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SPECIAL FEATURE: BRIEF COMMUNICATION

Total Synthesis of *trans*-Resorcylide via Macrocyclic Stille Carbonylation

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Abstract

The resorcylic macrolides are important natural products with a wide range of remarkable biological activities. So far, most of the reported resorcylic macrolide syntheses use either macrolactonization or ring closing metathesis to build the corresponding macrocycle. In continuation of our efforts in developing novel carbonylation reactions to facilitate natural product total synthesis, we report herein a total synthesis of *trans*-resorcylide (**1**) featuring a palladium-catalyzed macrocyclic Stille carbonylation to build its 12-membered macrocycle.

The resorcylic macrolide is an important family of natural products featuring a 6-alkyl-2,4-dihydroxybenzoic acid (the β-resorcylate moiety) fused with a macrocyclic lactone ring. These resorcylic macrolides have demonstrated a wide range of important biological activities. For example, *trans*-resorcylide (**1**, Fig. 1) and *cis*-resorcylide (**2**) are plant growth inhibitors [1, 2]. Radicicol (**3**) was originally isolated from *Monicillium nordinii* in 1953 [3] and has shown antibiotic anticancer activity. It was later discovered as a potent and selective heat shock protein 90 (Hsp90) inhibitor with IC_{50} of 20 nM [4]. Hsp90 is a chaperon protein and has been an important therapeutic target for developing new cancer treatment. Monocillin VI (**4**) was recently isolated from the cultures of *Paecilomyces* sp. SC0924. It exhibited potent growth inhibition activity against quite a few cancer cell lines including MCF-7, A549, and Hela cells as well as antifungal activity against *Peronophythora litchi* [5].

These resorcylic macrolides, due to their diverse structures and remarkable biological activities, have garnered a significant amount of synthetic attention. For example, Couladouros et al. reported the first total synthesis of *trans*-resorcylide (**1**) and *cis*-resorcylide (**2**) in 2004 [6]. Miller and Mennen reported a formal synthesis of *trans*-resorcylide (**1**) in 2007 [7]. Tsuji et al. synthesized dehydroxy-*trans*-resorcylide by an intramolecular alkylation [8]. Radicicol (**3**) has been synthesized by the groups of Lett [9, 10], Danishefsky [11–13], and Winssinger [14]. The Danishefsky group also synthesized cycloproparadicicol to improve the corresponding pharmacokinetics and reduce nonspecific toxicities [15]. The key for synthesizing these resorcylic macrolides is to construct the β-resorcylate moiety and the macrolactone moiety. While most of the syntheses relied on starting materials already equipped with the resorcylate core, Danishefsky and co-workers reported a remarkable Diels-Alder reaction of strained ynolides to build the β-resorcylate moiety. For the macrolactone moiety, macrolactonization and ring closing metathesis are the two common strategies to form the desired macrolactones. Notably, in Miller's formal synthesis of *trans*-resorcylide (**1**), an acyl-anion equivalent macrocyclization was used to build the corresponding macrocycle.

Our group has been developing novel palladium-catalyzed carbonylation reactions to facilitate the total synthesis of complex natural product [16, 17]. For example, we have developed a palladium-catalyzed alkoxycarbonylative macrolactonization to streamline the synthesis of tetrahydropyran/tetrahydrofuran-containing bridged macrolactones including 9-demethylneopeltolide

Dedication: This article is dedicated to Professor Samuel J. Danishefsky for his great scientific contributions to total synthesis of highly complex and biologically important natural products.

