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Total synthesis of riccardin C and (±)-cavicularin via Pd-catalyzed Ar–Ar cross couplings

Kenichi Harada [a], Kosho Makino [a], Naoki Shima [a], Haruka Okuyama [a], Tomoyuki Esumi [a], Miwa Kubo [a], Hideaki Hioki [b], Yoshinori Asakawa [a], Yoshiyasu Fukuyama [a,*]

[a] Faculty of Pharmaceutical Sciences, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan
[b] Faculty of Education, Gunma University, Maebashi, Gunma 371-8510, Japan

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ABSTRACT

Riccardin C, a specific LXRα agonist, is a representative macrocyclic bisbibenzyl-type natural product. As part of our synthetic studies on macrocyclic bisbibenzyls, the synthesis of riccardin C and its analog cavicularin was examined. The total synthesis of riccardin C was accomplished via a Pd-catalyzed intramolecular Suzuki–Miyaura coupling as the key macrocyclization step. This synthetic strategy was also extended in the synthesis of (±)-cavicularin, which was then attained by constructing the dihydrophenanthrene moiety using a Pd-catalyzed Ar–Ar coupling reaction.

1. Introduction

Macrocyclic bisbibenzyls are natural products that occur mainly in liverworts and feature two bibenzyl structures double-linked by ether bonds and/or biphenyl bonds. It is known that macrocyclic bisbibenzyl compounds exhibit a variety of biological activities.[1] Riccardin C (**1**), originally isolated from *Reboulia hemisphaerica*, is a representative bisbibenzyl compound with notable biological activity[2] (Fig. 1). Compound **1** was found to bind directly to the liver X receptor α (LXRα), a member of the nuclear receptor super family, leading to the activation of LXRα/RXR-dependent reporter gene transcription.[3] Interestingly, riccardin C acts as an antagonist, not an agonist, of LXRβ. Moreover, it has no ability to activate other nuclear receptors, such as PPARγ, RARα, RARβ, RARγ, FXR, and RXRα, and increases LXR-target gene expression in macrophages. On the basis of these results, **1** has been expected to be a lead compound for the treatment of cardiovascular-related diseases, such as arteriosclerosis, because LXRs are thought to regulate cholesterol metabolites.

Investigation of the structure–activity relationships of **1** is a current important assignment, and riccardin C analogs and derivatives are also expected to be LXRα agonist candidates.[3,4] In particular, highly strained cavicularin (**2**), which is assumed to be biosynthetically formed via an intramolecular oxidative coupling between the 3′ and 10′ positions of riccardin C, has attracted

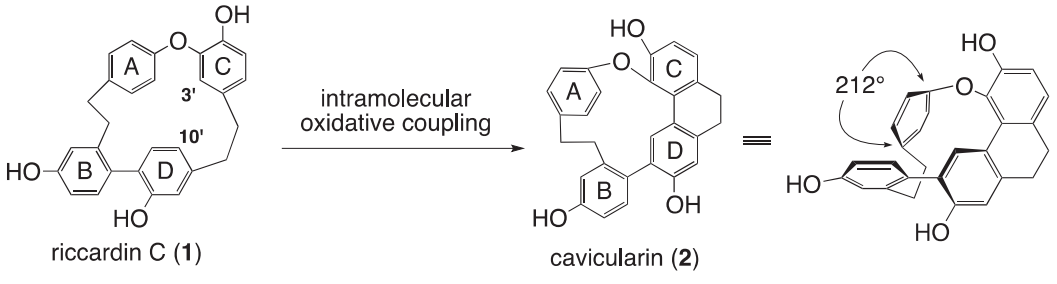

Fig. 1. Structures of riccardin C (**1**) and cavicularin (**2**).

* Corresponding author. Tel.: +81 88 602 8435; fax: +81 88 655 3051; e-mail address: fukuyama@ph.bunri-u.ac.jp (Y. Fukuyama).

