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Synthesis of cordiaquinone J and K via *B*-alkyl Suzuki–Miyaura coupling as a key step and determination of the absolute configuration of natural products

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Abstract—A versatile methodology for the synthesis of various terpenoids via *B*-alkyl Suzuki–Miyaura coupling as a key step is established. Synthesis of cordiaquinone J and K, new antifungal and larvicidal meroterpenoids, was achieved by using this methodology. The absolute configurations of cordiaquinone J and K were confirmed by the synthesis.

1. Introduction

Cordiaquinones are antifungal and larvicidal meroterpenoids isolated from Panamanian plants such as *Cordia linnaei*. In 1990, Messana and co-workers reported the isolation and structures of cordiaquinones A (**1**) and B (**2**) (Fig. 1).[1] After their identification of cordiaquinones from the plant, several cordiaquinones have been isolated.[2,3] In 2000, Hostettmann and co-workers reported the structures of cordiaquinones J (**3**) and K (**4**) isolated from *C. curassavica* (Fig. 1).[4] These compounds exhibit antifungal activities against phytopathogenic fungus such as *Cladosporium cucumerinum* and larvicidal activity against the larvae of the yellow fever-transmitting mosquito *Aedes aegypti*. The structures of cordiaquinone J and K were established on the basis of HRMS, UV and 1D and 2D NMR spectra. In connection with our synthetic studies of biologically active natural terpenoids,[5] we became interested in clarifying the absolute configuration of cordiaquinones. The synthesis and absolute configuration of cordiaquinone B were reported by

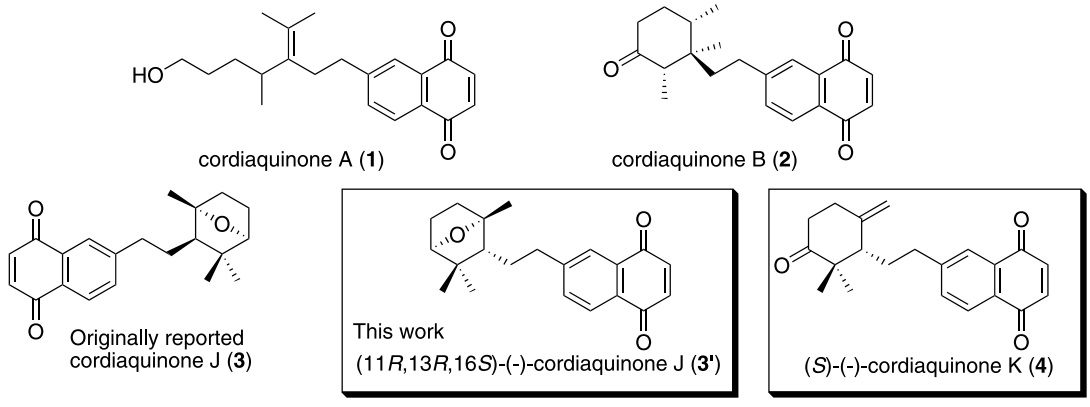

Figure 1. Structures of cordiaquinones.

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Asaoka and his co-workers.[6] In previous communications, we reported the synthesis of (*R*)-(+)-cordiaquinone K employing one-pot *B*-alkyl Suzuki–Miyaura coupling as a key step and the determination of the absolute configuration of the natural product.[7] Although the absolute configuration of cordiaquinone K was determined to be *S* as shown in Figure 1, the absolute configuration of cordiaquinone J remained unknown. In recent structural studies of natural products, NOE studies are a powerful tool, especially for relative stereochemistry determination. However, Hostettmann provided no clear information on the relative stereochemistry of cordiaquinone J, including NOE experiment.[4] To clarify the stereochemistry, we decided to synthesize cordiaquinone J. This paper describes details of the synthesis of (*R*)-(+)-cordiaquinone K, (11*R*,13*S*,16*R*)- and (11*S*,13*R*,16*S*)-cordiaquinone J employing one-pot *B*-alkyl Suzuki–Miyaura coupling[8] as a key step. This paper also describes the determination of the relative and absolute configuration of the natural products.

