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Total syntheses and endoplasmic reticulum stress suppressive activities of hericenes A–C and their derivatives

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ABSTRACT

We report the syntheses and neuroprotective activities of hericenes and their derivatives against endoplasmic reticulum (ER) stress-dependent cell death. Four natural products, including hericenes A–C and hericenol A, and five synthetic derivatives were synthesized and their protective activities were evaluated. In designing the synthetic derivatives, we focused on the binding position of the fatty chain. Hericenes B and C showed moderate protective activity against thapsigargin-induced ER stress-dependent cell death. In contrast, their regioisomers (with respect to the position of the fatty chain) exhibited higher protective activity against tunicamycin-induced ER stress. This study clearly shows that the number and the binding position of the fatty chain are critical for protective activity against ER stress-dependent cell death.

Hericium erinaceum, an edible mushroom named Yamabushitake in Japan, Houtouku in China, and Lion's Mane Mushroom in Europe, is known as a medicinal food that is effective for the prevention of various diseases, including cancer, inflammation, diabetes, immune disorders, and dementia.[1] Its unique and broader medicinal effects have stimulated many scientists to elucidate the structures and compositions of its bioactive components and their modes of actions.[2] Among its reported medicinal virtues, the observed anti-dementia effect is specific to this mushroom.[1d–f] Kawagishi et al. showed in a pioneering study that hericenones C–E isolated from the fruiting bodies of *H. erinaceum* stimulate mouse astrocytes to produce nerve growth factor (NGF), a neurotrophic factor responsible for the growth, maintenance, and survival of neurons.[3] In 2014, the Sabaratnam group independently demonstrated that hericenones C–E increased NGF levels in culture medium and potentiated neurite outgrowth in PC12 cells when induced with a low concentration of NGF.[4]

Kawagishi and one of the authors of this paper reported the neuroprotective effect of 3-hydroxyhericenone F (**1a**) against endoplasmic reticulum (ER) stress-dependent cell death (Fig. 1).[5] The ER is the major organelle responsible for Ca^{2+} storage and release, as well as protein synthesis, folding, and export. Accumulation of unfolded or misfolded proteins and alterations in calcium homeostasis lead to a disturbance in ER function, which is collectively called ER stress.[6] While various signal transduction pathways, including the unfolded protein response, are activated in response to ER stress, intense and prolonged ER stress ultimately leads to apoptosis.[7] A number of pathological analyses suggest that ER stress is involved in neurodegenerative disorders.[8] Therefore, ER stress suppressive compounds that enhance neuronal cell viability have attracted attention for the prevention and treatment of neurodegenerative disorders such as Alzheimer's, Parkinson's, and prion diseases.[9]

Structurally, 3-hydroxyhericenone F (**1a**) consists of a poly-substituted chromane core and a palmitate chain (Fig. 1). It can be assumed that hericenone C (i.e., 5′-oxohericene A, **1b**) is a biosynthetic precursor of **1a** and the tetrahydropyran ring is constructed by epoxidation of the C2′–C3′ double bond, followed by 6-*endo* cyclization. Another characteristic of **1a** is the presence of a hydroxyl group at C3, which is not found in other naturally-occurring geranyl resorcylates.[1b,2] Of the fungal-derived geranyl resorcylates isolated to date, only **1a** has been shown to possess cytoprotective activity against ER stress-dependent cell death.[5] It remains unknown if other geranyl resorcylates possess similar protective activities.[10] Hence, we undertook a synthesis and structure-activity relationship (SAR) study to clarify the fundamental structure critical for cytoprotective activity, and to discover novel drug

