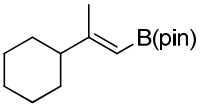
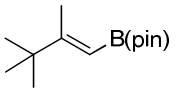
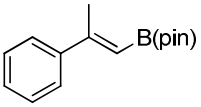
for the catalytic system, affording the desired methyl boronates **20a-b** and **20e** efficiently (80-83% yields, entries 2-3 and entry 6). Entries 4-5 showed that the catalytic process tolerated different functional groups, including a chloro and ester group, to give products **20c-d** with high regioselectivities and good yields. When terminal alkynes bearing a sterically demanding cyclohexyl or *tert*-butyl substituent were used, the corresponding methylboronated products were obtained with yields of 83-86% (entries 7-9), although a longer reaction time was required for the reaction with the *tert*-butyl substituted alkyne (24 h instead of 3 h). The methylboronation of phenylacetylene was less efficient than that of the alkyl-substituted terminal alkynes; the reaction was conducted for 24 h and furnished the phenyl-substituted product **20i** with a yield of 77% (entry 10). For the reaction with phenylacetylene, lithium *tert*-butoxide was used because of the preferable deprotonation of a hydrogen on phenylacetylene by potassium *tert*-butoxide.

Table 2. Cu-Catalyzed methylboronation of various alkynes[a]



19 **20** **21**

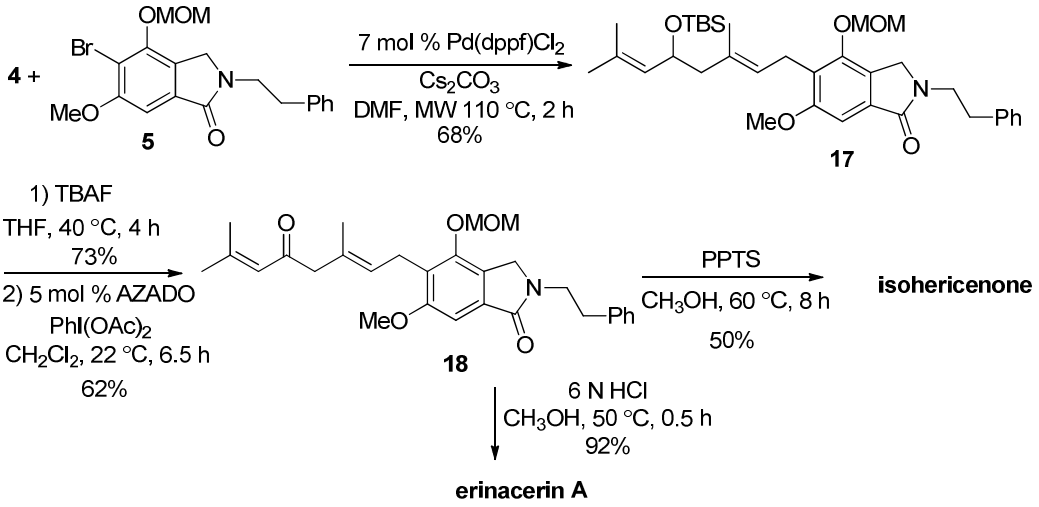
entry	products		**20**:**21**[b]	yield (%)[c]
1		**16a**	94:6	84
2		**20a**	93:7	83
3		**20b**	92:8	81
4		**20c**	92:8	84
5		**20d**	98:2	84
6		**20e**	91:9	80
7		**20f**	94:6	83

8		**20g**	96:4	86
9[d]		**20h**	>98:<2	86
10[e]		**20i**	>98:<2	77

[a]Reactions run on 0.4 mmol scale with respect to the alkyne. Conditions: 1.0 equiv. of terminal alkyne **19**, 3.0 equiv. of MeI, 1.3 equiv. of $B_2(pin)_2$, 1.5 equiv. of base and THF (0.2 M) under N_2. [b]Determined by ^{1}H NMR spectrum analysis of unpurified mixtures. [c]Yields of the isolated products. [d]24 h reaction time. [e]LiO*t*-Bu and 24 h reaction time used.

Next, with geranyl boronate product **4** in hand, we investigated the final stage of the synthesis of isohericenone and erinacerin A: forming the C-C bond between **4** and aryl bromide **5** *via* palladium-catalyzed cross-coupling (Scheme 4). The coupling reaction in the presence of 7 mol % Pd(dppf)Cl_2 and cesium carbonate afforded the desired product **17** with a yield of 68%. After deprotection of the TBS group with TBAF, the alcohol intermediate was oxidized with 5 mol % of 2-azaadamantane-*N*-oxyl (AZADO) and iodobenzene diacetate (PhI$(OAc)_2$), installing the carbonyl group at the C5' position of **18**.[4a] The MOM-protecting group in **18** would be removed under acidic conditions; however, isohericenone (**2**) was prone to further intramolecular cyclization to form erinacerin A (**3**) under acidic conditions. Hence, after briefly screening acids and reaction temperatures, we found that the MOM group of **18** was cleaved under mildly acidic conditions when pyridinium *p*-toluenesulfonate (PPTS) was used, providing the final isohericenone (**2**) product with a yield of 50% yield. By contrast, when **18** was subjected to HCl, the intramolecular ring closing reaction readily proceeded in one pot to deliver another natural product, erinacerin A (**3**), with a yield of 92%. The NMR spectral data of the three synthesized compounds (**1**-**3**) were identical to those of the natural products reported in the literature.[2,4a]

