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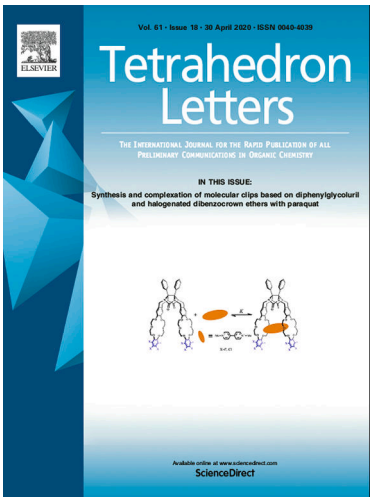

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Total synthesis of tanshinone IIA

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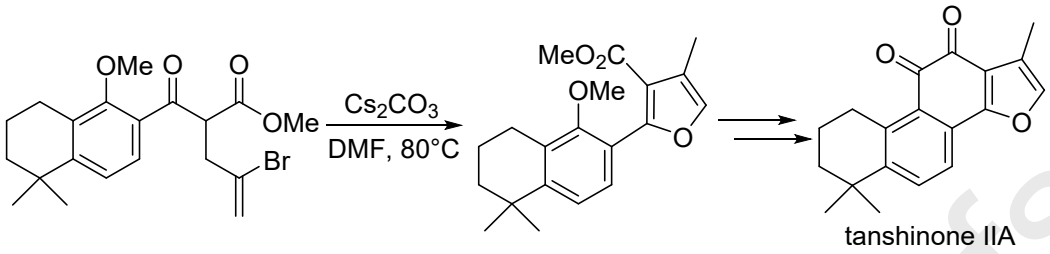


Abstract: A novel synthetic route toward tanshinone IIA has been developed. Key steps involve a base mediated furan ring formation, and an acyloin condensation reaction to construct the ortho-quinone ring.

Key words: tanshinone IIA; total synthesis; furan; acyloin

Tanshinones (Figure 1) are an important class of abietane diterpenes isolated from the roots of *Salvia miltiorrhiza* (Tanshen), a well-known traditional Chinese medicine widely used for the treatment of cardiovascular diseases [1]. As one of the major bioactive constituents from Tanshen, tanshinone IIA (**2**) has been well studied regarding its pharmacological activities during the past decades [2]. Researches revealed that tanshinone IIA exhibit various activities such as cardiovascular protection [3], neuroprotection [4], anticancer [5], anti-inflammatory [6] and anti-oxidative activities [7].