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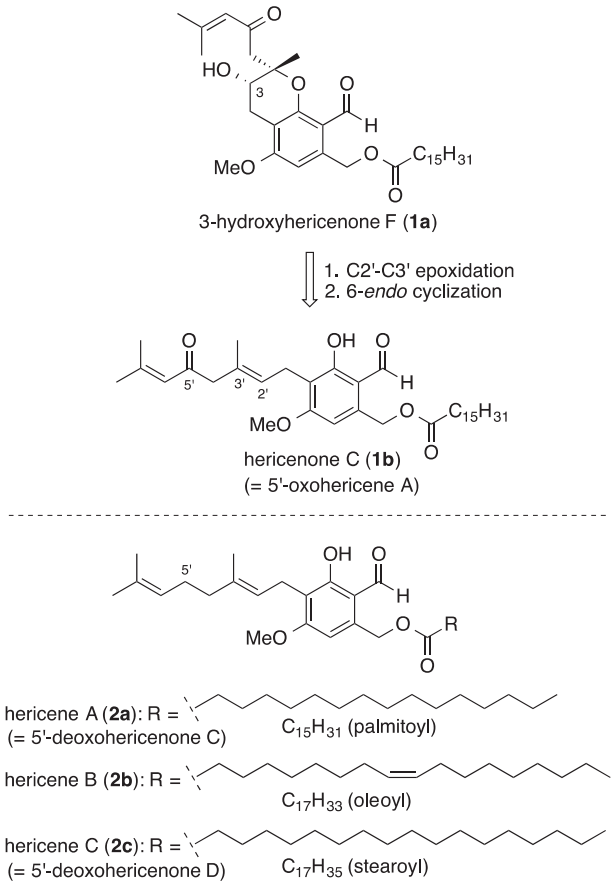


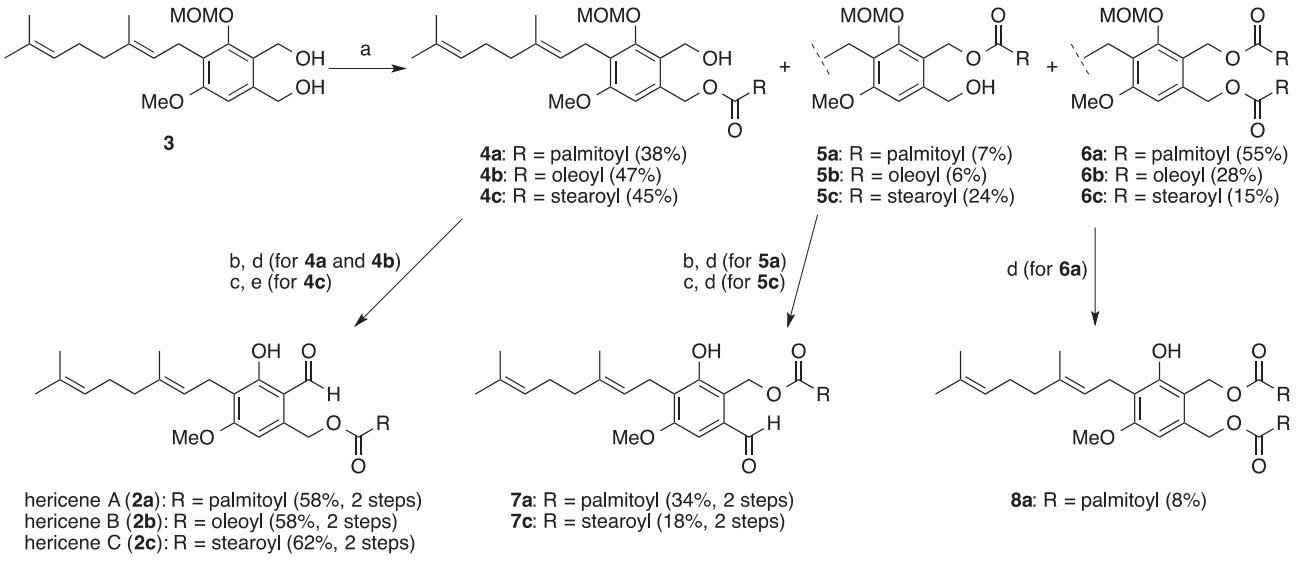
Fig. 1. Structures of 3-hydroxyhericenone F (**1a**), hericenone C (**1b**) and hericenes A–C (**2a–c**).

lead compounds that can suppress ER stress-dependent cell death. Herein, we report the synthesis and neuroprotective activity of hericenes A–C (5′-deoxohericenones) (**2a–c**) and their derivatives. The results show that the number and the binding position of the fatty chain are important for protective activity.