Scheme 4. Total synthesis of isohericenone and erinacerin A



CONCLUSIONS

In summary, we have successfully achieved efficient and straightforward total syntheses of isohericerin, isohericenone, and erinacerin A. The common isoindolinone core was synthesized in 3 steps. Specifically, Mannich reaction with hydroxybenzonate and an intramolecular cyclization with oxazine afforded bromo-substituted isoindolinone, which was then coupled with the geranyl boronate side chain under Suzuki-Miyaura conditions. For forming the C5'-oxidized geranyl unit in isohericenone and erinacerin A, we developed a mild and selective methylboronation reaction of terminal alkynes with $B_2(pin)_2$ and methyl iodide promoted by an NHC-Cu catalyst. This reacation effectively furnished the *cis*-methyl alkenyl boronate, which was transformed into the oxidized geranyl boronate under Matteson homologation conditions. Readily accessible terminal alkynes, including those normal alkyl, sterically demanding alkyl, ether, chloro, and ester substituents, were tolerated in the copper catalytic system, providing versatile *cis*-methyl alkenyl boronates with good yields. In the future, their biological activities will be evaluated.

EXPERIMENTAL SECTION

General. Infrared (IR) spectra were recorded in reciprocal centimeters (cm^{-1}). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). ^1H NMR spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane, with the solvent resonance as the internal standard ($CDCl_3$: δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet), coupling constants (Hz), and integration. ^{13}C NMR spectra were recorded on a 100 MHz spectrometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$: δ 77.00 ppm). High-resolution mass spectra (HRMS) were obtained using an electrospray ionization (ESI) time-of-flight mass spectrometer. Melting points were determined using a melting point apparatus and are uncorrected. Microwave reactions were conducted in sealed glass tubes (capacity 10 mL) using a CEM Discover microwave reactor (Model No. 908005) with temperature control *via* external infrared sensor. Unless otherwise noted, all reactions were carried out with distilled solvents under an atmosphere of dry N_2 in oven-dried (130 °C) glassware. *N*,*N*'-Dimethylformamide was purified by simple distillation over magnesium sulfate, and methanol was purified by distillation from sodium. Tetrahydrofuran and diethyl ether were purified by distillation from sodium benzophenone ketyl immediately prior to use, unless otherwise specified. Acetonitrile and dichloromethane were purified by distillation from calcium hydride. All work-up and purification procedures were carried out with reagent grade solvents in air. NHC-Cu complexes were prepared according to reported experimental procedures.[15]

Experimental procedures for the synthesis of isohericerin (1), isohericenone (2), and erinacerin A (3):

Methyl 8-bromo-7-methoxy-3-phenethyl-3,4-dihydro-2H-benzo[e][1,3]oxazine-5-carboxylate (9). Methyl 4-bromo-3-hydroxy-5-methoxybenzoate (**6**) (50.0 mg, 0.191 mmol), phenethylamine (30.0 μL, 0.230 mmol), 38% aqueous formaldehyde (55.6 μL, 0.230 mmol) and methanol (0.8 mL) were added

into a sealed tube. The reaction mixture was allowed to heat to 110 °C and stir for 3 h. Then, the reaction was quenched with water (3 mL) and washed with EtOAc (3 mL × 3). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 1:4), affording the desired product **9** (59.7 mg, 0.147 mmol, 77%) as a white solid. mp 115.7-116.6 °C; **IR** (neat): 1713 (w), 1659 (w), 1589 (w), 1466 (w), 1366 (w), 1319 (w), 1273 (w), 1134 (w), 1088 (w), 1049 (w), 1011 (w), 964 (w), 918 (w), 841(w), 756 (s); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.30-7.26 (m, 2H), 7.21-7.17 (m, 4H), 5.02 (s, 2H), 4.38 (s, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.88 (t, *J* = 7.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): 166.7, 155.0, 152.7, 139.7, 128.7, 128.4, 127.8, 126.2, 117.1, 106.0, 105.6, 83.2, 56.3, 53.1, 52.1, 49.6, 34.8; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}BrNO_4$ 406.0654, Found 406.0651.