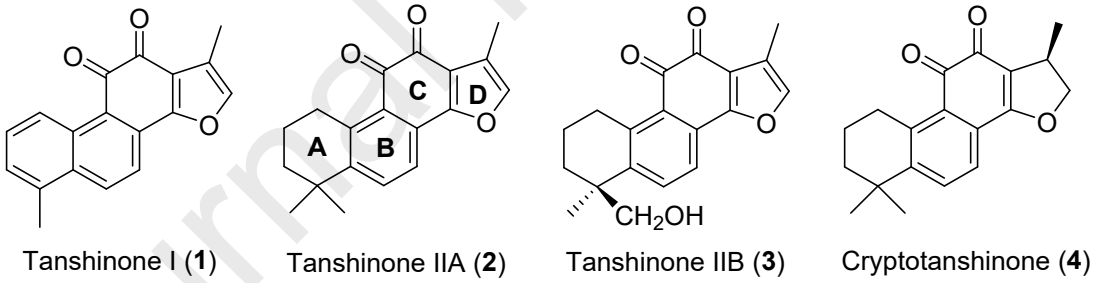
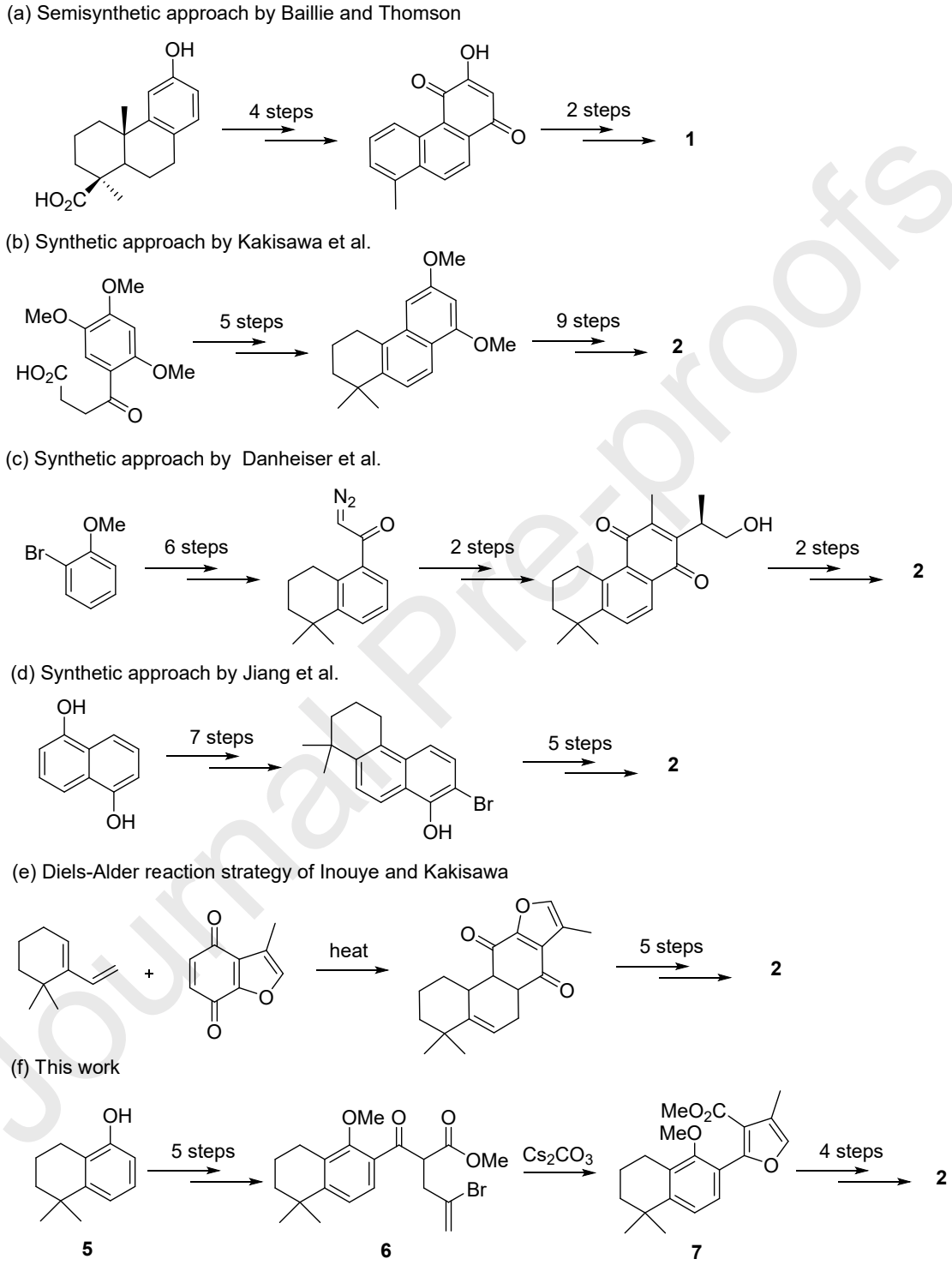


Figure 1. Selected examples of tanshinones.

Since the 1960s, many synthetic approaches toward tanshinones have been developed [8]. Based on the final ring closure step for the construction of tanshinone scaffold, these can be classified into two categories: (1) (Dihydro)furan ring D closure by varied methods (Scheme 1a-d) [9], and (2) phenyl ring B closure via Diels-Alder reaction (Scheme 1e) [10]. The former strategy either requires the use of less available natural materials or starts from simpler substrates with lengthy synthetic steps and is thus low yielding. The latter strategy, pioneered by Inouye and Kakisawa [10a], is more prevalent because of its convergent nature. However, the key Diels-Alder reaction suffers from substance instability, low regioselectivity and difficulties in product purification. Therefore, it is desirable to develop alternative strategies to access tanshinones. As part of our continued interest in quinone natural products synthesis

