Synthesis S. Kobayashi THIEME OPEN ACCESS Short Review

Total Synthesis of Geranyl-Resorcinols Isolated from Mushrooms of Genus *Hericium*

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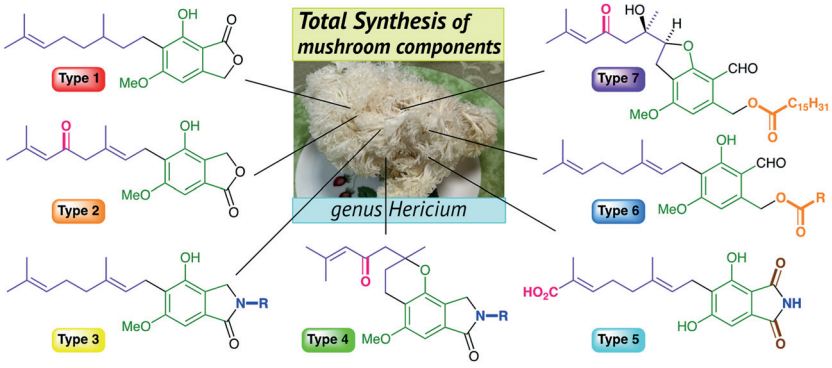

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Abstract This Short Review covers the total synthesis of tetraketide-based meroterpenoids, i.e. geranyl-resorcinols, isolated from the mushrooms of genus *Hericium*. Some of these compounds are believed to be involved in the unique health-promoting effects of *Hericium erinaceus*. Herein, more than seventy natural products identified so far have been classified into seven-types based on both assumed biosynthetic pathways and chemical structures, and the successful total syntheses are summarized according to the structural type.

Key words mushroom, *Hericium erinaceus*, meroterpenoid, geranyl-resorcinol, total synthesis, biosynthetic pathway

Shoji Kobayashi was born in 1973. He obtained his Ph.D. in 2003 from Tohoku University under the direction of Professor Masahiro Hirama, where he studied natural product synthetic chemistry. After one year of postdoctoral research, he was promoted to Assistant Professor at the same laboratory. Then he moved to Osaka Prefecture University to work with Professor Masahiro Toyota and Professor Ilhyong Ryu as Assistant Professor (2005–2010). In 2010, he moved to Osaka Institute of Technology, Faculty of Engineering as Lecturer, and was promoted to Associate Professor in 2014. In 2018, he spent as Research Fellow at University of Lincoln (UK). He was awarded Aoba Science Promotion Association Award in 2003, and 19th Society of Synthetic Organic Chemistry Kansai Region Award in 2021. His current research focuses on natural product synthesis and green organic chemistry.

1 Introduction

Fungi produce thousands of structurally unique small molecules of biological interest.[1–5] These small molecules are considered to give characteristic properties to the fungi, especially the function of mushrooms. Meroterpenoid is one of the major metabolites found in fungi, of which the geranyl-resorcinols, tetraketide-terpenoid hybrids bearing a resorcinol and a geranyl unit, are representative metabolites characteristic of the fungi of the genus *Hericium*.[6–8] To date, more than seventy geranyl-resorcinols have been isolated from natural sources, and most were discovered from the fruiting bodies of *Hericium erinaceus*, an edible mushroom showing a range of health-promoting effects when used as a nutritional supplement (Figure 1).[8–17] Biological testing of the isolated geranyl-resorcinols revealed some significant biological activities including induction of neurotrophic factor expression,[18–23] neuroprotection against endoplasmic reticulum stress-dependent cell death,[24,25] inhibition of collagen-induced platelet aggregation,[26] cytotoxicity against cancer cells,[27–31] antioxidant and anti-osteoporotic activities,[32] α-glucosidase inhibition,[33–37] protein tyrosine phosphatase-1B inhibition,[35] inhibition of nuclear factor kappa B transcriptional activity,[38] PPARγ activation,[39]

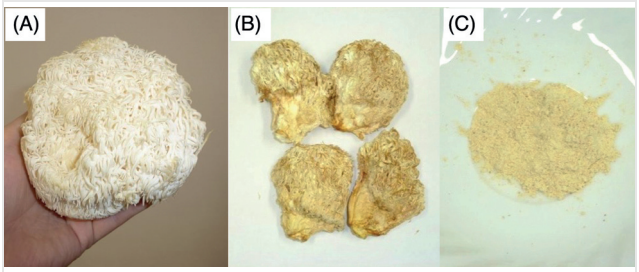


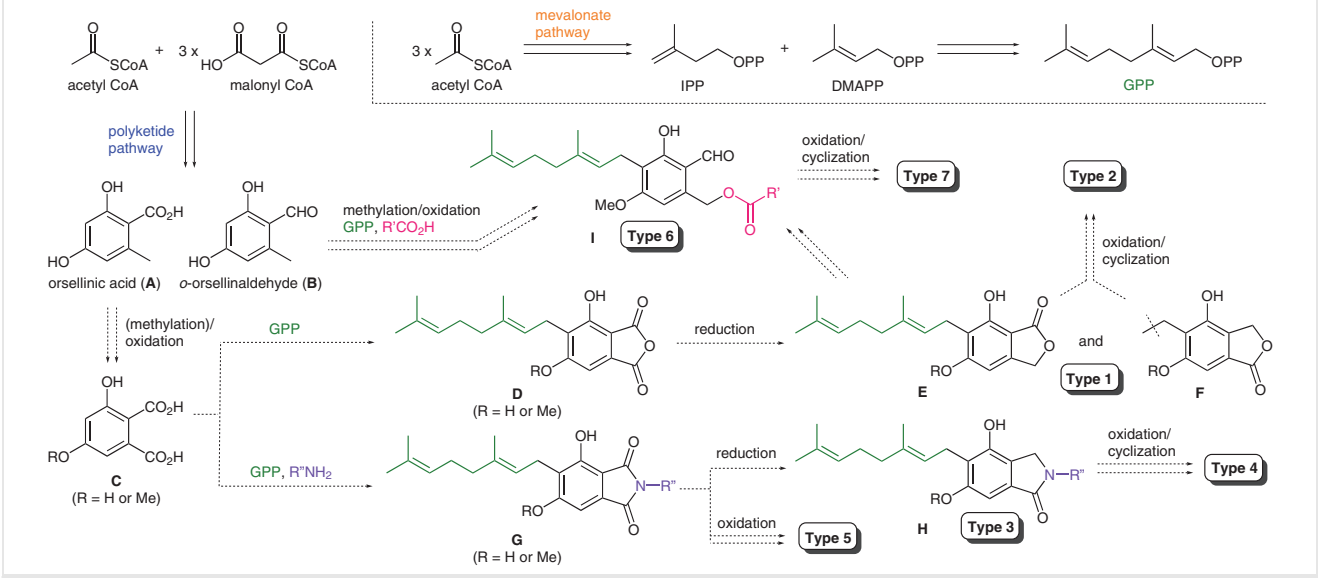
Figure 1 *Hericium erinaceus*: (A) raw, (B) dried, and (C) powdered

as well as plant growth regulation such as inhibition of pollen germination and growth.[40]

From a biosynthetic viewpoint, a variety of geranyl-resorcinols are thought to be generated from malonyl CoA and acetyl CoA via the hybrid polyketide/mevalonate pathways,[30,34,41] although detailed gene/enzyme-based biosynthetic studies[42] have not been reported for these specific molecules (Scheme 1). Orsellinic acid (**A**) and its advanced intermediates **C** are proposed as precursors to acid anhydride **D**, phthalides **E** and **F**, phthalimides **G**, and isoindolinones **H**.[30,34] *o*-Orsellinaldehyde (**B**) is also suggested as precursors of **F**, **G**, and **H**.[4] Given the general biosynthesis and observed structures of natural products, it is considered that geranyl pyrophosphate (GPP) produced from isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) is the origin of the geranyl segment, and a nitrogen substituent in the structures **G** and **H** is derived from an amine or amino acid ($R''NH_2$). For instance, erinacerin F (**38**) and erinacerin K (**28**) include an isoleucine ($R = R^8$) and a phenylalanine ($R = R^9$) moiety, respectively (shown as Type 4 in Figure 2). Although biogenetic routes for fatty ester-containing molecules **I** have not yet been proposed, it can be assumed that they arise from either *o*-orsellinaldehyde (**B**) via O-methylation, benzylic oxidation, geranylation with GPP, and condensation with fatty acids ($R'CO_2H$), or phthalide **E**, via reductive ring opening followed by condensation with fatty acids. Moreover, a variety of oxidation products on the geranyl side chain are probably produced by oxidative metabolism of **D**–**I**.

