

**A NOVEL ROUTE TO 1,8-DIHYDROXYNAPHTHALENE-DERIVED
NATURAL PRODUCTS. SYNTHESIS OF (±)-CJ-12,372[†]**

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Abstract—1,8-Dihydroxynaphthalene-derived natural products show a wide variety of biological activities, and thus have attracted the interest of both the chemical and biological communities. We report a novel and efficient approach to these natural products and its application to the total synthesis of (±)-CJ-12,372, a representative example of this class of compounds.

Since the early 1990s, large numbers of natural products with a naphthalene spiroketal have been isolated and structurally determined. Several examples are shown in Figure 1 [CJ-12,372 (**1**),¹ diepoxin σ (**2**),² preussomerin G (**3**),³ and spiroxin A (**4**)⁴].⁵ Structurally, they all have a spiro-ketal entity formally derived from 1,8-dihydroxynaphthalene and 1,4-naphthoquinone at various oxidation levels. The diverse pharmacological effects of these molecules, as well as their unusual, highly oxygenated, structures have generated significant interest in laboratory synthesis. To date, several total syntheses have been achieved utilizing key transformations such as biomimetic cyclizations^{6a} and oxidative^{6c,d} or acid-catalyzed ketalizations^{6b,e,f} to build these intriguing ring systems.⁷ In this communication, we report our own strategy for constructing the core structure of these natural products and its application to the total synthesis of (±)-CJ-12,372 (**1**), a novel DNA gyrase inhibitor.^{1,6f}

To develop a general route to the 1,8-dihydroxynaphthalene-derived natural products, we focused our

[†] This paper is dedicated with great personal and professional admiration to Professor Yuichi Kanaoka as he celebrates his 75th birthday.

attention on the core structure (**5**) (Scheme 1), which is shared by the majority of natural products of this class (see **1-4**, Figure 1). In principle, raising the oxidation level of **5** would lead to **1-4**, where **5** would serve as a common precursor. To build **5** efficiently and concisely, we planned a novel strategy starting from readily available materials, in which **5** can be derived from the cationic cyclization of the monothio-orthoester (**6**) to form a 6-membered ring by selective activation of the sulfide moiety. Compound (**6**) would be prepared by Suzuki-Miyaura coupling between the olefin (**7**) and 1-iodo-2,4-dimethoxybenzene (**8**).^{8,9}

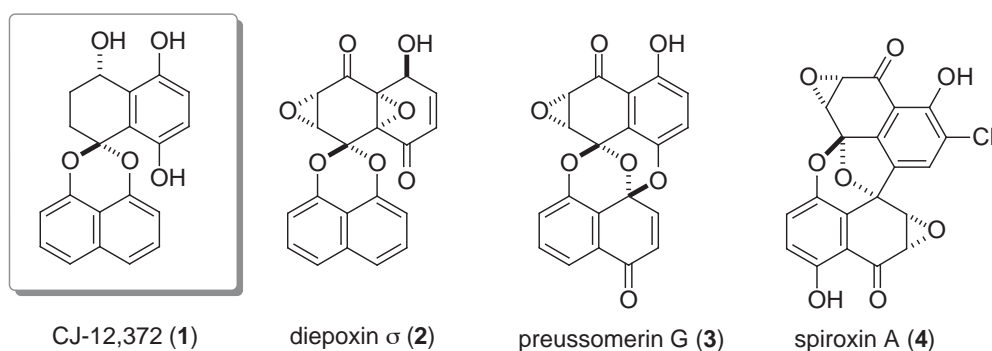
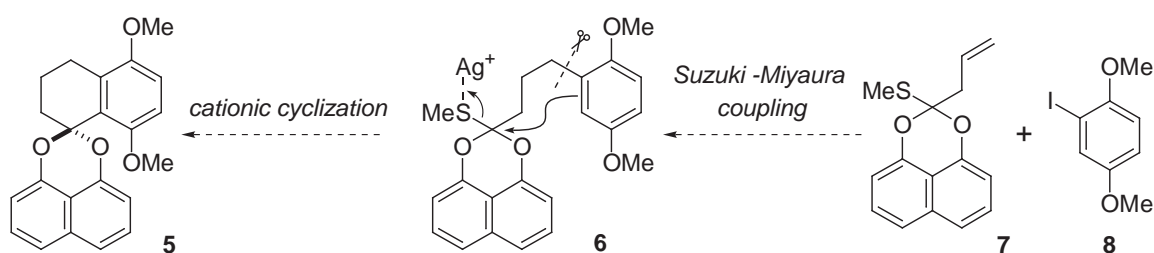