In 2011, we reported the first total syntheses of hericenone J and hericene A (5′-deoxohericenone C, **2a**), using $CuBr_2$-mediated one-pot phthalide formation and Stille coupling as key reactions.[11,12] In the present study, the common intermediate **3**[11] was prepared using our established method (Scheme 1). Esterification of **3** with various acid chlorides afforded monoesters **4a–c** (38–47%), along with their regioisomers **5a–c** (6–24%) and diesters **6a–c** (15–55%). Importantly, these reactions were initiated at low temperature to suppress diesterification. In addition, LiCl was added with the expectation that one of the hydroxyl groups would be deactivated by lithium-mediated chelation with a MOM-oxygen. Although the effect was subtle, the natural-type compounds **4a–c** prevailed over their regioisomers **5a–c**.[13] Oxidation[14,15] of **4a–c** followed by deprotection[11,16] afforded hericenes A–C (**2a–c**) in 58–62% yield over two steps. Similarly, two selected regioisomers (**7a** and **7c**) and diester **8a** were synthesized from **5a**, **5c**, and **6a**, respectively. It is noted that in the synthesis of **2a–c**, deprotection was facilitated by the presence of the ortho formyl group, which could coordinate with the Lewis acid, whereas this interaction was absent in the case of the regioisomers (**7a** and **c**) and diester **8a**. The low solubility of **6a** in CH_2Cl_2 at low temperature may also account for the unsatisfactory formation of **8a**.

To circumvent this deprotection issue, the regioisomer of hericene B (**7b**) and its diester derivative (**8b**) were prepared by changing the phenolic protective group (Scheme 2). Thus, the phenolic hydroxyl group of hericenone J (**9**), synthesized previously,[11] was protected as its TBS ether and the lactone moiety was reduced with $LiAlH_4$. Unexpectedly, the phenolic TBS group migrated to the primary alcohol and the regioisomeric alcohol **11** predominated over the expected product **10**. Furthermore, the fully deprotected triol **12** (i.e., hericenol A[17]) was isolated in 21% yield, which represents the second total synthesis of this molecule.[18] The alcohol **10** was then esterified with oleoyl chloride and converted into hericene B (**2b**), the regioisomer **7b**, and diester **8b**.[19]

With these natural and synthetic hericenes in hand, a cell protection assay was carried out using murine neuroblastoma cell line (Neuro2a).[9e] Tunicamycin (TM), an inhibitor of *N*-linked glycosylation in the ER, and thapsigargin (TG), an inhibitor of sarcoplasmic/endoplasmic reticulum Ca^{2+}-ATPase, were used as inducers of ER stress.[6,20] In a typical experiment, Neuro2a cells were incubated with various concentrations of compounds (**2a–c**, **7a–c**, **8a**,**b** and



Scheme 1. Syntheses of hericenes A–C (**2a–c**) and their derivatives (**7a**, **7c** and **8a**). Reagents and conditions: (a) RCOCl, pyridine, LiCl, THF, −78 or −30 °C to −30 ~ 0 °C; (b) 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), $PhI(OAc)_2$, CH_2Cl_2, rt; (c) 2-azaadamantane *N*-oxyl (AZADO), $PhI(OAc)_2$, CH_2Cl_2, rt; (d) Me_2BBr, amylene, CH_2Cl_2, −78 °C; (e) $TiCl_4$, 2,6-di-*tert*-butyl-4-methylpyridine, CH_2Cl_2, −78 to −30 °C.