Historically, the first isolation report was made by Kawagishi and co-workers in 1990 on the hericenones A and B.[27] After their breakthrough discovery, a number of structurally analogous molecules were discovered and individually named as hericenone,[18,19,21,24,27–29,43] hericerin,[29,33,40] erinacerin,[31,34,35,44,45] hericene,[36,46,47] hericenol,[48] erinaceolactam,[30] hericerinol,[23] erinacenol,[37] corallocin,[22] and caputmedusin[41] (Figure 2). Except for the hericenols, isolated from submerged cultures of a *Stereum* species,[48] all compounds were isolated from genus *Hericium*, which indicates that some of them are contributing to the unique medicinal properties of *H. erinaceus* such as improvement of cognitive impairment[10,14,49,50] and depression in humans.[11,16]

To organize a broad range of geranyl-resorcinols discovered so far, they were classified into seven types, from Type 1 to Type 7, based on both the assumed biosynthetic pathways and chemical structures rather than the compound names (Scheme 1 and Figure 2). The main classification points are: (1) the oxidation level of a geranyl side chain, (2) the structure of the tetraketide nucleus, and (3) the inclusion of the fatty acid chain. For instance, the Type 3 compounds possess an isoindolinone nucleus with a geranyl side chain, while Type 4 compounds have the same nucleus but with an oxidized geranyl-derived side chain. Although



Scheme 1 Overview of proposed biosynthetic pathways for geranyl-resorcinols

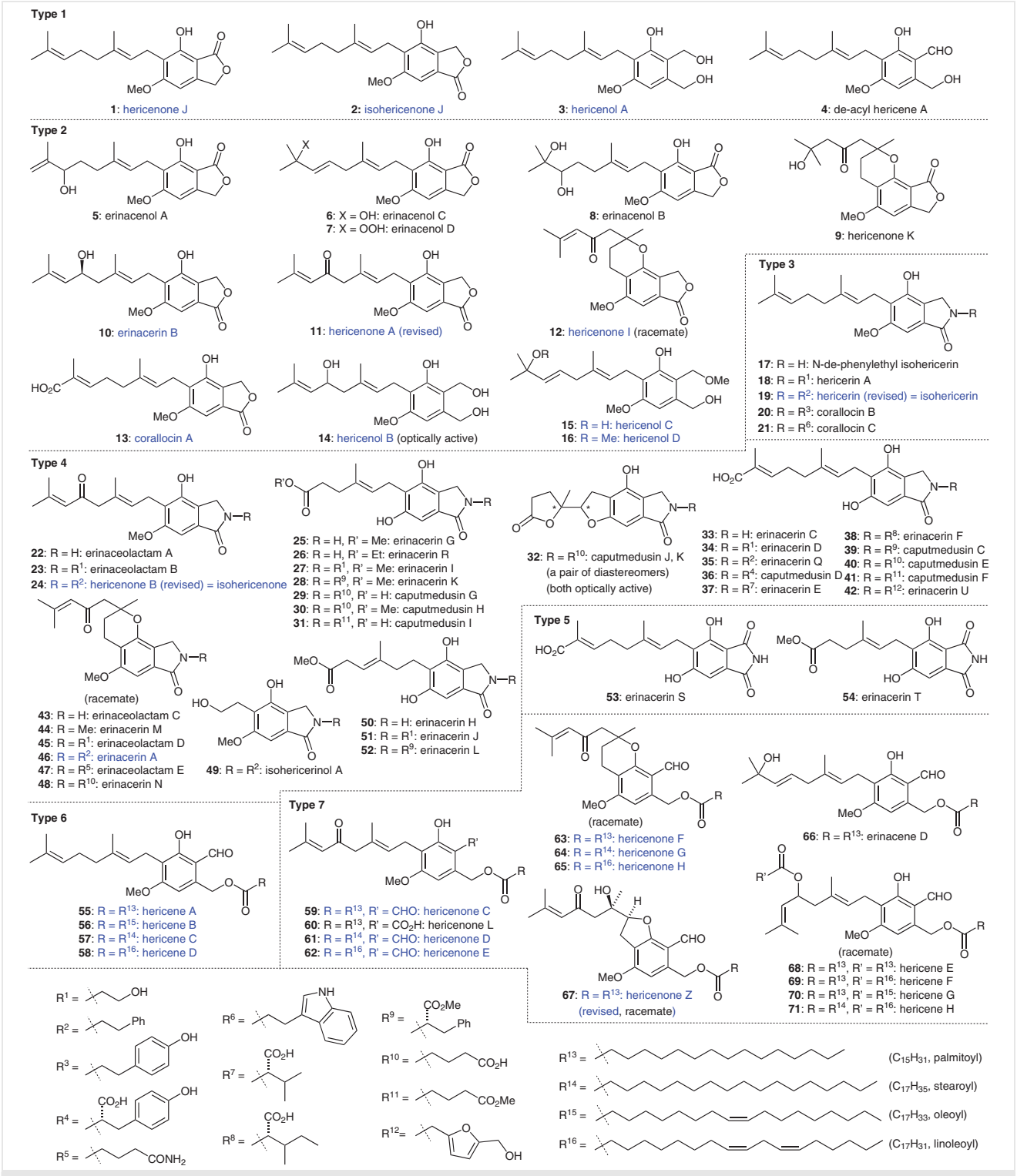
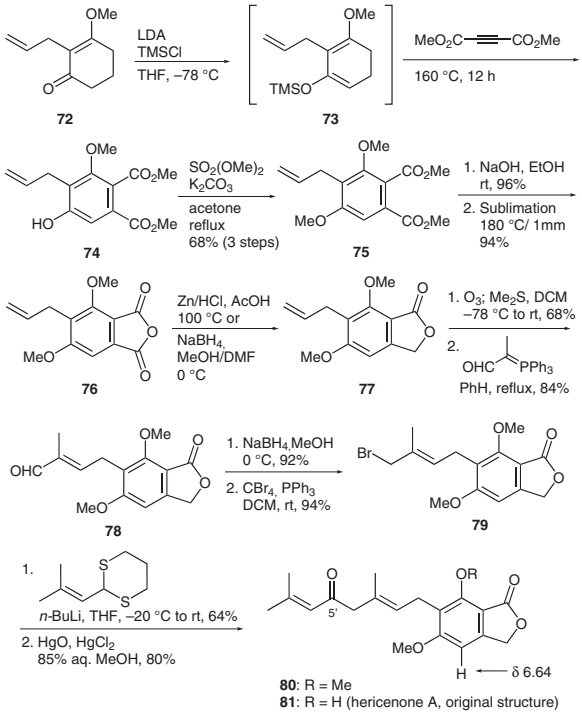


Figure 2 Structures and classification of geranyl-resorcinols isolated from the genera *Hericium* and *Stereum*; compounds for which total synthesis has been achieved are represented in blue

the grouping of a few compounds such as **3** and **4** is unclear, this classification gives a clear-cut overview of metabolites belonging to the geranyl-resorcinol family. It should be noted that Figure 2 covers most of the isolated compounds, but omits some molecules including dimeric isoindolinones such as caputmedusins A and B[41] that can be classified as Type 4, and unnamed congeners or unpublished compounds.

With this classification in mind, this short review summarizes the total synthesis of fungi-derived geranyl-resorcinols published up to December 2021. Some of these syntheses led to corrections of the structures of several natural products and demonstrate proposed biosynthetic pathways. A related review on the tetraketide-terpenoid hybrid, mycophenolic acid and its mycophenolate mofetil immunosuppressive prodrug, has been reported by Churchill and co-workers regarding biogenesis, biological activities, and total syntheses.[51] Some of the synthetic methods described herein are closely related to those for mycophenolic acid, and therefore this review complements the previous review, but chiefly focuses on the geranyl-resorcinols derived from mushrooms of genus *Hericium*, which do not have a methyl substituent in the aromatic moiety.

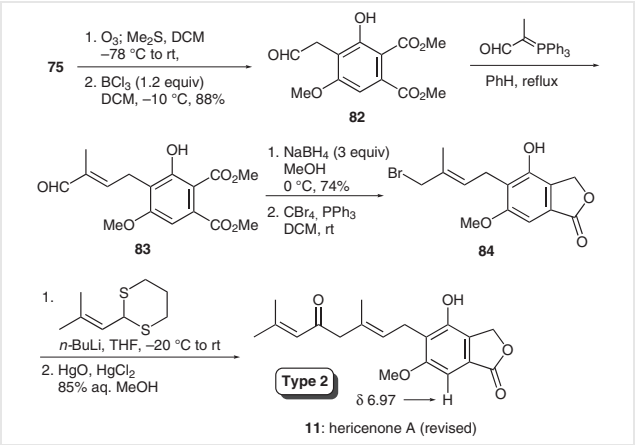


Scheme 2 Rama Rao's approach for the original structure of hericenone A

2 Pioneering Synthetic Study

A pioneering synthetic study on the geranyl-resorcinol family isolated from *H. erinaceus* was reported by Rama Rao and Reddy in 1992,[52] two years after the initial discovery of hericenone A. Hericenone A is classified as Type 2 and was originally reported to contain a phthalide nucleus with a carbonyl group at the benzylic position located *ortho* to the phenolic hydroxyl group (i.e., **81** in Scheme 2).[27] The synthesis commenced with methyl enol ether **72** that was prepared from 2-allylcyclohexane-1,3-dione. The first crucial step was a Diels–Alder cycloaddition between silyloxydiene **73** and dimethyl acetylenedicarboxylate. This reaction involved elimination of ethylene after cycloaddition, yielding the aromatic product **74**, similar to a typical Alder–Rickert reaction.[53] O-Methylation of **74** and ester hydrolysis provided phthalic anhydride **76**. The second key step, the regioselective carbonyl reduction to phthalide **77**, was achieved with zinc/HCl in acetic acid or sodium borohydride in methanol/DMF. Although yields are not mentioned, it is mentioned that 70:30 regioselectivity was obtained under the latter conditions. The following four-step conversion, including ozonolysis of **77**, *E*-selective Wittig reaction, reduction, and bromination, afforded allylic bromide **79**. The final stage was to elongate the carbon chain, which was realized by an umpolung strategy by protecting the C5′-ketone as its 1,3-dithiane. Thus, the addition of lithiated dithioacetal to **79** followed by dethioketalization with mercuric reagents afforded the methyl ether of the reported hericenone A (**80**). However, in the ^{1}H NMR spectrum, an aromatic proton of **80** was observed at δ 6.64, which is about 0.3 ppm upfield as compared to the signal of the natural product (δ 6.97). In view of the large chemical shift differences and IR stretching data (1760 cm^{-1}) indicating the absence of hydrogen bonding between the carbonyl oxygen and the phenolic hydrogen for the natural product, a revised structure was proposed in which the carbonyl group was located *syn* to the aromatic hydrogen (i.e., **11** in Scheme 3).