5-Bromo-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one (10). An aqueous solution of K_3PO_4 (2.5 M, 0.63 mL) was added to a solution of compound **9** (57.1 mg, 0.140 mmol) in acetonitrile (0.31 mL). The reaction mixture was allowed to heat to 100 °C and stir for 15 h. The reaction was quenched with brine (30 mL) and washed with $CHCl_3$ (3 × 30 mL). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by washing with hexane to obtain the desired product **10** (48.3 mg, 0.133 mmol, 95%) as a white solid. mp 237.5-237.7 °C; **IR** (neat): 1643 (s), 1566 (s), 1474 (s), 1435 (m), 1342 (m), 1296 (s), 1242 (w), 1165 (m), 1142 (m), 1088 (s), 1026 (w), 972 (w), 895 (w), 833 (m), 748 (m), 702 (s), 617 (m); **^{1}H NMR** (400 MHz, DMSO-d_6): δ 7.28-7.20 (m, 5H), 6.80 (s, 1H), 4.25 (s, 2H), 3.86 (s, 3H), 3.75 (t, *J* = 7.2 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 166.9, 157.1, 150.1, 139.0, 133.0, 128.6, 128.5, 126.3, 121.3, 103.5, 97.0, 56.6, 47.8, 43.3, 33.9; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{17}BrNO_3$ 362.0392, Found 362.0393.

5-Bromo-6-me hoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (5). To a solution of compound **10** (9.00 mg, 0.0248 mmol) in *N*,*N'*-dimethylformamide (0.1 mL) was added NaH (60% in paraffin, 1.50 mg, 0.0372 mmol) at 0 °C (ice bath). The mixture was allowed to stir at 0 °C for 5 min,

then warm to room temperature and stir for 15 min under N_2 gas. Next, chloromethylmethyl ether (2.82 μL, 0.0372 mmol) was added, and the reaction mixture was allowed to stir at 0 °C for 5 min and stir at room temperature for 15 min. The resulting solution was quenched with water (2 mL) and washed with CH_2Cl_2 (3 × 3 mL). The organic layers were washed with 1 M NaOH (9 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 1:1), affording the desired product **5** (9.90 mg, 0.0244 mmol, 98%) as a white solid. mp 85-86 °C; **IR** (neat): 2361 (w), 1690 (m), 1612 (w), 1466 (m), 1427 (w), 1327 (w), 1265 (w), 1157 (w), 1080 (w), 980 (w), 918 (w), 825 (w) 733 (s); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.23 (m, 5H), 7.18 (s, 1H), 5.11 (s, 2H), 4.24 (s, 2H), 3.97 (s, 3H), 3.87 (t, J = 7.2 Hz, 2H), 3.51 (s, 3H), 3.00 (t, J = 7.2 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 167.6, 157.9, 150.5, 138.8, 134.0, 128.8, 128.7, 126.7, 125.6, 110.2, 101.9, 98.2, 57.2, 56.9, 49.0, 44.3, 34.8; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}BrNO_4$ 406.0654, Found 406.0645.

(*E*)-5-(3,7-dimethylocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (12). $PdCl_2(dppf)•CH_2Cl_2$ (3.30 mg, $3.97x10^{-3}$ mmol), cesium carbonate (27.7 mg, 0.0851 mmol) and compound **5** (23.0 mg, 0.0566 mmol) were added into a 10 mL microwave tube in a glove box. After removing the tube from the glove box, it was filled with N_2 gas and then a solution of (*E*)-2-(3,7-dimethylocta-2,6-dien-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (**11**) (22.5 mg, 0.0851 mmol) in DMF (0.2 mL) was added. The reaction mixture was sealed in a microwave tube and stirred at 110 °C under focused microwave irradiation (100 W) for 2 h, maintaining the temperature using an external IR sensor. The resulting solution was cooled to room temperature, quenched with water (2 mL) and washed with EtOAc (3 × 1 mL). The organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (3 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 1:1), furnishing the desired product **12** (16.5 mg, 0.0356 mmol, 63%) as a white solid. (This compound has been previously reported, and its spectral data match those described in the literature).[7] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.23 (m, 5H), 7.14 (s, 1H), 5.13

(t, *J* = 6.6 Hz, 1H), 5.05 (t, *J* = 6.7 Hz, 1H), 5.00 (s, 2H), 4.25 (s, 2H), 3.88 (s, 3H), 3.85 (br t, *J* = 7.4 Hz, 2H), 3.48 (s, 3H), 3.41 (d, *J* = 6.8 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 2.06-2.02 (m, 2H), 1.98-1.94 (m, 2H), 1.76 (s, 3H), 1.64 (s, 3H), 1.44 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 168.4, 159.1, 150.9, 139.0, 135.5, 132.6, 131.4, 128.8, 128.7, 126.5, 126.4, 124.4, 124.3, 122.1, 101.0, 97.9, 56.7, 56.0, 49.4, 44.1, 39.7, 34.9, 26.6, 25.6, 23.4, 17.6, 16.1.