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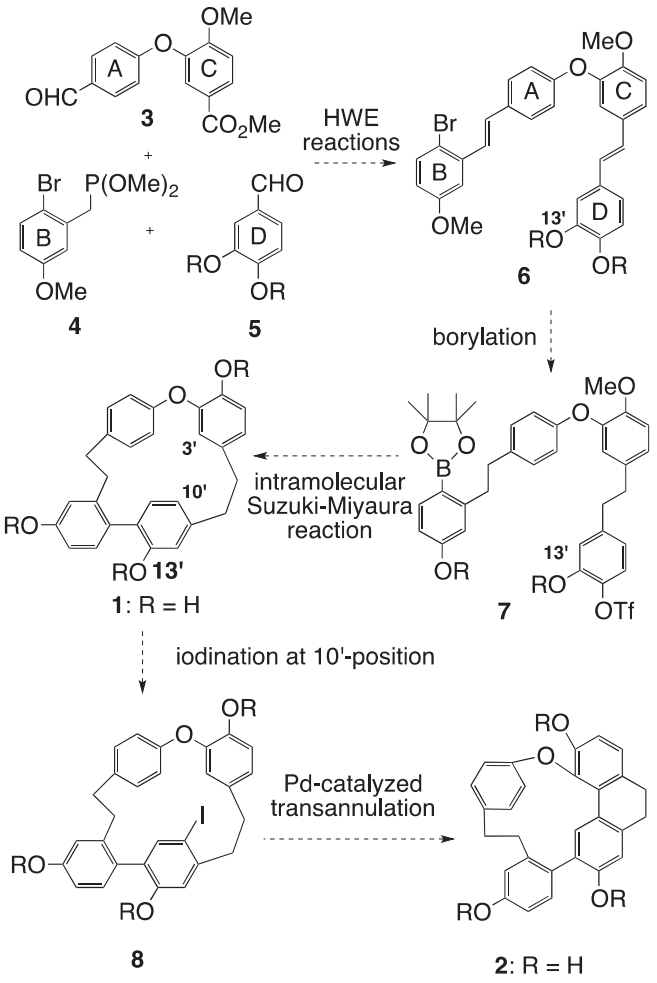
attention as not only a biologically active compound,[1a] but also a synthetic target. Cavicularin was isolated from the liverwort *Cavicularia densa* by Toyota and Asakawa in 1996[5] and is one of the most interesting natural products from a synthetic perspective (Fig. 1). The rigid cyclophane structure of **2** causes benzene ring A to bend into a boat-like form with a dihedral angle of 212°; therefore, **2** is an optically active compound with planar chirality ($[\alpha]_D^{21}$ +168, *c* 0.25, MeOH).

Thus, the intriguing structures and biological activity of the macrocyclic bisbibenzyls have made them attractive synthetic targets.[6] The synthesis of riccardin C has been reported by five groups to date. Nógrádi et al. achieved the first total synthesis of **1** in 1988.[7] They used Wurtz coupling to construct the 18-membered macrocyclic ring. Eicher et al.[8] and Harrowven et al.[9] separately applied Wittig olefination reactions to the macrocyclization to accomplish the total synthesis of **1**. Recently, Suzuki et al.[10] and Kagechika et al.[11] each reported syntheses of **1** that employed an S_NAr reaction for the key macrocyclization step. On the other hand, cavicularin has been synthesized by just three groups. In 2005, Harrowven et al. reported the first total synthesis of (±)-cavicularin by applying a radical transannulation for the formation of the dihydrophenanthrene moiety,[9] and subsequently reported improvements to the protocol in 2011.[12] Dam and Baran applied an intramolecular [4+2] cyclization of ring A for the synthesis of **2**.[13,14] Recently, Zhao and Beaudry reported a similar synthesis of **2** using a highly regioselective Diels–Alder reaction.[15] We also have continued synthetic studies of macrocyclic bisbibenzyl compounds using an independent strategy involving Pd-catalyzed macrocyclization and previously reported the syntheses of plagiochin A and D,[16] isoplagiochin D,[17] and asterelin A.[18] Herein, we describe the synthesis of riccardin C[4] and (±)-cavicularin by applying two types of Pd-catalyzed reactions, one to form the 18-membered macrocyclic rings, and the other to construct the highly strained dihydrophenanthrene moiety of **2**.