The synthesis of the new target **11** again started with diester **75**. Ozonolysis and regioselective deprotection with boron trichloride afforded phenol **82**, which was reacted with the Wittig reagent to yield aldehyde **83**. Treatment of **83** with sodium borohydride in methanol effected both reduction of aldehyde and a selective reduction of the methyl ester located *ortho* to phenol followed by concomitant lactonization, giving phthalide **84** after dehydroxybromination. It is noteworthy that the hydrogen-bonded methyl ester reacted selectively with the reductant.[54] Similar to Scheme 2, the terminal enone moiety was constructed by the dithiane strategy. The ^{1}H NMR and IR data of the synthetic compound **11** fully matched those of the natural product, which accomplished the first total synthesis and structure revision of hericenone A.



Scheme 3 Rama Rao's first total synthesis of hericenone A and its structure revision

3 Total Synthesis of Geranyl-Resorcinol with a Geranyl Side Chain (Types 1, 3, and 6)

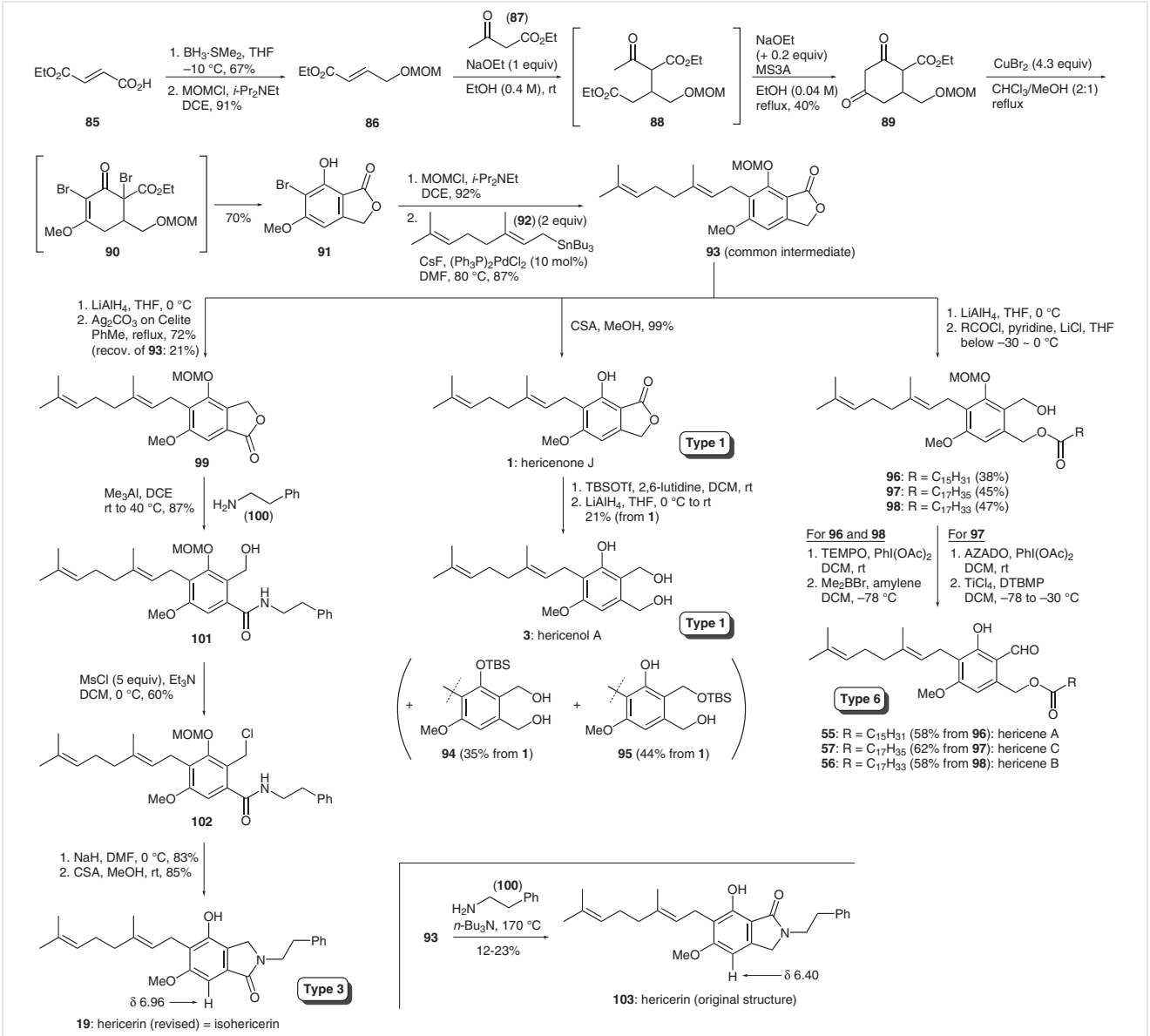
About twenty years after Rama Rao's first total synthesis of hericenone A, the Kobayashi group achieved divergent total syntheses of a series of geranyl-resorcinols of Types 1, 2, 3, 4, and 6 through a geranyl-phthalide **93** as the common intermediate.[25,55–57] Scheme 4 consolidates synthetic routes to Type 1, Type 3, and Type 6 natural products.[25,55,56] Commercially available (*E*)-4-ethoxy-4-oxobut-2-enoic acid (**85**) was chosen as a starting material and was converted into its MOM-protected α,β-unsaturated ester **86** by chemoselective reduction and protection. The first key step was successive Michael addition and Dieckmann cyclization to yield cyclic diketone **89**. This conversion was achieved by treating the Michael acceptor **86** and ethyl acetoacetate (**87**) in the presence of sodium ethoxide at room temperature followed by refluxing the mixture under dilute conditions. The second key step was a tailored one-pot phthalide synthesis mediated by copper(II) bromide and methanol. This reaction involved regioselective bromination and methanol insertion, aromatization, deprotection, and lactonization yielding the fully functionalized phthalide nucleus **91**. After protection of the phenolic hydroxyl group as a MOM group, the geranyl side chain was installed under optimized Stille coupling conditions[58] using $(Ph_3P)_2PdCl_2$ and cesium fluoride[59] to yield the product **93** exclusively as its *E*-isomer in 87% yield. Regarding the coupling process, addition of an arylcopper reagent preprepared from **91** to geranyl bromide resulted in a lower yield.

With key intermediate **93**, hericenone J (**1**), a representative member classified as Type 1, was synthesized first by removal of the MOM group with 10-camphorsulfonic acid (CSA) in methanol in 99% yield.[55] In addition to total synthesis, the Kobayashi group evaluated the neuroprotective effects of a variety of geranyl-resorcinols including synthetic derivatives. Although not aiming to synthesize hericenol A (**3**), the TBS protection and reduction of **1** provided hericenol A (**3**) as a minor product, along with the intended diol **94** and the TBS-migrated product **95** as major products.[25] The important observation here is that the phenolic TBS group can migrate to the neighboring hydroxyl group under hydride reduction conditions. In their divergent total syntheses, therefore, a relatively stable small protective group, such as the MOM group, was selected.

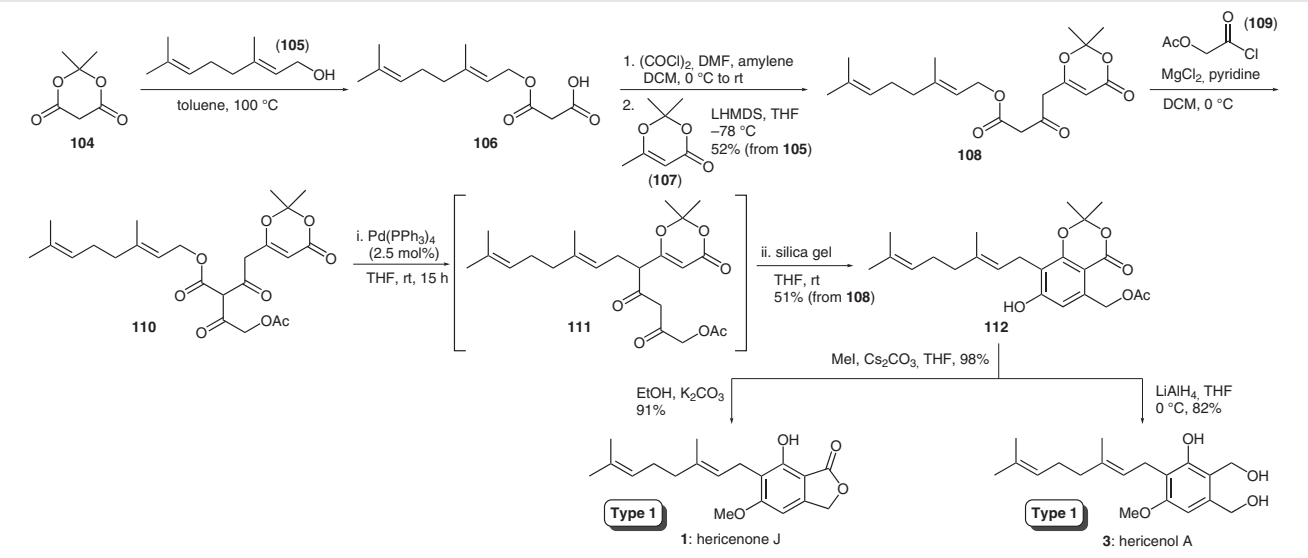
The Kobayashi group next targeted Type 6 geranyl-resorcinols, namely the hericenes A–C (**55**–**57**). Reduction of lactone **93** with $LiAlH_4$ followed by esterification under strictly controlled conditions afforded the mono-esters **96**–**98** in preference to their structural isomers. The remaining alcohol was then oxidized by virtue of nitroxy radical catalysis,[60] and the MOM group was removed carefully by dimethylboron bromide or titanium chloride to furnish the hericenes A–C (**55**–**57**).[25,55] Parallel experiments revealed that deprotection was facilitated by the presence of the *ortho* formyl group. They showed that hericenes B (**56**) and C (**57**), and their structural isomers in which the positions of fatty ester and aldehyde were inverted, exhibited neuroprotective effect against endoplasmic reticulum stress-dependent cell death.[25]