(*E*)-5-(3,7-Dimethylocta-2,6-dienyl)-6-methoxy-4-(methoxy-methoxy)-2-phenethylisoindolin-1-one (isohericerin, 1). To a solution of compound **12** (2.50 mg, $5.39x10^{-3}$ mmol) in methanol (0.3 mL) was added 0.2 M HCl (in methanol, 269 μL, 0.0539 mmol). The reaction mixture was allowed to stir at room temperature for 3 h. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (1 mL) and washed with EtOAc (3 × 1 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 2:1) to provide isohericerin (2.20 mg, 0.00524 mmol, 97%) as a white solid. (This compound has been previously reported, and its spectral data match those described in the literature).[2,7] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.22 (m, 5H), 6.97 (s, 1H), 5.77 (s, 1H), 5.25 (t, *J* = 6.7 Hz, 1H), 5.05-5.02 (m, 1H), 4.14 (s, 2H), 3.87-3.84 (m, 5H), 3.50 (d, *J* = 7.1 Hz, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 2.13-2.11 (m, 4H), 1.82 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): 169.0, 158.6, 150.6, 139.4, 138.8, 132.2, 132.2, 128.7, 128.6, 126.5, 123.7, 121.3, 121.2, 118.5, 97.6, 56.1, 48.1, 44.2, 39.6, 34.8, 26.2, 25.6, 22.7, 17.6, 16.1; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{27}H_{34}NO_3$ 420.2539, Found 420.2532.

6-Methylhept-5-en-1-yn-4-ol (14). Zinc activated by HCl (149 mg, 2.28 mmol) and THF (2.5 mL) were added into a 2-neck flask at 0 °C (ice bath) under N_2 gas. Iodine (20.0 mg) was added and the mixture was allowed to stir until the dark brown color of iodine faded. A solution of propargyl bromide (**13**) (80% in toluene, 201 μL, 1.81 mmol) in THF (2 mL) was added to the reaction mixture slowly by using a dropping funnel, and the resulting solution was allowed to stir at 0 °C for 1 h. Next, 3-methyl-2-butenal (**8**) (91.0 μL, 0.951 mmol) was added, and the mixture was allowed to stir at 0 °C for an

additional 30 min. The resulting solution was passed through a short plug of Celite, quenched by adding a saturated aqueous solution of $NaHCO_3$ (10 mL) and washed with ether (15 mL × 3). The organic layers were combined, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/Et_2O, 3:1) to provide the desired alcohol product **14** (114 mg, 0.918 mmol, 97%) as a yellow oil. (This compound has been previously reported, and its spectral data match those described in the literature).[17] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.26 (d, *J* = 8.5 Hz, 1H), 4.55-4.49 (m, 1H), 2.42-2.39 (m, 2H), 2.04 (t, *J* = 2.6 Hz, 1H), 1.95 (d, *J* = 3.9 Hz, 1H), 1.74 (s, 3H), 1.71 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 136.9, 125.9, 80.8, 70.4, 66.7, 27.6, 25.6, 18.2.

***tert*-Butyldimethyl((6-methylhept-5-en-1-yn-4-yl)oxy)silane (15)**. To a solution of compound **14** (927 mg, 7.47 mmol), 4-dimethylaminopyridine (456 mg, 3.73 mmol) and *tert*-butyldimethylchlorosilane (2.30 g, 14.9 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (2.30 mL, 16.4 mmol). The reaction mixture was allowed to stir at room temperature for 15 h. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (30 mL) and washed with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/Et_2O, 20:1) to provide product **15** (1.47 g, 6.19 mmol, 83%) as a yellow oil. (This compound has been previously reported, and its spectral data match those described in the literature).[17] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.15 (d, *J* = 8.8 Hz, 1H), 4.55-4.49 (m, 1H), 2.39 (ddd, *J* = 16.3, 6.3, 2.4 Hz, 1H), 2.28 (ddd, *J* = 16.6, 6.3, 2.4 Hz, 1H), 1.94-1.93 (m, 1H), 1.72 (s, 3H), 1.67 (s, 3H), 0.88 (s, 9H), 0.07 (s, 3H), 0.04 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 133.0, 127.9, 81.8, 69.2, 68.4, 28.5, 25.7, 25.6, 18.4, 18.1, -4.5, -4.9.

(*E*)-*tert*-Butyl((2,6-dimethyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hepta-1,5-dien-4-yl)oxy)dimethylsilane (16a). Bis(pinacolato)diboron (132 mg, 0.520 mmol), BenzICyCuCl (4.60 mg, 0.012 mmol) and KO*t*-Bu (67.3 mg, 0.600 mmol) were added into an 8 mL vial in a glove box. The vial was sealed with a PTFE/silicone septa using an open top screw cap and removed from the glove box. The vial was filled with N_2 gas and THF (1.6 mL) was added at 0 °C (ice bath). The mixture was

allowed to stir at 0 °C for 10 min. Next, a solution of compound **15** (95.2 mg, 0.400 mmol) in THF (0.4 mL) and iodomethane (74.0 μL, 0.12 mmol) were added at -78 °C (dry ice/acetone bath). The resulting mixture was allowed to warm to room temperature and stir for 3 h. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (2 mL) and washed with ether (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/Et_2O, 60:1), affording the desired product **16a** (128 mg, 0.337 mmol, 84%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.14-5.11 (m, 2H), 4.51-4.45 (m, 1H), 2.28 (dd, J = 12.7, 8.0 Hz, 1H), 2.13 (dd, J = 12.9, 5.1 Hz, 1H), 2.00 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.25 (s, 12H), 0.84 (s, 9H), 0.00 (s, 3H), -0.02 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) :δ 160.1, 131.0, 129.4, 116.2, 82.4, 69.4, 51.1, 25.8, 25.5, 24.7, 24.7, 22.1, 18.1, 18.1, -4.4, -5.0; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{42}BO_3Si$ 381.2996, Found 381.2974.