The common synthetic strategy for riccardin C and cavicularin is shown in Scheme 1. Starting units **3**, **4**, and **5** would be condensed by Horner–Wadsworth–Emmons (HWE) reactions. After borylation of the bromide on ring B, the macrocycles of **1** and **2** could be formed via intramolecular Suzuki–Miyaura coupling. For the synthesis of cavicularin, regioselective iodination on the C-10′ position would then be required, which would be made possible by protecting the phenolic hydroxyl group at C-13′ as a MOM ether. After iodination, transannulation between C-3′ and C-10′ via Pd-catalyzed Ar–Ar coupling would construct the dihydrophenanthrene embedded within the cavicularin skeleton. Although Pd-catalyzed Ar–Ar coupling has already proved to be an effective method for the formation of a biphenyl bond,[19] the synthetic strategy based on Pd-chemistry described here is not only challenging, but also attractive for constructing the highly strained and hindered cavicularin skeleton.



Scheme 1. Synthetic strategy for riccardin C (**1**) and cavicularin (**2**).

2. Results and discussion

The synthesis of **1** commenced with commercially available 4-bromobenzaldehyde (**9**), which corresponds to ring A (Scheme 2). In the presence of CuO and K_2CO_3, the Ullmann coupling of **9** with methyl 3-hydroxy-4-methoxybenzoate (**10**) afforded biphenyl ether **3** in 76% yield. Next, the HWE reaction with phosphonate **4** proceeded smoothly to give **11**. Successive $LiAlH_4$ reduction of **11** and bromination of the resulting alcohol **12** with $SOBr_2$ followed by Arbuzov reaction of bromide **13** gave phosphonate **14** in 96% yield over three steps. Subsequently, the HWE reaction of **14** with aldehyde **15** afforded **16**, which contains all four of the arene rings of **1** and **2**, in 87% yield. Reduction of the two alkenes and removal of the MOM groups were achieved by treatment with Et_3SiH in TFA to give **17** in 74% yield.[20] The liberated hydroxy group of **17** was then converted to a triflate with Tf_2NPh and Cs_2CO_3. Subsequently, chemoselective borylation[21] of the bromide over the triflate of **18** was carried out with $Pd(PPh_3)_4$, bis(pinacolato)diboron, and K_3PO_4 in dioxane, giving rise to **19** in 95% yield.

With boron ester **19** successfully obtained, Suzuki–Miyaura coupling was attempted to achieve the 18-membered macrocyclization (Table 1). Firstly, 10 mol % $Pd(PPh_3)_4/K_3PO_4$/DMF, which was effective for the synthesis of isoplagiochin D, was employed for this cyclization. However, the desired product **20** was obtained in only 9% yield (entry 1). Using 5 mol % $Pd_2(dba)_3$/SPhos/aqNa_2CO_3/DMF, the yield was improved to 16% (entry 2). Then, it was found that this macrocyclization is highly dependent on the base. Aqueous Na_2CO_3 enhanced the reactivity to give the desired product in 48% yield, along with 25% of the undesired cyclic dimer **21** (entry 3). Other solvents such as toluene, THF, and DMSO were less effective for this cyclization (entries 4–6).

Finally, treatment of **20** with BBr_3 in DCM completed the synthesis of riccardin C. The spectroscopic data for synthetic **1** were consistent with those for natural riccardin C (Scheme 3).

Next, our attention was focused on the synthesis of cavicularin (Scheme 4). The synthesis began with the common intermediate **14**. The HWE reaction with aldehyde **22**, which contained a protected phenolic 3-OH group as the MOM ether, afforded **23** in 94% yield. After diimide reduction[22] of the two alkenes and removal of the benzyl group to give **24**, the liberated hydroxyl group was converted to a triflate with Tf_2O and DMAP. Selective borylation of **25** was carried out using the same conditions as described above, giving rise to **26** in 81% yield. Subsequently, Suzuki–Miyaura