Hericerin of Type 3 was originally reported to possess an isoindolinone framework in which the carbonyl group orientates in the same direction as the phenolic hydroxyl group (i.e., **103** in Scheme 4).[40] To synthesize the reported hericerin structure directly, the common intermediate **93** was treated with 2-phenylethylamine (**100**) in the presence of n-Bu_3N at high temperature.[56] Lactamization and deprotection occurred simultaneously, providing the expected isoindolinone **103** in low yield. However, the NMR data of synthetic and natural products did not match, and the reported structure needed reassigned. In light of a selection of structure–chemical shift correlations for some isoindolinone molecules, the carbonyl group was predicted to be at the opposite side, same as the revised structure of hericenone A (**11**) (cf. Scheme 3). Migration of the carbonyl group was achieved by reduction of lactone **93** followed by oxidation of the resultant diol with silver carbonate on Celite. The separated major isomer **99** was reacted with **100** in the presence of trimethylaluminum to afford hydroxyamide **101**. The ring closure was achieved in a stepwise fashion via alcohol-chlorination and intramolecular N-alkylation. Finally, the MOM group was removed to give hericerin (**19**) whose spectral data were identical to those of the natural product. The same year as Kobayashi's synthesis, Miyazawa and co-workers reported the isolation of the same compound as the revised hericerin (**19**) from *H. erinaceus* and named it isohericerin.[33] Although the naming is a bit confusing, both 'hericerin' and 'isohericerin' should be accepted for the structure **19** according to the process of discovery.[61]

In 2012, Barrett and co-workers reported the total syntheses of hericenone J (**1**) and hericenol A (**3**), both of which are classified as Type 1, by employing a migratory geranylation–aromatization sequence as one of the key steps.[62] They started with the condensation of Meldrum's acid (**104**) with geraniol (**105**) under heating conditions (Scheme 5). The resulting malonic acid monoester **106** was converted into its acid chloride and reacted with lithiated dioxinone **107** to afford the keto ester **108**. In the formation of the acyl chloride, addition of excess amylene as an acid scavenger was crucial. Otherwise, hydrogen chloride adducts formed at the olefin near the geranyl terminus. The acetoxyacetyl unit was installed on **108** by a Claisen condensation with acyl chloride **109** in the presence of magnesium chloride and pyridine, providing diketo ester **110** that was ready for the key geranyl migration–aromatization reaction. Decarboxylative geranyl migration was achieved with a catalytic amount of $Pd(PPh_3)_4$ at room temperature. The intermediate **111** was subsequently treated with silica gel, inducing aromatization to **112** in one-pot. There are two points worth noting. One is that *E*-configuration of olefin in the geranyl chain survived at the migration step, although palladium-catalyzed geranylation reactions are known to give *E*/*Z* mixtures of products. The second point is that the efficiency of migration depends on the migratory group. Migration of the prenyl group completed within a few minutes at 0 °C in the presence of cesium carbonate and $Pd(PPh_3)_4$, while application of the same conditions to **110** resulted in



Scheme 4 Kobayashi's total syntheses of hericenone J, hericenol A, hericenes A–C, and revised hericerin (isohericerin)

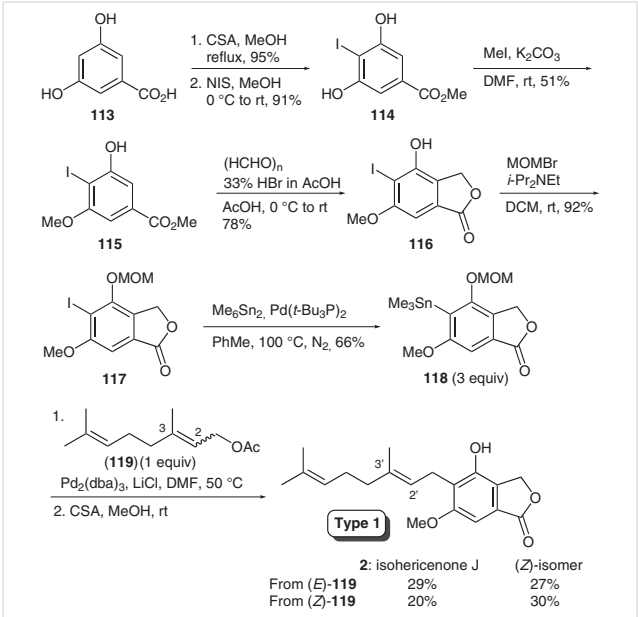


Scheme 5 Barrett's total syntheses of hericenone J and hericenol A

decomposition of the substrate. From a strategic point of view, it is remarkable that the entire geranyl-resorcinol framework was able to be constructed in short steps starting from non-aromatic substrates. From the product **112**, both hericenone J (**1**) and hericenol A (**3**) were synthesized via O-methylation followed by either deprotective lactonization or reduction.

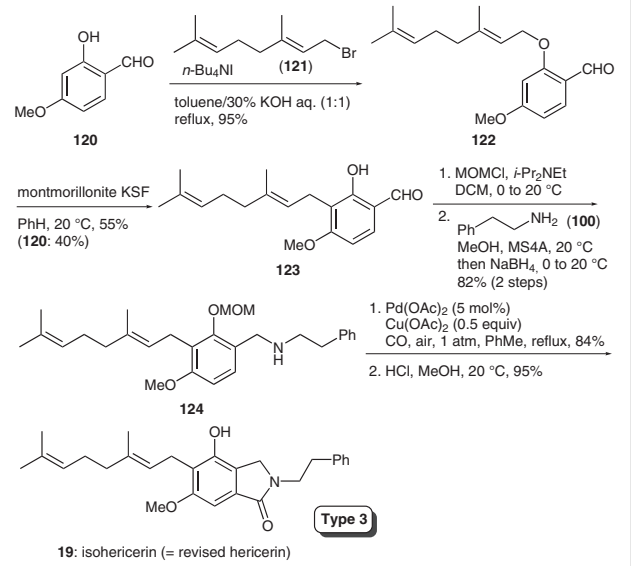
In 2020, Tang and co-workers reported the first total synthesis of isohericenone J (**2**), a Type 1 geranyl-resorcinol, with Stille coupling as a key reaction (Scheme 6).[63] 3,5-Dihydroxybenzoic acid (**113**) was chosen as starting material and converted into iodo-resorcinol **114** by esterification and regioselective iodination. After mono-methylation of **114**, lactonization was accomplished through a sequential hydroxymethylation and cyclization using paraformaldehyde and hydrobromic acid in acetic acid.[64] After MOM protection of phenol, aryl iodide **117** was converted into arylstannane **118** to examine its coupling with geranyl acetate (**119**). By optimizing reaction conditions with (*E*,*E*)-farnesyl acetate as a model coupling substrate, $Pd_2(dba)_3$ and DMF were selected as catalyst and solvent, respectively.[65] Although three equivalents of arylstannane **118** relative to **119** were required, the expected isohericenone J (**2**) was obtained in 29% yield after deprotection by CSA in methanol. It should be noted that both (*E*)- and (*Z*)-isomers formed even if an isomerically pure (*E*)- or (*Z*)-**119** was submitted to the coupling reaction.

In 2013, Gómez-Prado and Miranda reported a concise total synthesis of isohericerin (**19**), classified as Type 3, with a [1,3]-sigmatropic rearrangement (O→C rearrangement) and a carbonylative ring closure as key reactions (Scheme 7).[66] They commenced with O-geranylation of 2-hydroxy-4-methoxybenzaldehyde (**120**). The resulting geranyl ether **122** was treated with montmorillonite KSF in benzene, according to Dauben's conditions,[67] to afford the geranyl migration product **123** in 55% yield along with phenol **120** (40% recovery). After protection of phenol by the MOM group, a 2-phenylethylamino group was inserted by the reductive amination method, yielding the secondary amine **124** in 82% yield over two steps. By following Orito's method,[68] the carbonylative ring closure with palladium acetate and copper(II) acetate in an atmosphere of carbon monoxide containing air gave the desired isoindolinone in 84% yield. Intriguingly, a significant decrease in yield was observed under high carbon monoxide pressures. Final re-



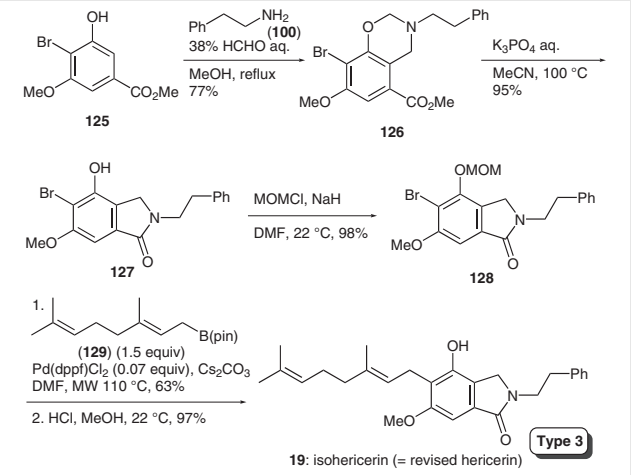
Scheme 6 Tang's total synthesis of isohericenone J

moval of the MOM group in acidic methanol provided isohericerin (**19**), the structure of which was unambiguously confirmed by X-ray crystallographic analysis.