(*E*)-*tert*-Butyl((2,6-dimethyl-8-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)octa-2,6-dien-4-yl)oxy)dimethylsilane (4). To a solution of compound **16a** (61.9 mg, 0.163 mmol) in diethyl ether (1 mL) was added chloroiodomethane (18.0 μL, 0.244 mmol) at -78 °C (dry ice/acetone bath). Next, *n*-BuLi (72.0 μL, 0.179 mmol) was added very slowly at -78 °C. The resulting mixture (light sensitive) was allowed to stir at -78 °C for 1 h. Then, the reaction mixture was allowed to warm to room temperature and stir for 19 h. The reaction was quenched with water (2 mL) and washed with ether (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/Et_2O, 20:1 with 1% Et_3N), providing the desired product **4** (56.4 mg, 0.143 mmol, 88%) as a yellow oil. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.25 (t, *J* = 7.2 Hz, 1H), 5.10 (d, *J* = 8.8 Hz, 1H), 4.42-4.37 (m, 1H), 2.20 (dd, *J* = 12.9, 6.8 Hz, 1H), 2.02 (dd, *J* = 12.9, 5.8 Hz, 1H) 1.67 (s, 3H), 1.60 (s, 6H), 1.24 (s, 12H), 0.86 (s, 9H), 0.01 (s, 3H), -0.01 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 131.9, 130.7, 129.7, 121.4, 83.0, 69.3, 48.7, 25.8, 25.6, 24.7, 18.1, 16.7, -4.5, -4.9; **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{43}BO_3SiNa$ 417.2972, Found 417.2979.

(*E*)-5-(5-((*tert*-Butyldimethylsilyl)oxy)-3,7-dimethylocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (17). $PdCl_2(dppf)•CH_2Cl_2$ (7.00 mg, 0.00861 mmol), cesium carbonate (60.3 mg, 0.185 mmol) and compound **5** (50.0 mg, 0.123 mmol) were added into a 10 mL microwave tube in a glove box. After removing the tube from the glove box, it was filled with N_2 gas and a solution of compound **4** (73.0 mg, 0.185 mmol) in DMF (0.8 mL) was added into the tube. The reaction mixture was sealed in a microwave tube and stirred at 110 °C under focused microwave irradiation (100 W) for 2 h, maintaining the temperature using an external IR sensor. Next, the reaction was cooled, quenched with water (2 mL) and washed with EtOAc (3 × 2 mL). The organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (2 mL), dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 2:1 with 1% Et_3N), providing the desired product **17** (49.8 mg, 0.0839 mmol, 68%) as a yellow oil. (This compound has been previously reported, and its spectral data match those described in the literature).[4a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.20 (m, 5H), 7.13 (s, 1H), 5.17 (t, *J* = 6.9 Hz, 1H), 5.05 (d, *J* = 8.8 Hz, 1H), 5.00 (s, 2H), 4.42-4.36 (m, 1H), 4.24 (s, 2H), 3.88-3.84 (m, 5H), 3.48 (s, 3H), 3.41-3.38 (m, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 2.15 (dd, *J* = 12.9, 7.0 Hz, 1H), 1.99 (dd, *J* = 13.1, 5.6 Hz), 1.78 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H), 0.82 (s, 9H), -0.04 (s, 3H), -0.05 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.4, 159.0, 150.9, 139.0, 132.6, 132.2, 130.8, 129.5, 128.8, 128.7, 126.5, 126.2, 124.9, 124.2, 100.9, 97.8, 68.8, 56.7, 56.0, 49.4, 48.7, 44.1, 34.9, 25.8, 25.7, 25.5, 23.5, 18.1, 18.0, 16.9, -4.5, -5.0.

(*E*)-5-(5-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (17`). To a solution of compound **17** (8.70 mg, 0.0146 mmol) in THF (1.6 mL) was added tetrabutylammonium fluoride (1 M in THF, 66.0 µL, 0.0659 mmol). The reaction mixture was allowed to stir at 40 °C for 4 h. Next, the resulting solution was directly loaded on silica gel for column chromatography (hexanes/EtOAc, 1:1 with 1% Et_3N), providing the desired product **17`** (5.10 mg, 0.0106 mmol, 73%) as a yellow oil. (This compound has been previously reported, and its

spectral data match those described in the literature).[4a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.21 (m, 5H), 7.14 (s, 1H), 5.26 (t, *J* = 6.5 Hz, 1H), 5.12 (d, *J* = 8.5 Hz, 1H), 5.03-4.99 (m, 2H), 4.44-4.40 (m, 1H), 4.24 (s, 2H), 3.88-3.84 (m, 5H), 3.48 (s, 3H), 3.46-3.43 (m, 2H), 2.99 (t, *J* = 7.4 Hz, 2H), 2.16-2.06 (m, 2H), 1.82 (s, 3H), 1.69 (s, 3H), 1.68 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.3, 159.0, 150.8, 139.0, 134.9, 132.9, 132.0, 128.8, 128.7, 127.5, 126.6, 126.6, 125.6, 124.2, 101.0, 97.7, 65.7, 56.8, 56.1, 49.4, 48.1, 44.1, 34.9, 25.7, 23.5, 18.1, 16.2.