2. Results and discussion

Our synthetic plans for the synthesis of cordiaquinone J and K are shown in Scheme 1. Appropriate transformations of the oxygen functionality at C-13 led to hydroxyolefines **A** and **B**, respectively. Disconnection between C-6 and C-9 gave γ-cyclohomogeranyl units **D** and **E**, respectively, and naphtoquinone derivative **C**. We planned to apply *B*-alkyl Suzuki–Miyaura coupling reaction to connect these units. This methodology would be useful for not only the synthesis of cordiaquinones but also various terpenoids such as ambrein,[9] luffarin W,[10] penlanpallescensin.[11] (Fig. 2), because these compounds have a common structural feature with cordiaquinones, namely, a γ-cyclohomogeranyl unit connecting with an aryl or a vinyl unit. Optically active γ-cyclohomogeranyl units could be derived from known hydroxyketone **F**, [12] obtained by yeast-mediated asymmetric reduction of the corresponding diketone. Naphtoquinone derivative **C** would be synthesized from known 6-bromonaphtoquinone.[13]

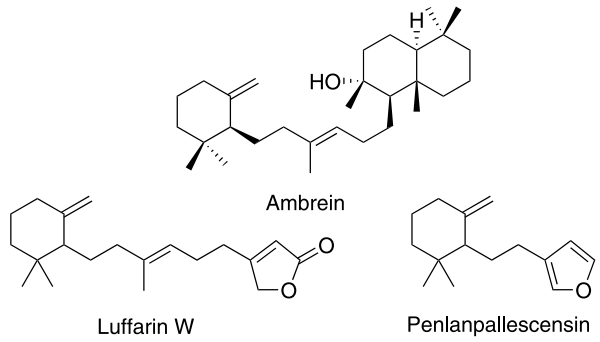
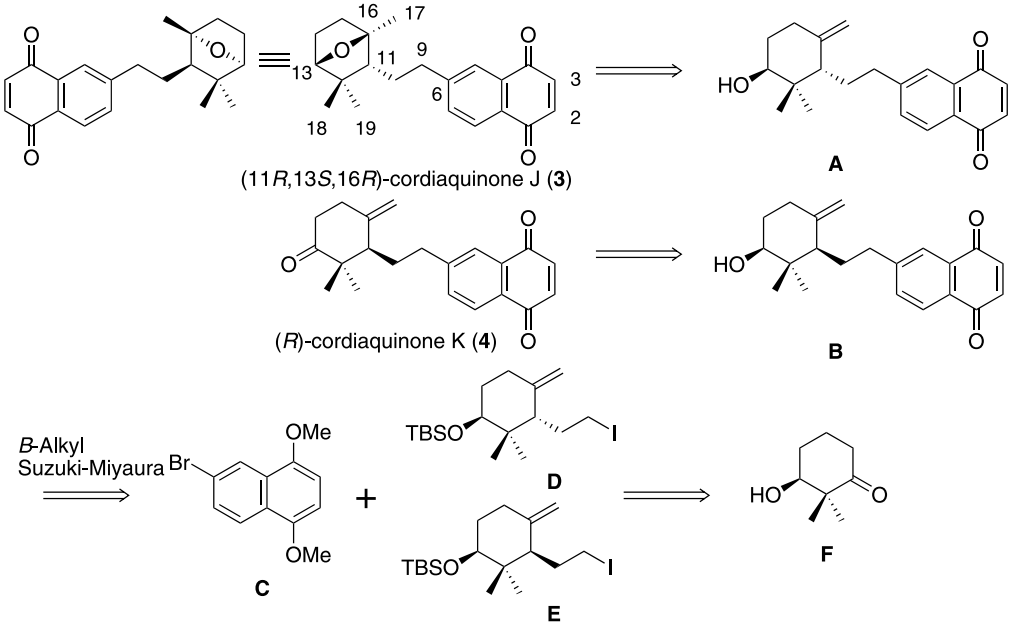


Figure 2. Structures of natural products with related structure of cordiaquinones.

As our target, we first chose (±)-13-deoxocordiaquinone K (**5**), since there was an urgent need to establish the appropriate conditions of the coupling reaction. Scheme 2 summarizes our synthesis of (±)-13-deoxocordiaquinone K (**5**). 6-Bromonaphtoquinone[13] (**6**) and (±)-γ-cyclohomogeranyl iodide[5a,14] (**8**) were selected as the starting materials. 6-Bromonaphtoquinone (**6**) was first hydrogenated with PtO_2 followed by methylation of the resulting hydroxyl groups to give **7**. (±)-γ-Cyclohomogeranyl iodide (**8**) was derived from the corresponding alcohol.[15] To connect the γ-cyclohomogeranyl unit (**8**) and the naphtoquinone derivative (**7**), we examined one-pot *B*-alkyl Suzuki–Miyaura coupling reaction. As a preliminary experiment for the coupling of **8** with **7**, the conditions reported by Marshall and Johns[16] {$PdCl_2$(dppf) as a catalyst} were examined to give the desired product (**9**) in only 10% yield based on **8**. Then we examined various conditions. Table 1 summarizes reaction conditions and yields of **9**. Although $PdCl_2$(dppf) was not an effective catalyst (entries 1–3), $Pd(PPh_3)_4$ was superior in yield (entry 4). Moreover, by heating the reaction mixture to



Scheme 1. Retrosynthetic analyses of cordiaquinone J and K.