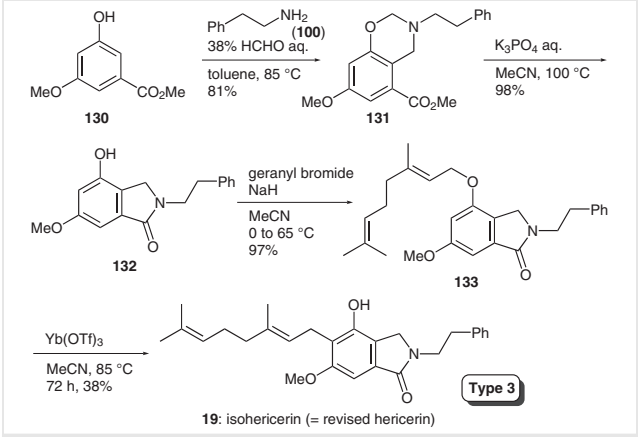
Scheme 7 Miranda's total synthesis of isohericerin

In 2017, Lee and co-workers reported total syntheses of three isoindolinone natural products classified as Types 3 and 4 by employing a sequential Mannich reaction and lactamization approach, and a Suzuki–Miyaura coupling reaction as key steps.[69] Scheme 8 summarizes the synthetic route to isohericerin (**19**). The synthesis began with the properly functionalized tetrasubstituted benzene **125**, which was subjected to a Mannich reaction with 2-phenylethylamine and formalin.[70] The *N*,*O*-acetal bond formation occurred concurrently with *ortho*-aminomethylation of phenol, providing oxazine **126** in 77% yield. The product **126** was then treated with aqueous potassium phosphate at 100 °C, resulting in the formation of lactam **127** in 95% yield. It is notable that cleavage of the *N*,*O*-acetal bond and the formation of lactam occurred in one-pot under the same basic conditions. After protection of phenol, the resulting aryl bromide **128** was coupled with geranyl boronate **129** under microwave irradiation conditions in the presence of $Pd(dppf)Cl_2$ and cesium carbonate. These optimized conditions produced the coupling product in 63% yield, which is noteworthy due to the challenge of using allylboron compounds in Suzuki–Miyaura reactions. Finally, the MOM group was removed by hydrogen chloride in methanol to yield isohericerin (**19**).



Scheme 8 Lee's total synthesis of isohericerin

In 2020, Liu and co-workers developed a shorter route to isohericerin (**19**) by taking advantage of the Lee's isoindolinone synthesis and Miranda's O→C rearrangement strategy (Scheme 9).[39] Starting from methyl 3-hydroxy-5-methoxybenzoate (**130**), isoindolinone **132** was constructed by a Mannich reaction and lactamization sequence, similar to Scheme 8.[69] The phenolic hydroxyl group of **132** was geranylated to give phenyl ether **133**, which was subjected to the O→C geranyl rearrangement similar to Scheme 7.[66] Although known activators such as montmorillonite and DIBAL-H were found ineffective, probably due to the presence of the electrophilic amide group in **133**, the use of ytterbium(III) triflate in acetonitrile promoted the rearrangement to give isohericerin (**19**). Although the yield was moderate, this seems the first example of using ytterbium(III) triflate as a promoter of the [1,3]-sigmatropic rearrangement. In addition to total synthesis, they undertook a transcriptome analysis and showed that **19** was an agonist of the proliferator-activated receptor γ (PPARγ).

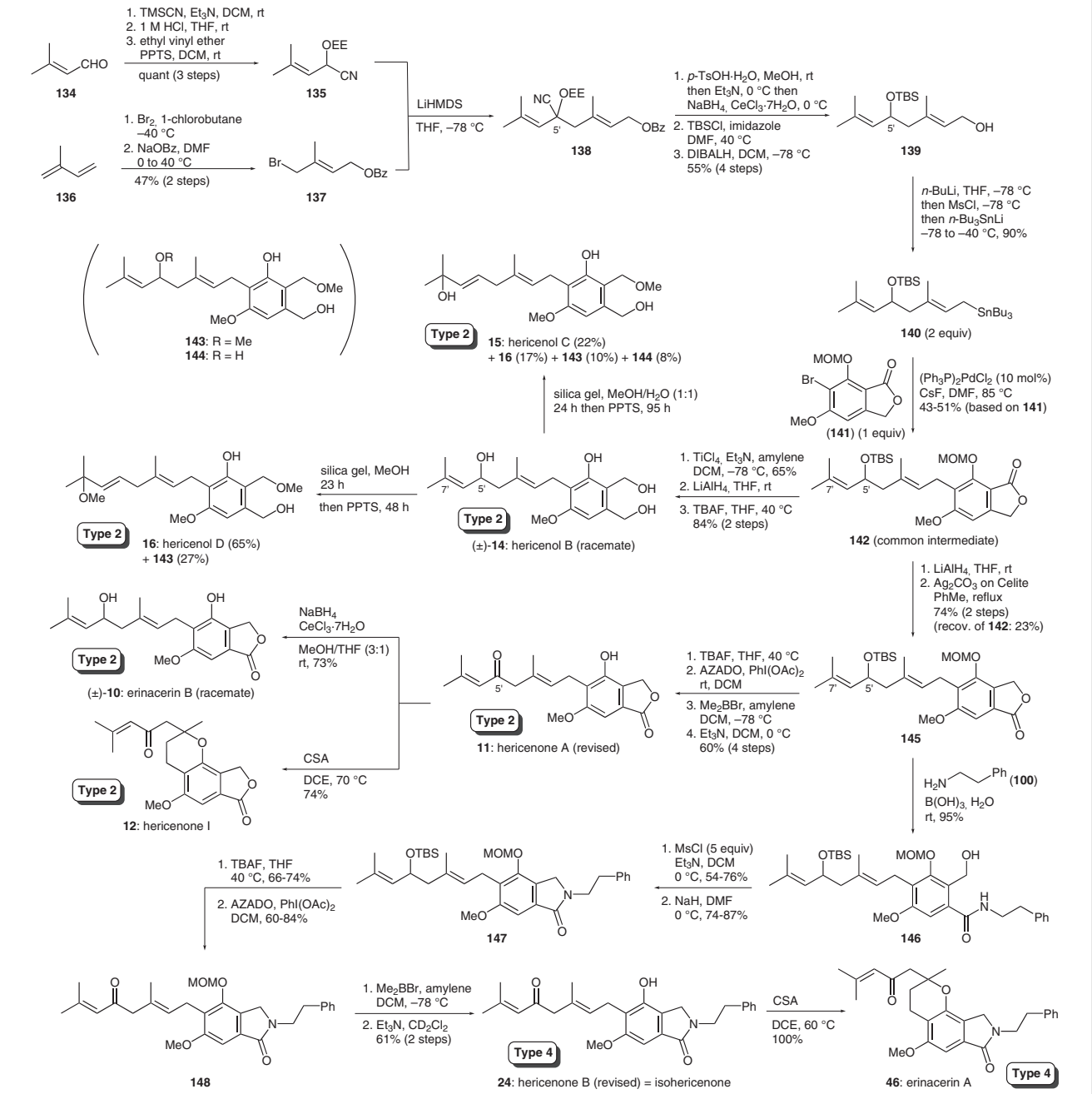


Scheme 9 Liu's total syntheses of isohericerin

4 Total Synthesis of Geranyl-Resorcinol with an Oxidized Geranyl-Derived Side Chain (Types 2, 4, and 7)

The presence of oxygen functional groups in the geranyl-derived side chain for natural products of Types 2, 4, and 7 needed new synthetic tactics to install them. In 2014,

the Kobayashi group succeeded in the divergent total syntheses of Type 2 and Type 4 geranyl-resorcinols having the oxygen functional groups at C5′ or C7′.[57] Scheme 10 shows a summary of the synthetic routes of eight geranyl-resorcinols. Initially, they sought to install the oxygen functional group of C5′ by following the dithiane-based method adopted in the synthesis of hericenone A by Rama Rao and Reddy (cf. Schemes 2 and 3)[52] and use Stille coupling reaction as previously shown by Scheme 4.[55] However, the initial plan was abandoned because of the failure of the coupling reaction with the dithiane substrate. Therefore, cyanohydrin chemistry was adopted.[71] The protected cyanohydrin **135** (EE = 1-ethoxyethyl) and allyl bromide **137** were prepared from 3-methylbut-2-enal (**134**) and isoprene (**136**) in three and two steps, respectively. The two segments were connected by alkylation with lithium hexamethyldisilazide, and the product **138** was converted into the C5′-silyloxy alcohol **139** via formation of ketone, 1,2-reduction, protec-