(*E*)-5-(3,7-dimethyl-5-oxoocta-2,6-dien-1-yl)-6-methoxy-4-(methoxymethoxy)-2-phenethylisoindolin-1-one (18). A solution of compound **17`** (20.6 mg, 0.0429 mmol), $PhI(OAc)_2$ (68.9 mg, 0.215 mmol) and AZADO (0.340 mg, 0.00215 mmol) in CH_2Cl_2 (1 mL) was allowed to stir at room temperature for 6 h under N_2 gas. Then, additional $PhI(OAc)_2$ (27.0 mg, 0.0838 mmol) and AZADO (1.00 mg, 0.00657 mmol) were added. The resulting mixture was allowed to stir for additional 30 min. The reaction was quenched by adding a saturated aqueous solution of $NaHCO_3$ (1 mL), and a saturated aqueous solution of NaS_2CO_3 (1 mL) and was washed with EtOAc (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 1:1 with 1% Et_3N) to afford the desired product **18** (12.7 mg, 0.0266 mmol, 62%) as a yellow oil. (This compound has been previously reported, and its spectral data match those described in the literature).[4a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.32-7.21 (m, 5H), 7.14 (s, 1H), 6.07 (s, 1H), 5.28 (t, *J* = 6.8 Hz, 1H), 5.01 (s, 2H), 4.25 (s, 2H), 3.88-3.84 (m, 5H), 3.48-3.46 (m, 5H), 3.02-2.98 (m, 4H), 2.13 (s, 3H), 1.84 (s, 3H), 1.79 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 199.4, 168.3, 159.1, 155.6, 150.9, 139.0, 132.8, 130.1, 128.8, 128.7, 127.0, 126.5, 125.5, 124.2, 122.9, 100.9, 97.8, 56.7, 56.0, 55.4, 49.4, 44.1, 34.9, 27.6, 23.6, 20.6, 16.4.

(*E*)-5-(3,7-Dimethyl-5-oxoocta-2,6-dien-1-yl)-4-hydroxy-6-methoxy-2-phenethylisoindolin-1-one (isohericenone, 2). To a solution of compound **18** (3.10 mg, 0.00649 mmol) in methanol (0.2 mL) was added PPTS (16.3 mg, 0.0649 mmol), and the reaction mixture was allowed to warm to 60 °C and stir for 8 h. The resulting solution was quenched by adding a saturated aqueous solution of $NaHCO_3$ (0.5

mL) and washed with EtOAc (3 × 0.5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/EtOAc, 1:1), providing the desired product isohericenone (1.40 mg, 0.00323 mmol, 50%) as a yellow oil. (This compound has been previously reported, and its spectral data match those described in the literature).[2,4a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.31-7.22 (m, 5H), 6.98 (s, 1H), 6.33 (s, 1H), 6.08 (s, 1H), 5.31 (t, *J* = 6.8 Hz, 1H), 4.19 (s, 2H), 3.88-3.84 (m, 5H), 3.57 (d, *J* = 7.1 Hz, 2H), 3.16 (s, 2H), 2.99 (t, *J* = 7.3 Hz, 2H), 2.17 (s, 3H), 1.90 (s, 3H), 1.82 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.8, 168.8, 158.4, 156.9, 150.8, 138.9, 133.4, 132.5, 128.8, 128.6, 126.5, 126.3, 123.1, 122.1, 118.1, 97.8, 56.1, 54.5, 48.1, 44.1, 34.8, 29.6, 27.7, 23.0, 20.9.

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(2H)-one (erinacerin A, 3). A solution of compound **18** (3.00 mg, 0.00628 mmol) and 6 M HCl (in methanol, 200 µL) in methanol (0.4 mL) was allowed to stir at 50 °C for 30 min. Next, the solvent was removed, and the crude product was purified by silica gel column chromatography (hexanes/EtOAc, 1:1), affording the desired product erinacerin A (2.50 mg, 0.00577 mmol, 92%) as a yellow oil. (This compound has been previously reported, and its spectral data match those described in the literature).[4a,5] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33-7.21 (m, 5H), 6.91 (s, 1H), 6.05 (s, 1H), 4.15 (d, *J* = 5.9 Hz, 2H), 3.88 (s, 3H), 3.86-3.82 (m, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 2.76 (d, *J* = 14.1 Hz, 1H), 2.71-2.67 (m, 2H), 2.64 (d, *J* = 14.4 Hz, 1H), 2.15 (s, 3H), 2.06-1.99 (m, 1H), 1.95-1.89 (m, 1H), 1.85 (s, 3H), 1.41 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 198.2, 169.0, 158.6, 155.7, 148.7, 138.8, 132.3, 128.8, 128.7, 126.5, 125.1, 121.9, 113.5, 96.2, 75.9, 55.9, 52.2, 47.9, 44.1, 34.9, 30.5, 27.8, 24.7, 20.7, 17.3.

