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# Synthesis of arylnaphthalene lignan lactone using benzoin condensation, intramolecular thermal cyclization and Suzuki coupling

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ABSTRACT

Arylnaphthalene lactones, which are natural lignans and isolated from a wide range of plants, exhibit significant biological activity, including anticancer and antiviral activities. In this work, we have developed a versatile and convergent synthetic method for arylnaphthalene lactones, which involves the use of benzoin condensation and thermal intramolecular cyclization for preparing the key intermediate, naphthol. A high-yielding Suzuki reaction is utilized to introduce the aryl group to the C9 position of the naphthalene lactones, which allows for the construction of the arylnaphthalene lactone skeleton.



## 1. Introduction

Arylnaphthalene lactones are naturally occurring lignans, which are widely isolated from traditional medicinal plants. Much research attention has been paid to these lactones because of their significant biological activities (Fig. 1). In particular, justicidin B (**1**) is reported to display *anti*-fungal and *anti*-proliferative properties,[1–3] and its trimethoxy congener (**2**) has been studied for its *anti*-viral and *anti*-PDE activity.[4–6] More recently, daurinol (**3**) was demonstrated to be efficacious in an in vivo cancer xenograft model, and its efficacy was comparable with that of etoposide or irinotecan, which are clinically used anticancer drugs.[7–9]

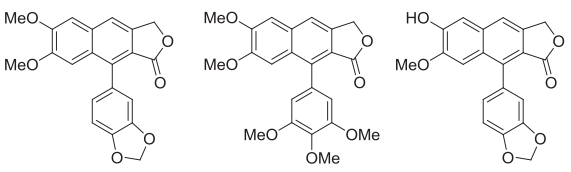


**Fig. 1.** Structures of some bioactive arylnaphthalene lactones.

Structurally, arylnaphthalene lactones are 9-arylated naphthalene lactones in which the aromatic rings are usually polyoxygenated. To date, more than 17 arylnaphthalene lactone congeners, including justicidins, daurinol, chinensin, taiwanin, and diphyllin have been reported. Because of their unique structural features and important pharmacological properties, many elegant approaches for their synthesis have been reported. These approaches can be classified according to the key reactions, as intramolecular Diels–Alder reactions,[10–15] transition metal-catalyzed cyclizations,[16–20] acid-catalyzed cyclizations,[21–24] and multicomponent or other reactions.[25–28]

As previously stated, some arylnaphthalene lactones exhibit promising biological activity, and studies are ongoing in order to reveal their structure–activity relationship and eventually discover novel therapeutic agents.[2,29] In this regard, practical and versatile synthetic methods for introducing a wide range of substituents into the main arylnaphthalene skeleton are urgently needed in order to facilitate the synthesis of natural and designed arylnaphthalene lactones. Although significant advances in the synthesis of arylnaphthalene lactones have been made, there are still limitations in the reported methods in terms of the scope of their application, especially with regard to the installation of the C9-aryl ring. Consequently, we have designed a novel convergent protocol for the

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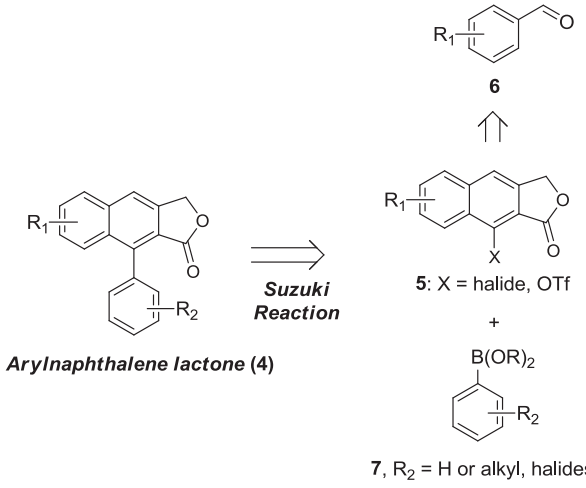
synthesis of arylnaphthalene lactones, which allows the introduction of various substituents to the aromatic rings. This approach facilitates the synthesis of not only natural naphthalene lactones, but also a variety of synthetic analogs.

## 2. Results and discussion

Aryl halides, or their chemical equivalents such as aryl triflates, are valuable precursors in materials chemistry and the synthesis of natural or medicinally important compounds, as halides on aryl rings can be easily substituted with aryl, heteroaryl, and alkyl groups, or heteroatoms, by metal-catalyzed cross-coupling reactions. Many transition metals such as palladium, rhodium, nickel, and iron are utilized in cross-coupling reactions. The Suzuki reaction, which employs alkyl or arylboronic acids and palladium as the catalyst, is commonly adopted because of its chemical efficiency and the eco-friendliness of boronic acids. Hence, we envisioned that the Suzuki reaction of a 9-halonaphthalene lactone with the appropriate arylboronates would afford naturally occurring or synthetic arylnaphthalene lactones (Scheme 1). A wide range of arylboronic acids **7** with various substituents are commercially available for coupling with these lactones. Therefore, a convenient synthesis of 9-halo- or 9-TfO-naphthalene lactone intermediates **5** was considered as a key challenge. We reasoned that **5** could be synthesized from substituted benzaldehydes **6**.