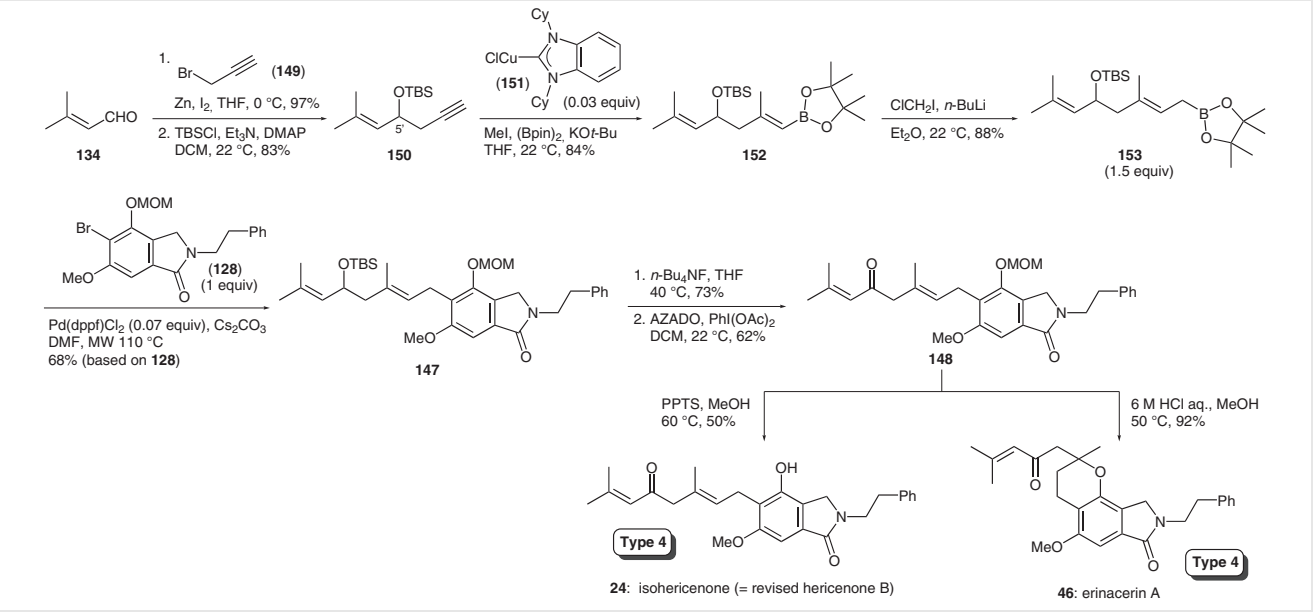
Scheme 10 Kobayashi's total syntheses of hericenols B–D, hericenones A, B, and I, and erinacerins A and B

tion of alcohol, and reductive cleavage of benzoate. One-pot stannylation of alcohol **139** gave allylstannane **140**, which was subjected to Pd coupling with phthalide **141**. Although the yield of the coupling product **142** was lower than that in the case of the C5′-deoxy substrate (cf. Scheme 4), the stable common intermediate **142** for several divergent total syntheses was provided reliably.

With the common intermediate **142**, the syntheses of hericenols B–D were undertaken, despite being metabolites of a *Stereum* species,[48] not *Hericium* species. Since the allylic ether moiety (C5′–C7′) in **142** was labile under acidic conditions, O-MOM deprotection was carefully performed with titanium chloride and triethylamine in the presence of amylene as an acid scavenger. Next, the lactone was reduced with lithium aluminum hydride and the TBS group was removed by tetrabutylammonium fluoride to provide hericenol B (**14**) as a racemate. The Kobayashi group proposed that hericenols C (**15**) and D (**16**) could be obtained from hericenol B (**14**) based on their experimental findings. Hence, treatment of **14** with silica gel and subsequently a weak acid (PPTS: pyridinium *p*-toluenesulfonate) in methanol or methanol/water, gave rise to hericenol D (**16**) in 65% yield from a methanol solution, and hericenol C (**15**) in 22% yield from a methanol/water solution, along with byproducts such as **143** and **144**. It is likely that nucleophilic allylic substitution occurred at mainly C7′ and methanol also added to a benzylic position via an *ortho*-quinone methide intermediate produced by elimination of water. These experimental results suggest that hericenols C (**15**) and D (**16**) are artifacts resulting from degradation of hericenol B (**14**) during isolation, since methanol/water is used in the purification process of natural products by HPLC.[48]

Back to intermediate **142**, the lactone carbonyl group was inverted as before (cf. Scheme 4) and a four-step conversion (including desilylation, oxidation, removal of MOM, and β-elimination of C7′-bromide that was partially formed in the third step) afforded the revised structure of hericenone A (**11**). 1,2-Reduction of **11** with a combination of sodium borohydride and cerium(III) chloride gave racemic erinacerin B (**10**), which was unstable in $CDCl_3$ because of the high reactivity of the allylic alcohol moiety in the side chain. Moreover, acid-catalyzed cyclization of **11** yielded hericenone I (**12**). The mechanism from **11** to **12** involves olefin isomerization and intramolecular oxy-Michael addition, not a direct 6-*endo* cyclization (the mechanism will be discussed in Scheme 13).

The isoindolinone natural products, hericenone B (**24**) and erinacerin A (**46**), were also synthesized from intermediate **145**. Although direct lactamization or amidation with trimethylaluminum on **145** failed, application of milder amidation conditions with boronic acid[72] afforded the amide-alcohol **146** in 95% yield. Ring closure was achieved in a stepwise fashion,[56] and the resulting isoindolinone **147** was converted into hericenone B (**24**) using the same procedure as described from **145** to **11**. It is important that the structure of hericenone B (**24**) was revised as the carbonyl regioisomer of the original structure,[27] as was the case for hericenone A (**11**) and hericerin (**19**). Prior to Kobayashi's total synthesis, the Lee group isolated compound **24** from *H. erinaceus* and named it isohericenone.[43] Again the naming issue is a bit inconsistent, but both 'hericenone B' and 'isohericenone' should be accepted for structure **24**. If the carbonyl regioisomer of **24** is discovered in the future, it is advisable to allocate a different name other than herice-



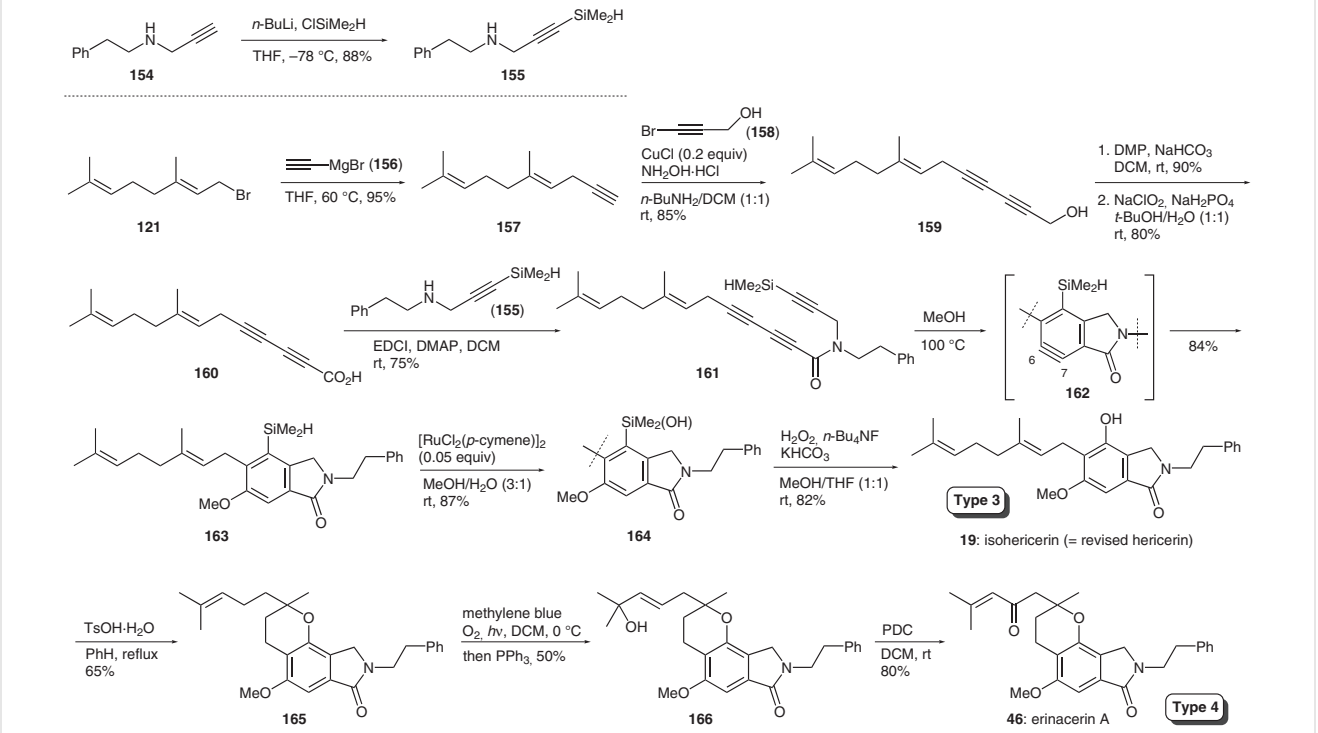
Scheme 11 Lee's total syntheses of isohericenone and erinacerin A

none B. Finally, hericenone B (**24**) was converted into erinacerin A (**46**) quantitatively by acidic cyclization. Overall, Kobayashi's systematic total syntheses clarified the structural and biosynthetic correlations of geranyl-resorcinols.

In addition to the total synthesis of isohericerin (cf. Scheme 8), Lee and co-workers reported the total synthesis of isohericenone (**24**) (i.e., revised hericenone B) and erinacerin A (**46**) utilizing a Suzuki–Miyaura coupling strategy in 2017 (Scheme 11).[69] The oxygen-containing geranyl segment **153** was prepared from aldehyde **134** and propargyl bromide (**149**) in four steps. Addition of the propargylzinc reagent to **134** followed by protection of the resultant hydroxyl group by TBS afforded alkyne **150**. The conversion of **150** into allylic boronate **153** needed extensive optimization of the reaction conditions. The initial attempt was carboalumination of **150** followed by trapping of the alkenylaluminum intermediate by formaldehyde to give an allylic alcohol. However, less than 2% yield of the allylic alcohol was obtained due to decomposition of substrates under the harsh reaction conditions. Therefore, alternative mild conditions were investigated to efficiently synthesize the boronate **153** from **150**. Eventually, the copper-catalyzed methylboronation with methyl iodide and bis(pinacolato)diboron as developed by Tortosa was applied.[73] Although the original conditions using catalytic amounts of copper(I) chloride and Xantphos ligand gave **152** in 33% yield, application of N-heterocyclic carbene based copper catalysts, in particular the use of BenzICyCuCl **151** (3 mol%) in the presence potassium *tert*-butoxide, gave rise to **152** in 84% yield with high stereo- and regioselectivities. It is noteworthy that a variety of methylated *E*-alkenylboronates were synthesized from the corresponding terminal alkynes in good yields by this modified methylboronation conditions.