Representative experimental procedures for the Cu-catalyzed methylboronation of terminal alkynes:

General procedure A: Bis(pinacolato)diboron (132 mg, 0.520 mmol), BenzICyCuCl (4.60 mg, 0.012 mmol) and KO*t*-Bu (67.3 mg, 0.600 mmol) were added into an 8 mL vial in a glove box. The vial was sealed with a PTFE/silicone septa using an open top screw cap and removed from the glove box. The vial was filled with N_2 gas and THF (1.6 mL) was added at 0 °C (ice bath). The mixture was allowed to stir at 0 °C for 10 min. Then, a solution of compound **15** (95.2 mg, 0.400 mmol) in THF (0.4 mL) and iodomethane (74.0 μL, 0.12 mmol) were added at -78 °C (dry ice/acetone bath). The resulting mixture was allowed to warm to room temperature and stir for 3 h. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (2 mL) and washed with ether (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/Et_2O, 60:1), providing the desired product **16a** (128 mg, 0.337 mmol, 84%) as a yellow oil.

General procedure B: Bis(pinacolato)diboron (66.0 mg, 0.260 mmol), BenzICyCuCl (2.30 mg, 0.006 mmol) and LiO*t*-Bu (24.0 mg, 0.300 mmol) were added into an 8 mL vial in a glove box. The vial was sealed with a PTFE/silicone septa using an open top screw cap and removed from the glove box. The vial was filled with N_2 gas and THF (1.5 mL) was added at room temperature. The mixture was allowed to stir for 10 min, and then phenylacetylene (22.0 μL, 0.200 mmol) and iodomethane (37.0 μL, 0.600 mmol) were added at room temperature. The resulting mixture was allowed to stir at room temperature for 3 h. The reaction was quenched by adding a saturated aqueous solution of NH_4Cl (2 mL) and washed with ether (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica gel column chromatography (hexanes/Et_2O, 60:1), providing the desired product **20i** (37.7 mg, 0.154 mmol, 77%) as a colorless oil.

(*E*)-4,4,5,5-Tetramethyl-2-(2-methyloct-1-en-1-yl)-1,3,2-dioxaborolane (20a). According to general procedure A, compound **20a** was synthesized using 1-octyne (59.0 μL, 0.400 mmol) and obtained as a colorless oil with a yield of 83% (83.3 mg, 0.330 mmol). (This compound has been previously reported, and its spectral data match those described in the literature.)[18] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.10 (s,

1H), 2.07 (t, *J* = 7.7 Hz, 2H), 1.96 (s, 3H), 1.44-1.39 (m, 2H), 1.25 (s, 18H), 0.86 (t, *J* = 6.4 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.4, 112.8, 82.5, 42.1, 31.7, 28.9, 27.5, 24.7, 22.5, 21.0, 14.0. **(*E*)-4,4,5,5-tetramethyl-2-(non-2-en-3-yl)-1,3,2-dioxaborolane (21a). ^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.08 (q, *J* = 6.8 Hz, 1H), 2.08 (t, *J* = 7.1 Hz, 2H), 1.88 (d, *J* = 6.8, 3H), 1.35-1.25 (m, 8H), 1.28 (s, 12H), 0.88 (t, *J* = 7.0Hz , 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 140.1, 82.8, 36.9, 31.7, 30.2, 28.9, 24.7, 22.5, 17.1, 14.0; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{30}BO_2$ 253.2339, Found 253.2332.

(*E*)-4,4,5,5-Tetramethyl-2-(2-methylhex-1-en-1-yl)-1,3,2-dioxaborolane (20b). According to general procedure A, compound **20b** was synthesized using 1-hexyne (45.8 μL, 0.400 mmol) and obtained as a colorless oil with a yield of 81% (72.8 mg, 0.325 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.11 (s, 1H), 2.09 (t, *J* = 7.6 Hz, 2H), 1.97 (s, 3H), 1.46-1.38 (m, 2H), 1.34-1.30 (m, 2H), 1.26 (s, 12H), 0.88 (t, *J* = 7.2, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 163.4, 112.5, 82.5, 41.8, 29.7, 24.8, 22.3, 21.1, 13.9; **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{13}H_{25}BO_2Na$ 247.1845, Found 247.1851.

(*E*)-2-(5-Chloro-2-methylpent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20c). Compound **20c** was synthesized according to general procedure A using 5-chloro-1-pentyne (42.4 μL, 0.400 mmol) to obtain as colorless oil in 84% yield (81.7 mg, 0.334 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.13 (s, 1H), 3.52 (t, *J* = 6.8 Hz, 2H), 2.23 (t, *J* = 7.4 Hz, 2H), 1.98 (s, 3H), 1.96-1.89 (m, 2H), 1.26 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 160.8, 113.7, 82.7, 44.5, 38.8, 30.3, 24.8, 24.7, 21.1; **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{12}H_{22}BClO_2Na$ 267.1299, Found 267.1306.