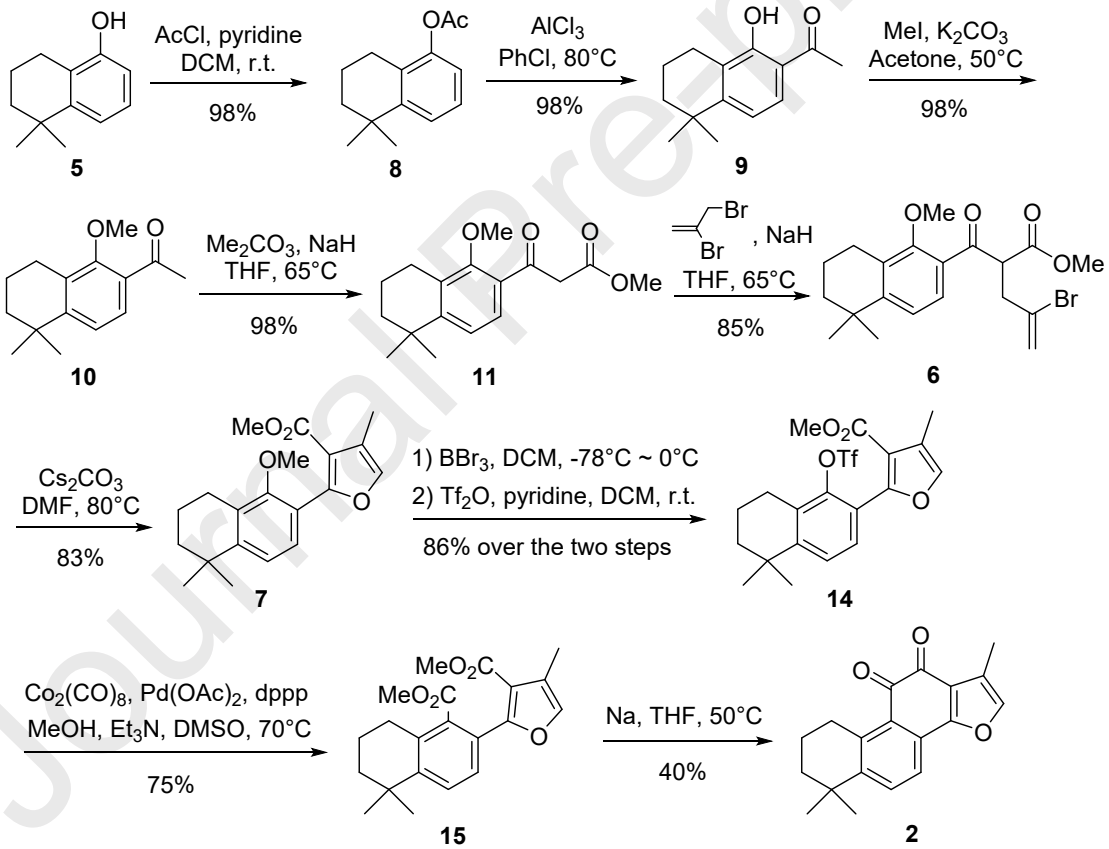
[11], we herein report a novel strategy toward tanshinone IIA featuring a base mediated furan ring D formation [12], and a late-stage acyloin condensation reaction [13] for the construction of the ortho-quinone ring C (Scheme 1f).



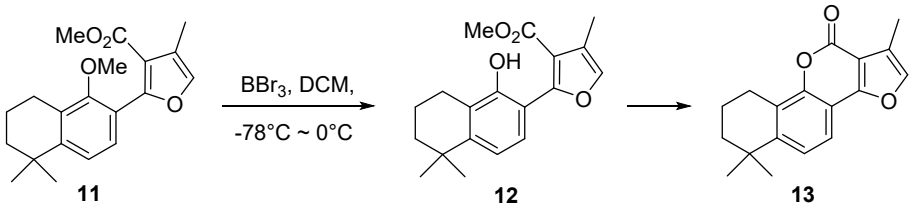
Scheme 1. Comparison of literature and our own approach toward tanshinones.

As depicted in Scheme 2, our synthesis started from known building block **5** [9e]. Acetylation of

5, followed by Fries rearrangement [14] and methylation furnished compound **10** in excellent yield over the three steps. Treatment of **10** with sodium hydride and dimethyl carbonate resulted in the formation of *β*-keto ester **11** in 98% isolated yield. Nucleophilic substitution of 2,3-dibromopropene with **11** in the presence of NaH gave **6** in 85% isolated yield. Following the procedure previously developed by us [12a], furan **7** was obtained in 83% isolated yield by treatment of compound **6** with Cs_2CO_3 in DMF. Demethylation of **7** with BBr_3 produced phenol **12**, which was prone to lactonization during purification (Scheme 3) and was thus treated directly with triflic anhydride to provide **14** in 86% isolated yield over the two steps. To complete the synthesis, we next needed to convert triflate **14** into diester **15**. Palladium catalyzed methoxycarbonylation of **14** following a known literature procedure [15b] provided diester **15** in 48% isolated. After some optimization, the yield of **15** could be improved to 75% by treatment of **14** with $Pd(OAc)_2$, $Co_2(CO)_8$, dppp, MeOH, and Et_3N in DMSO at 70 °C for 20 h. Finally, treatment of **15** with sodium in THF afforded tanshinone IIA **2** in moderate yield through acyloin condensation and auto oxidation [13]. The spectroscopic and analytical data obtained for compound **2** were identical to those reported in the literature [9e].



Scheme 2. Synthetic route to tanshinone IIA **2**.



Scheme 3. Lactonization of **12** to **13**.

In summary, we have developed a novel synthetic route toward the total synthesis of tanshinone IIA, which is obtained in 17% overall yield following a ten-step synthesis. Key steps involve a base mediated furan ring D formation, and a subsequent acyloin condensation reaction to construct the ortho-quinone ring C. This strategy is well adapted to the total synthesis of other tanshinones and related bioactive derivatives for pharmacological activity study.

Acknowledgment

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

- A new method toward the total synthesis of tanshinone IIA has been developed.
- The furan ring was constructed through a base-mediated cyclization.
- An acyloin condensation was used for the formation of the *o*-quinone ring.