The resulting alkenylboronate **152** was converted into allylic boronate **153** by a Matteson homologation reaction[74] with chloroiodomethane and *n*-butyllithium. The Suzuki–Miyaura coupling reaction of **153** with the functionalized isoindolinone **128** proceeded in 68% yield, which was comparable with the coupling of the unoxidized geranyl boronate (cf. Scheme 8). Removal of the TBS group followed by alcohol-oxidation afforded ketone **148**. Although deprotection in the final step was slightly problematic due to competing cyclization to erinacerin A (**46**) under acidic conditions, the use of pyridinium *p*-toluenesulfonate (PPTS) as a mild acid at 60 °C provided isohericenone (**24**) in 50% yield. Alternative treatment with 6 M hydrochloric acid at 50 °C afforded erinacerin A (**46**) in 92% yield.

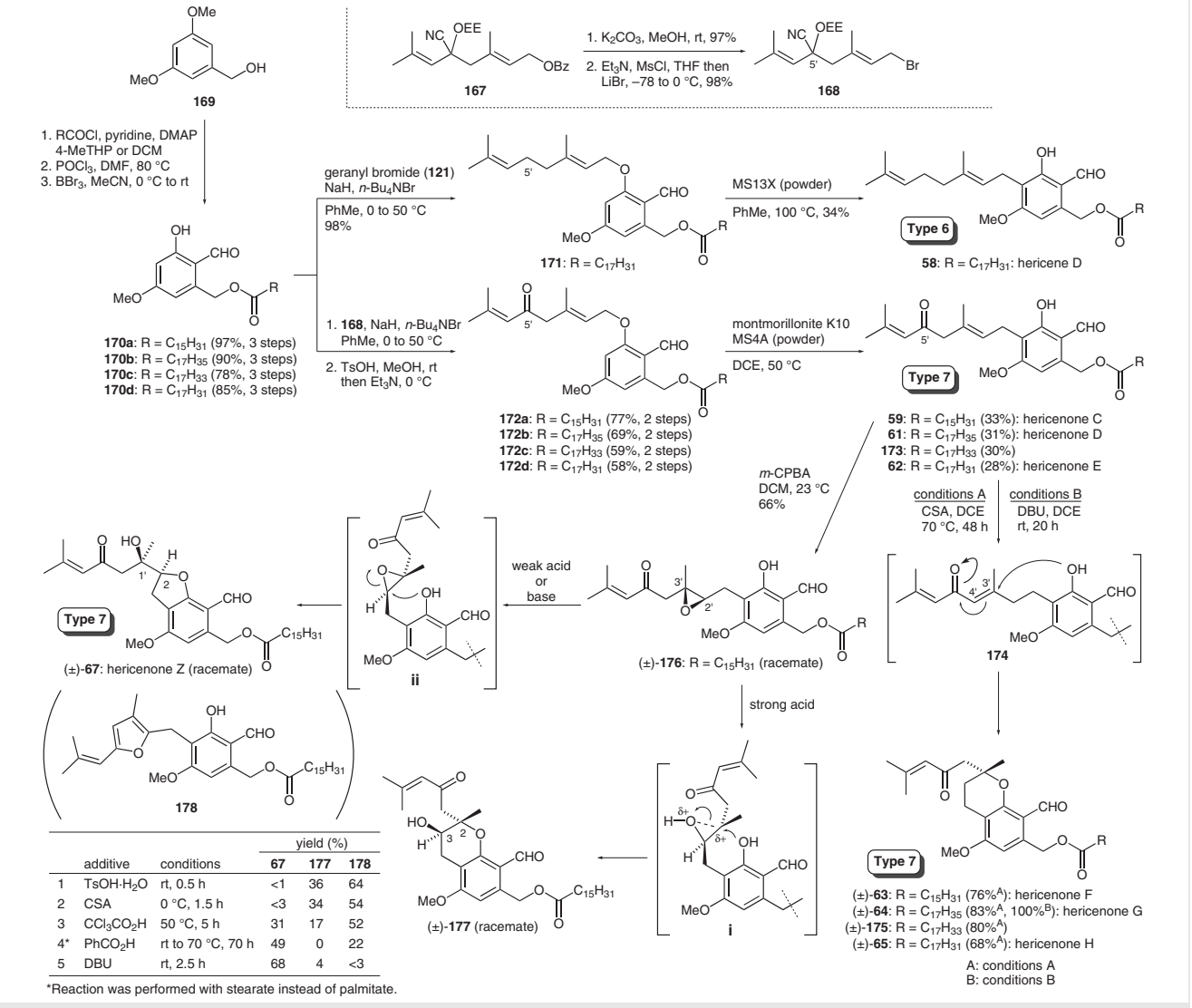
In 2021, Hoye and co-workers reported a unique approach to the isoindolinone framework of Type 3 and Type 4 geranyl-resorcinols from an acyclic amide-triyne intermediate utilizing a hexadehydro-Diels–Alder reaction (Scheme 12).[75] Their synthesis began with introduction of the alkyne part to geranyl bromide (**121**) by a Grignard reaction. The resulting dienyne **157** was subjected to a Cadiot–Chodkiewicz cross-coupling reaction with 3-bromoprop-2-yn-1-ol (**158**) to provide the conjugated diyne **159**.



Scheme 12 Hoye's total syntheses of isohericerin and erinacerin A

The terminal alcohol of **159** was oxidized to carboxylic acid **160** in a stepwise fashion and condensed with the secondary amine **155**, which was prepared from amino alkyne **154** in a single step, to provide the key amide-triyne intermediate **161**. Heating a solution of **161** in methanol at 100 °C for 4 h provided the expected isoindolinone **163** in 84% yield. The regioselectivity for methanol addition is rationalized by the electrophilic nature of C6 in the *o*-benzyne **162**, based on density functional theory calculations by which the distortion angle reflecting the electrophilicity is larger in C6 than in C7. The next step, conversion of arylsilane into phenol by a Fleming–Tamao–Kumada oxidation, required the careful tuning of silyl substituents. Eventually, a two-step method was adopted, involving conversion of silane **163** into silanol **164** with a ruthenium catalyst in methanol/water[76] followed by oxidation to phenol **19** with hydrogen peroxide and tetrabutylammonium fluoride, by reference to Anderson's studies.[77] This two-step conversion afforded isohericerin (**19**), a Type 3 geranyl-resorcinol, in 71% overall yield from **163**.

Next, Hoye and co-workers set out to convert isohericerin (**19**) into erinacerin A (**46**). Treatment of **19** with *p*-toluenesulfonic acid monohydrate under the reflux conditions gave the cyclization product **165** in 65% yield, along with two diastereomeric tetracyclic byproducts where two double bonds in the geranyl chain reacted. Oxidation of the side chain was achieved via a singlet oxygen based ene reaction. The generated hydroperoxide was reduced with triphenylphosphine, yielding allylic alcohol **166** in 50% yield. Finally, oxidation of **166** with pyridinium dichromate (PDC) afforded erinacerin A (**46**), a Type 4 geranyl-resorcinol. It is noteworthy that the oxygen functional group in



	additive	conditions	yield (%) 67	177	178
1	$TsOH·H_2O$	rt, 0.5 h	<1	36	64
2	CSA	0 °C, 1.5 h	<3	34	54
3	CCl_3CO_2H	50 °C, 5 h	31	17	52
4*	$PhCO_2H$	rt to 70 °C, 70 h	49	0	22
5	DBU	rt, 2.5 h	68	4	<3

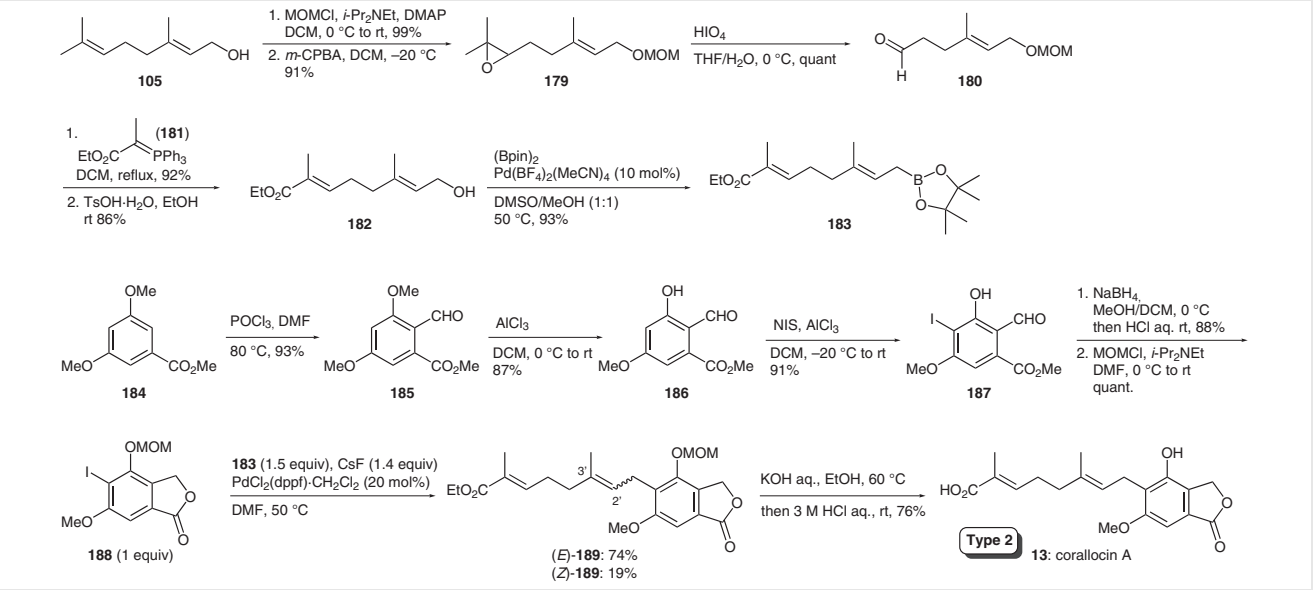
*Reaction was performed with stearate instead of palmitate.