(*E*)-*tert*-Butyl 6-methyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hept-6-enoate (20d). According to general procedure A, compound **20d** was synthesized using *tert*-butyl hept-6-ynoate (73.0 mg, 0.400 mmol)[19] and obtained as a colorless oil with a yield of 84% (108.6 mg, 0.335 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.09 (s, 1H), 2.19 (t, *J* = 7.3 Hz, 2H), 2.08 (t, *J* = 7.4 Hz, 2H), 1.95 (s, 3H), 1.59-1.53 (m, 2H), 1.46-1.45 (m, 2H), 1.42 (s, 9H), 1.24 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ

173.1, 162.6, 113.0, 82.5, 79.9, 41.6, 35.3, 28.0, 26.9, 24.7, 24.6, 20.9; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{34}BO_4$ 325.2550, Found 325.2570.

(*E*)-4,4,5,5-Tetramethyl-2-(2-methyl-4-phenylbut-1-en-1-yl)-1,3,2-dioxaborolane (20e). According to general procedure A, compound **20e** was synthesized using 4-phenyl-1-butyne (56.2 μL, 0.400 mmol) and obtained as a colorless oil with a yield of 80% (87.2 mg, 0.320 mmol). (This compound has been previously reported, and its spectra data match those described in the literature.)[18a,20] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.37-7.32 (m, 2H), 7.27-7.25 (m, 3H), 5.28 (d, *J* = 1.0 Hz, 1H), 2.86-2.82 (m, 2H), 2.49-2.45 (m, 2H), 2.11 (s, 3H), 1.35 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 162.2, 142.2, 128.4, 128.3, 125.8, 112.9, 82.6, 43.8, 34.2, 24.8, 21.3.

(*E*)-2-(3-Cyclohexyl-2-methylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20f). According to general procedure A, compound **20f** was synthesized using cyclohexyl-1-propyne (58.0 μL, 0.400 mmol) and obtained as a colorless oil with a yield of 83% (87.9 mg, 0.333 mmol). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.06 (s, 1H), 1.97 (d, *J* = 7.1 Hz, 2H), 1.95 (d, *J* = 0.7 Hz, 3H), 1.67-1.65 (m, 4H), 1.49-1.43 (m, 1H), 1.26 (s, 12H), 1.22-1.13 (m, 4H), 0.87-0.78 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 161.8, 114.3, 82.5, 50.7, 35.5, 33.2, 26.5, 26.3, 24.8, 21.1; **HRMS** (ESI-TOF) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{29}BO_2Na$ 287.2158, Found 287.2156.

(*E*)-2-(2-Cyclohexylprop-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (20g). According to general procedure A, compound **20g** was synthesized using cyclohexylacetylene (52.3 μL, 0.400 mmol) and obtained as a colorless oil with a yield of 86% (85.9 mg, 0.343 mmol).[18a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.10 (s, 1H), 1.96 (s, 3H), 1.91-1.86 (m, 1H), 1.76-1.64 (m, 4H), 1.26 (s, 12H), 1.20-1.13 (m, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 168.0, 110.5, 82.5, 49.4, 31.7, 26.6, 26.2, 24.8, 19.6.; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{28}BO_2$ 251.2182, Found 251.2182.

(*E*)-4,4,5,5-Tetramethyl-2-(2,3,3-trimethylbut-1-en-1-yl)-1,3,2-dioxaborolane (20h). According to general procedure A, compound **20h** was synthesized using 3,3-dimethyl-1-butyne (49.0 μL, 0.400

mmol) and obtained as a colorless oil with a yield of 86% (77.0 mg, 0.343 mmol).[21] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.21 (s, 1H), 2.00 (s, 3H), 1.27 (s, 12H), 1.06 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.2, 109.4, 82.6, 38.1, 28.9, 24.8, 17.4; **HRMS** (ESI-TOF) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{26}BO_2$ 225.2026, Found 225.2030.

(*E*)-4,4,5,5-Tetramethyl-2-(2-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane (20i). According to general procedure B, compound **20i** was synthesized using phenylacetylene (22.0 μL, 0.200 mmol) and obtained as a colorless oil with a yield of 77% (37.7 mg, 0.154 mmol). (This compound has been previously reported, and it spectral data match those described in the literature.)[8,18a] **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.53-7.51 (m, 2H), 7.36-7.29 (m, 3H), 5.77 (d, *J* = 0.7, 1H), 2.43 (s, 3H), 1.33 (s, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 157.9, 143.8, 128.2, 128.0 125.8, 115.5, 82.9, 24.8, 22.0.

ASSOCIATED CONTENT

Supporting Information. ^{1}H NMR and ^{13}C NMR spectra for all 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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