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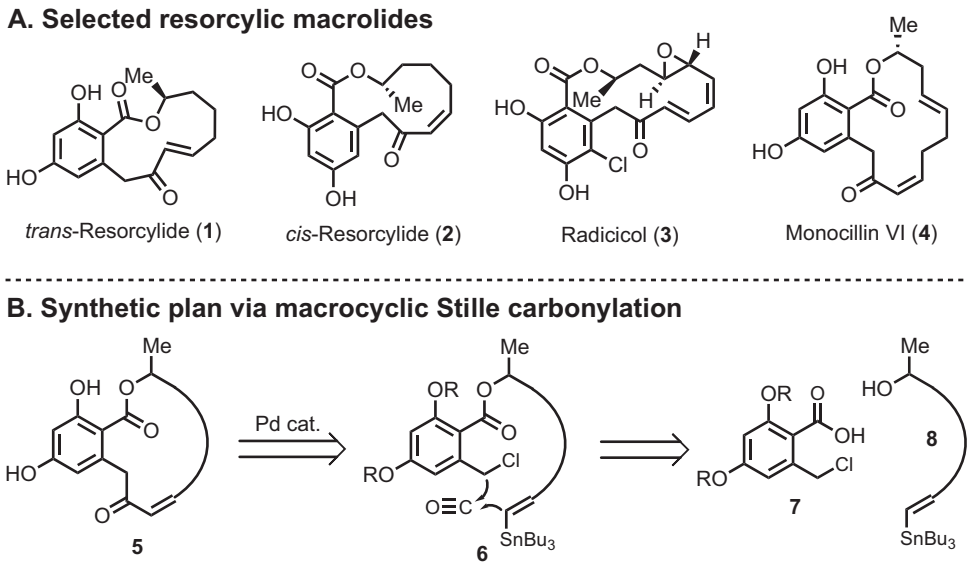
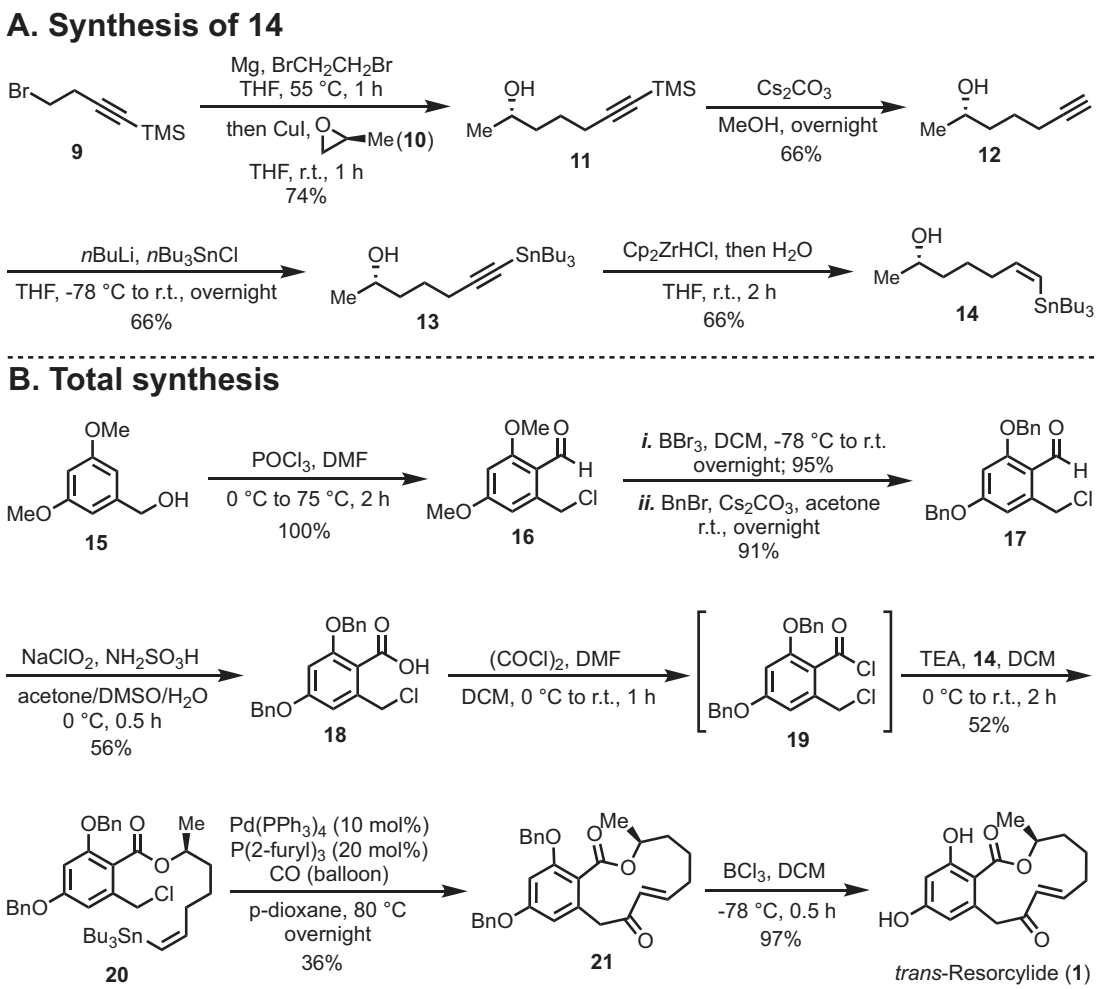


Fig. 1 Selected resorcylic macrolides and our synthetic plan via macrocyclic Stille carbonylation