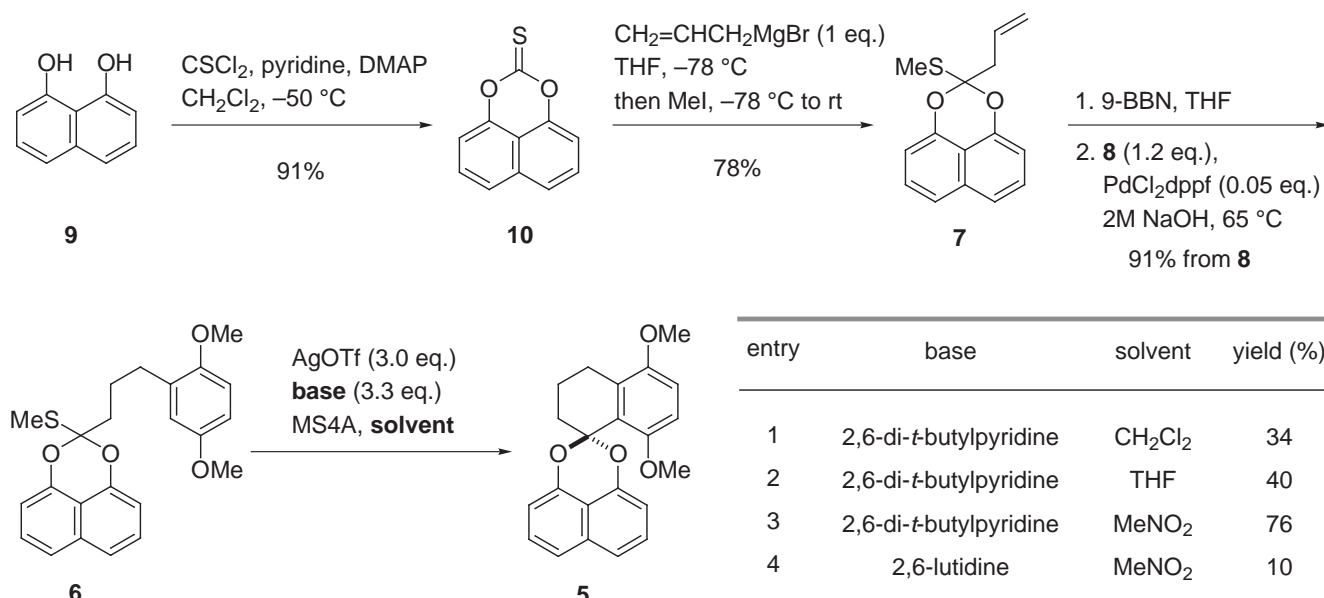
Figure 1. Representative 1,8-naphthalene-derived natural products.



Scheme 1. Synthetic plan of common intermediate (**5**)

Synthesis of monothio-orthoester (**6**) started with the known 1,8-dihydroxynaphthalene (**9**) (Scheme 2).^{6b,10} Compound (**9**) was converted to thiocarbonate (**10**) by using thiophosgene in the presence of base at $-50\text{ }^{\circ}\text{C}$ in 91% yield. Nucleophilic addition of allylmagnesium bromide to thiocarbonate (**10**) and then trapping the resulting thiolate with MeI gave **7** in 78% yield.¹¹ Hydroboration of olefin (**7**) and subsequent Suzuki-Miyaura coupling reaction with 1-iodo-2,4-dimethoxybenzene (**8**)¹² using catalytic amounts of PdCl_2dppf at $65\text{ }^{\circ}\text{C}$ afforded the desired adduct (**6**) in 91% yield.¹³