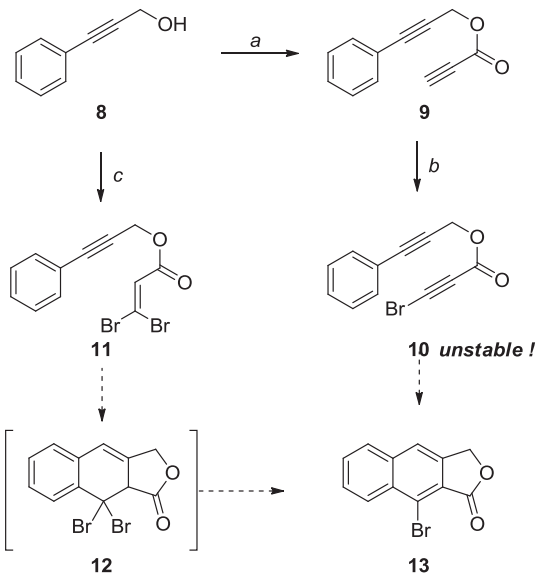



**Scheme 1.** Convergent strategy for the synthesis of arylnaphthalene lactones by the Suzuki reaction.

Initially, we attempted to synthesize 9-bromonaphtho[2,3-*c*]furan-1(3*H*)-one **13** as a model compound. As depicted in Scheme 2, 3-phenylprop-2-yn-1-ol **8** was coupled with propiolic acid to give ester **9**. Bromination of the alkyne was performed using *N*-bromosuccinimide and silver nitrate to give bromopropiolate **10**, which was stable in solution but extremely unstable without solvent. Therefore, we designed an alternative synthetic route to 9-bromonaphthalene **13**. 3-Phenylprop-2-yn-1-ol was combined with 3,3-dibromoacrylic acid to produce dibromoacrylate **11**. We expected that thermal cyclization and concomitant dehydrohalogenation would afford the desired bromonaphthalene **13**. However, attempts to synthesize bromonaphthalene under several thermal reaction conditions were unsuccessful.

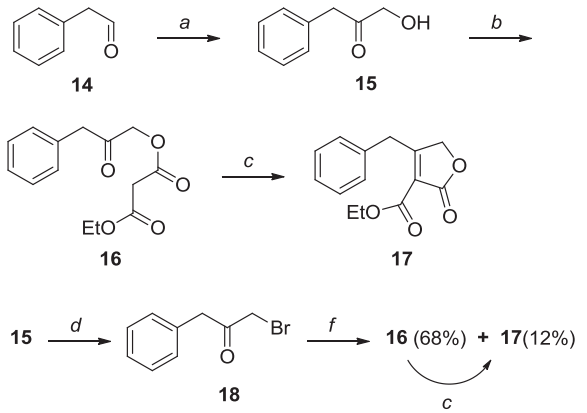
This result prompted us to change the synthetic methodology. Instead of using a halonaphthalene, we proposed naphthalene-*O*-triflate as a cross-coupling precursor; therefore, naphthol **19** was considered as the key synthetic intermediate.

The synthesis of the naphthol precursor is shown in Scheme 3. Phenylacetaldehyde **14** was transformed to hydroxy ketone **15** via the benzoin reaction catalyzed by a thiazolium reagent, and the




**Scheme 2.** Attempted synthesis of bromonaphthalene **13**. *Reagents and conditions*: a. Propiolic acid, DCC, $CH_2Cl_2$, 77% b. NBS, $AgNO_3$, acetone, rt c. 3,3-Dibromoacrylic acid, DCC, THF, rt, 82%.

resulting alcohol was acylated with ethyl malonylchloride to afford malonic diester **16**.[30,31] Treatment of ester **16** with NaH afforded the Knoevenagel condensation product **17**, a cyclization precursor, in excellent yield.[29] Alternatively, lactone **17** could be obtained by conversion of the hydroxyketone to haloketone **18**, followed by substitution with potassium ethyl malonate, and cyclization.[30]




**Scheme 3.** Synthesis of lactone **15**. *Reagents and conditions*: a. Paraformaldehyde, *N*-ethyl-benzothiazolium bromide, $Et_3N$, EtOH, reflux, 24 h, 65% b. Ethyl malonylchloride, $Et_3N$, $CH_2Cl_2$, 0 °C, 78% c. NaH, THF, 0 °C, 83% d. $CBr_4$, $PPh_3$, $CH_2Cl_2$, rt, 87% f. $EtO_2CCH_2CO_2K$, $CH_3CN$, rt.

One of the key steps of this approach is the synthesis of naphthol **19** from ester **17**. The results of this cyclization are summarized in Table 1. First, several organic and inorganic acids such as trifluoroacetic acid (TFA), sulfuric acid, hydrogen chloride, and polyphosphoric acid (PPA) were screened. Among them, only PPA afforded the desired naphthol **17** in 26% yield.[31] However, this yield was too low to carry out the planned protocol. Therefore, we attempted to carry out the cyclization under thermal conditions (Table 1, entries 6–8). Significantly improved results were achieved, and the desired naphthol was obtained in 74% yield when using acetamide as a solvent at a temperature of 220 °C. The microwave-assisted reaction showed no improvement in the yield, and changing the solvent to *N*,*N*-dimethylacetamide did not afford the naphthol. A plausible mechanism for the thermal cyclization is shown in Scheme 4, in which the formation of a reactive electrophilic ketene intermediate from ester having activated methylene