[18]. This effective method was also used as the key step in Harran's total synthesis of callyspongiolide [19]. An intramolecular carbonylative Heck macrolactonization has been realized and utilized by us to streamline the total synthesis of spinosyn A [20]. We also developed a novel palladium-catalyzed carbonylative spirolactonization of hydroxycyclopropanols to synthesize oxaspirolactone-containing C_{12}-oxygenated labdanolic diterpenes α-levantanolide and α-levantenolide [21] and stemona alkaloids bisdehydroneostemoninine and bisdehydrostemoninine [22]. Very recently, we have used a palladium-catalyzed hydrocarbonylative lactonization to synthesize three rare *abies* sesquiterpenoids, which in turn enabled the identification of novel selective covalent inhibitors of oncogenic protein tyrosine phosphatase SHP2 and elucidation of DNA polymerase epsilon subunit 3 (POLE3) as one of their potential cellular targets [23]. In this context, we considered the possibility of developing a palladium-catalyzed macrocyclic Stille carbonylation to build the desired macrocyclic enone moiety of these resorcylic macrolides (cf. **1**-**4**) by converting vinylstannane-containing benzyl chloride **6** to macrocyclic enone **5**. Macrocyclic Stille carbonylation has been rarely used in total synthesis [24, 25] and no macrocyclic Stille carbonylation of benzyl chloride has been reported so far. Therefore, we hope to develop a new strategy to access these important resorcylic macrolides and generalize the macrocyclic Stille carbonylation for macrocyclic enone synthesis.

We chose *cis*-resorcylide (**2**) as the initial target molecule to test the hypothesis of using the macrocyclic Stille carbonylation to build the corresponding macrocycle. For this purpose, benzyl chloride **20** (Scheme 1b) with an intramolecularly tethered vinylstannane need to be prepared. We planned to use an esterification of acyl chloride **19** and secondary alcohol **14** to synthesize the macrocyclic Stille carbonylation precursor **20**. Our synthesis of **14** started from known bromide **9** [26], which was treated with Mg metal and 1,2-dibromoethane followed by transmetalation with CuI. The resulting cuprate reagent underwent regioselective epoxide ring opening with epoxide **10** to afford alcohol **11** in 74% yield. After removal of the TMS group with Cs_2CO_3 in MeOH, the terminal alkyne was subsequently converted to alkynyl stannane via deprotonation with *n*BuLi followed by trapping the acetylide with nBu$_3$SnCl. Stereoselective reduction of the internal alkyne with the Schwartz's reagent gave *cis*-vinylstannane **14** in good yield. We then synthesized known benzoic acid **18** from commercially available starting material **15**. Vilsmeier-Haack formylation accompanied by in situ chlorodehydration gave aldehyde **16** in quantitative yield. Due to the difficulties we encountered in removing the methyl groups at a late stage, the two methyl ethers were switched to benzyl ethers via a sequence of BBr_3 deprotection and benzylation with BnBr in presence of Cs_2CO_3 in acetone. The resulting benzyl protected aldehyde **17** was then oxidized to benzoic acid **18**, which was subsequently converted to acyl chloride **19** with the treatment of oxalyl chloride and DMF in DCM. Acyl chloride **19**, without further purification was reacted with alcohol **14** to deliver the Stille carbonylation precursor **20** in modest yield.

With **20** in hand, we investigated various reaction conditions for the macrocyclic Stille carbonylation and were surprised to discover that, under the reaction conditions of 10 mol % of $Pd(PPh_3)_4$ and 20 mol% of P(2-furyl)$_3$ under balloon pressure of carbon monoxide in *p*-dioxane at 80 °C, macrocyclic product **21** with a *trans*-enone was obtained in 36% yield while compound **20** contains a *cis*-vinylstannane moiety. The expected macrocyclic *cis*-enone was not isolated. We didn't observe the direct intramolecular Stille cross coupling



Scheme 1 Total synthesis of *trans*-resorcylide (**1**)

product too. The detailed reaction mechanism for the formation of the macrocyclic *trans*-enone was not fully understood at this stage. One hypothesis is that the macrocyclic *cis*-enone was initially formed, but then quickly isomerized to the *trans* one under the carbonylation reaction conditions via either a reversible Michael-type addition with PPh_3 and/or P(2-furyl)$_3$ as the nucleophile at the relative high reaction temperature or a Pd-catalyzed isomerization probably involving in situ formed Pd-H species. Removal of the two benzyl groups with the treatment of BCl_3 at −78 °C in DCM [27] completed the total synthesis of *trans*-resorcylide (**1**). Notably, removal of these two benzyl groups was nontrivial at all. Couladouros and coworkers had experienced difficulties in converting **21** to *trans*-resorcylide (**1**) directly and developed a three-step detour. In our case, the use of solid $NaHCO_3$ and methanol to quench the final benzyl deprotection at low temperature is important and the use of aqueous $NaHCO_3$ solution led to decomposition of the final product. The ^{1}H NMR, ^{13}C NMR, and other spectroscopic data of our synthetic *trans*-resorcylide (**1**) match well with the reported ones.

In summary, we have developed a total synthesis of *trans*-resorcylide (**1**). The synthesis features a palladium-catalyzed macrocyclic Stille carbonylation to build the 12-membered macrocycle. Notably, while intermediate **20** contains a *cis*-vinylstannane, the palladium-catalyzed macrocyclic Stille carbonylation delivered product **21** with a *trans*-enone moiety. We are currently using the macrocyclic Stille carbonylation strategy to synthesize other family members of the resorcylic macrolides as well as probe molecules to understand their mode of actions.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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