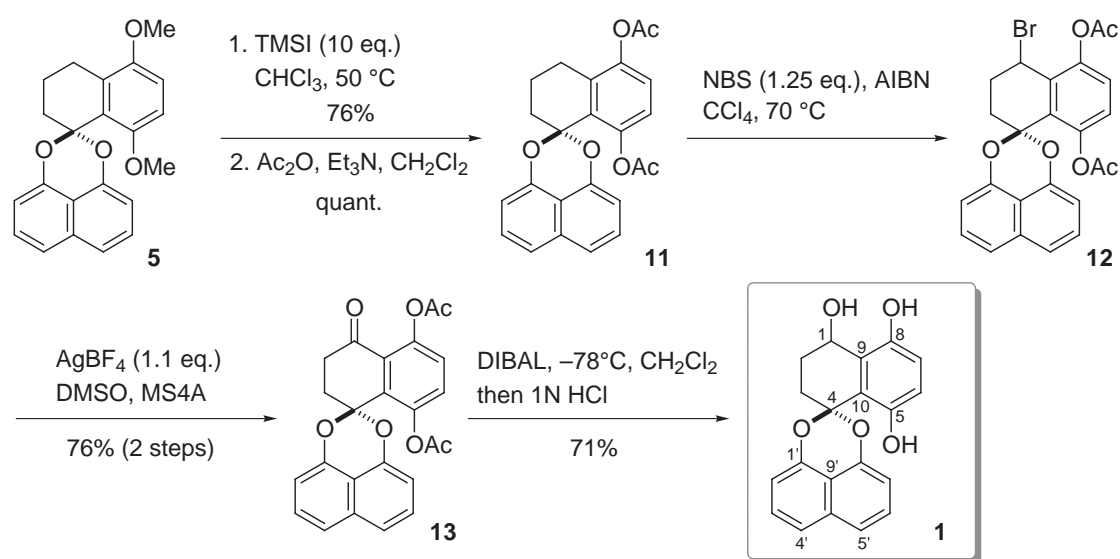
Having the monothio-orthoester (**6**) in hand, the cationic cyclization to construct the 6-membered ring was pursued.¹⁴ In doing so, we selected silver trifluoromethanesulfonate (AgOTf) as an activator using 2,6-di-*t*-butylpyridine as the buffer in various solvents. The results showed that the best solvent for the reaction was nitromethane (entry 3, Scheme 2). In this way, the bulky naphthalene moiety was successfully installed onto the benzene ring in 76% yield. In addition, neither the enol ether nor its hydrolyzed products, potential by-products from elimination of the sulfide, were observed under these conditions. Solvents with lower dielectric constants such as tetrahydrofuran (entry 2) or dichloromethane (entry 1) led to lower yield. As seen from entries 3 and 4, the bulkier base is likely to be far more efficient. Thus, we developed a simple assembly of the common intermediate (**5**) using Suzuki-Miyaura coupling and cationic cyclization only through 5 synthetic steps (4 separate operations) from 1,8-dihydroxynaphthalene (**9**). The neutral nature and high chemoselectivity of the protocol will likely be high applicable to the synthesis of other multi-functional natural products of this class.



Scheme 2. Synthesis of common intermediate (**5**)

To test the utility of compound (**5**), total synthesis of (\pm)-CJ-12,372 was carried out (Scheme 3). The methyl groups of **5** were removed by the action of iodotrimethylsilane to provide a hydroquinone (76%

yield), whose phenols were re-protected to give the diacetate (**11**) in quantitative yield. Bromination of the benzylic position of **11** using NBS in the presence of AIBN led to bromide (**12**), which was treated with AgBF₄ and DMSO in the presence of MS4A to afford ketone (**13**) in 76% yield over 2 steps.¹⁵ Finally, reduction of **13** using DIBAL gave rise to the fully synthetic (±)-CJ-12,372 (**1**) (71% yield), of which the physical data was identical to those of the authentic natural product (¹H-, ¹³C-NMR, and IR spectroscopy).^{1,6f,16}



Scheme 3. Total synthesis of (±)-CJ-12,372 (**1**)

In conclusion, we have developed a novel and concise method for synthesizing **5** using Suzuki-Miyaura coupling and Ag⁺-mediated cationic cyclization as key steps, and compound (**5**) has then been applied to the total synthesis of CJ-12,372 (**1**). We are currently extending our strategy toward the synthesis of other natural products of this class with different oxidation levels.

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