Scheme 13 Kobayashi's total syntheses of hericenones C–H and Z

the side chain was introduced at a late stage of the synthesis, enabling conversion from Type 3 into Type 4 natural products.

In 2021, the Kobayashi group reported divergent total syntheses of the fatty ester-containing geranyl-resorcinols classified as Type 7 for the first time (Scheme 13).[78] Since it was found impractical to make Type 7 molecules by previous strategies (cf. Schemes 4 and 10), due to moderate coupling yields, poor regioselectivity in esterifications, and functional group incompatibilities, an alternative strategy relying on the O→C geranyl rearrangement with substrates preinstalled with fatty ester components was developed. 3,5-Dimethoxybenzyl alcohol (**169**) was chosen as a starting material and first condensed with four kinds of acyl chlorides. The resulting esters were converted into the formylated phenols **170a–170d** by a regioselective Vilsmeier–Haack formylation and demethylation with boron tribromide. Before addressing the synthesis of Type 7 compounds, the rearrangement of a C5′-deoxo derivative **171** corresponding to Type 6 was investigated. After extensive trials of solid additives, the addition of powdered molecular sieves 13X (MS13X) was found to promote the O→C rearrangement, giving rise to hericene D (**58**) in 34% isolated yield. Remarkably, the Type 6 geranyl-resorcinol was prepared in only five steps from commercially available substrate **169**, which is a significant improvement over the first-generation synthesis (cf. Scheme 4). Based on this success, rearrangement of the C5′-oxo geranyl ethers **172a–172d**, prepared by the O-geranylation of **170a–170d** with allylic bromide **168**, was surveyed. Although hericenone C (**59**) formed under the optimized conditions with MS13X, cyclization to hericenone F (**63**) was partially accompanied by rearrangement, necessitating re-optimization of the reaction conditions. After various attempts, the combined use of montmorillonite K10 and powered molecular sieves 4Å (MS4A) in dichloroethane (DCE) at 50 °C produced hericenones C–E (**59**, **61**, and **62**) and the oleoyl analogue **173** in approximately 30% isolated yields. Although yields were modest due to side reactions involving [1,5]-geranyl rearrangement and elimination giving phenols **170a–170d**, it is noteworthy that more functionalized Type 7 geranyl-resorcinols were synthesized with the minimal use of protective groups in a straightforward manner.

Next, the Kobayashi group surveyed the cyclization propensities of hericenones C–E to generate other family members. Specifically, hericenones F–H and 3-hydroxyhericenone F (later revised as hericenone Z) are proposed to be biosynthetically generated from hericenones C–E. In practice, under acidic conditions with (+)-10-camphorsulfonic acid (CSA) (conditions A), cyclization progressed gradually at 70 °C to give hericenones F–H (**63**, **64**, and **65**) and the oleoyl analogue **175** in 68–83% yields. When the reaction was carried out under basic conditions with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (conditions B), cyclization occurred at room temperature, even at 0 °C, yielding hericenone G (**64**) quantitatively. Detailed NMR spectroscopic analyses revealed that cyclization does not proceed through a concerted 6-*endo* fashion but through olefin isomerization and intramolecular oxy-Michael addition via intermediate **174**. Promotion of cyclization by a C5′-ketone accounts for the occurrence of keto-containing cyclic natural products in Types 2, 4, and 7 (cf. Figure 2). In contrast, the ketone-free cyclic geranyl-resorcinols classified as Types 1, 3 and 6 have not yet been found in nature.



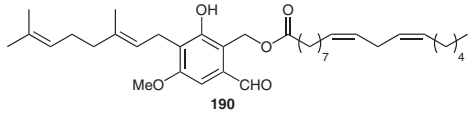
Scheme 14 Sugita's total synthesis of corallocin A

Finally, a biomimetic conversion from hericenone C (**59**) into 3-hydroxyhericenone F (**177**) was investigated. The racemic C2′–C3′ epoxide **176** was prepared by treating **59** with *m*-chloroperbenzoic acid (*m*-CPBA) in 66% yield. Since S_N1-like cyclization (formal 6-*endo* cyclization) giving 3-hydroxyhericenone F is expected under acidic conditions via intermediate **i**, stronger organic acids such as $TsOH·H_2O$ and CSA were tested first. The expected 6-*endo*-type cyclization product **177** formed in 34–36% yield, together with the furan derivative **178** (54–64% yield). However, the NMR data of **177** did not match those of the natural product. To identify the actual structure of natural product, other cyclization conditions were therefore explored. When weak acid (benzoic acid) or base (DBU) was used, the 5-*exo*-cyclization product **67** was generated preferentially, presumably via conformation **ii**. The spectral data of **67** were all identical to those of the isolated compound,[24] which unambiguously determined the structure of the natural product. The Kobayashi group named the revised structure **67** as 'hericenone Z'. Kawagishi and co-workers reported that the natural product, revised as **67**, was isolated in racemic form, as based on CD spectrum data,[24] although this finding could be argued due to enzymatic epoxidation in nature usually giving chiral epoxides. Overall, Kobayashi's synthesis followed putative biosynthetic pathways and clarified structural correlation and reactivities of Type 7 geranyl-resorcinols.

In 2021, Sugita and co-workers reported the first total synthesis of corallocin A (**13**), a Type 2 geranyl-resorcinol with an oxygen functional group at the geranyl terminus, by use of Suzuki–Miyaura coupling as the key reaction (Scheme 14).[79] The geranyl segment **183** was prepared from geraniol (**105**) in six steps. After protection of **105**, regioselective epoxidation and oxidative cleavage of epoxide afforded the aldehyde **180**. *E*-Selective Wittig reaction with phosphorus ylide **181** and deprotection afforded alcohol **182**. The conversion of **182** into boronate **183** was realized in 93% yield by the treatment with bis(pinacolato)diboron in the presence of catalytic $Pd(BF_4)_2(MeCN)_4$.[80] Meanwhile, the phthalide core **188** was prepared from methyl 3,5-dimethoxybenzoate (**184**) in 5 steps. Vilsmeier–Haack formylation and cleavage of methyl ether afforded the formylated phenol **186** regioselectively. Iodination of **186** with *N*-iodosuccinimide and aluminum chloride proceeded selectively at the *ortho* position of the phenol,[81] yielding aryl iodide **187** in 91% yield. Sequential treatment of **187** with sodium borohydride and hydrochloric acid promoted reduction and lactonization in one-pot, providing the requisite phthalide core **188** after MOM protection. The key coupling reaction between **188** and **183** was significantly affected by the choice of palladium catalyst, base, and temperature. Under optimized conditions with $PdCl_2(dppf)·CH_2Cl_2$ and cesium fluoride at 50 °C, the desired coupling product (*E*)-**189** was produced in 74% yield without formation of the reduction product. Olefin isomerization at C2′–C3′ occurred partially under the coupling conditions and (*Z*)-**189** was generated in 19% yield. After separation of isomers by preparative HPLC, the ethyl ester of (*E*)-**189** was hydrolyzed with potassium hydroxide and the MOM group was removed with hydrochloric acid to complete corallocin A (**13**).

5 Conclusion

This short review summarizes the total syntheses of tetraketide-based meroterpenoids, namely geranyl-resorcinols, isolated mainly from *H. erinaceus* known as an edible medicinal mushroom. These molecules are believed to contribute to a variety of medicinal functions of mushrooms, and even now, new members of the geranyl-resorcinol family are being discovered and their biological activities evaluated. By organization of published papers, approximately seventy geranyl-resorcinols found in mushrooms have been grouped into seven types based on assumed biosynthetic pathways and structural correlations. Some of the total syntheses have led to confirmation of the biosynthetic pathways and revision of misassigned structures of natural products. Since the isolation of specific ingredients in large quantities from random mushroom components or collections is not easy, chemical synthesis offers an important means to provide and advance materials for various studies. Besides total synthesis, analogue synthesis opens the possibility of using mushroom ingredients as bioactive sources for drug discovery and health supplement research. For instance, the synthetic analogue of hericene D (**190**) with a linoleate ester at the *ortho* position of the phenol showed stronger neuroprotective effect than other natural hericenes and hericenones (Figure 3),[78] which suggests that rational molecular design based on the structure-activity relationships may lead to improved biological properties. Since the structures of geranyl-resorcinols are relatively less complex than other natural terpenoids or polyketides of fungi-origin, more practical synthetic routes able to provide various structural types are anticipated in the future[82]. In the short term, new synthetic and bioactivity studies of yet-to-be-synthesized natural products, such as the amino acid hybrids of Type 4, like the erinacerins and caputmedusins, are anticipated to provide interesting insights into the geranyl-resorcinol family of natural products.



190
neuroprotective effect at 3 μM
against endoplasmic reticulum-stress dependent cell death

Figure 3 A synthetic analogue showing stronger biological activity than the parent natural product.

Conflict of Interest

The authors declare no conflict of interest.

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