

# Biomimetic Total Synthesis of Angelicoin A and B via a Palladium-Catalyzed Decarboxylative Prenylation-Aromatization Sequence

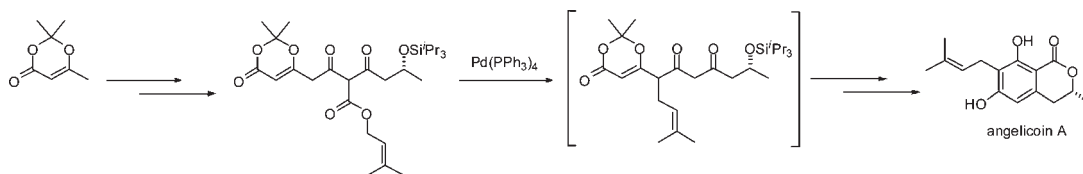
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## ABSTRACT



Five-step total syntheses of angelicoin A and B from 2,2,6-trimethyl-4-dioxinone are reported using late stage biomimetic aromatization reactions via diketo-dioxinones as intermediates. In addition, with angelicoin A, this aromatization was coupled with a palladium-catalyzed decarboxylative prenylation in a one-pot sequence as the key step.

The roots of the herb *Pleurospermum angelicoides*, found in the Himalayan Mountains, are used locally as treatments for typhoid and dysentery and as antipyretic and diaphoretic agents.<sup>1</sup> In 2006, a detailed chemical investigation of the root extracts was undertaken by Baba et al., resulting in the isolation of angelicoin A (**1**) and B (**2**) (Figure 1). Common to both is the presence of a methyl-substituted resorcylate  $\delta$ -lactone.<sup>2</sup> Resorcylates are common structural motifs found in a wide range of natural products, and there are a number of total syntheses of these important natural products reported.<sup>3</sup> However, the major

ity of these approaches required multistep sequences with the need for phenol protection. Inspired by the elegant work of Harris,<sup>4</sup> Hyatt,<sup>5</sup> and Boeckmann,<sup>6</sup> we have developed an alternative strategy for the synthesis of resorcylate natural products employing a late-stage biomimetic aromatization of oligo-keto-esters.<sup>7–9</sup>

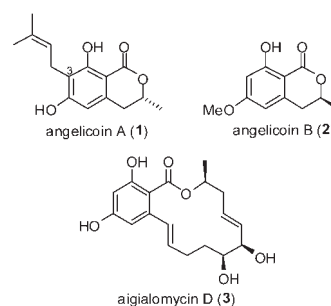


Figure 1. Angelicoin A (**1**) and B (**2**) and aigialomycin D (**3**).

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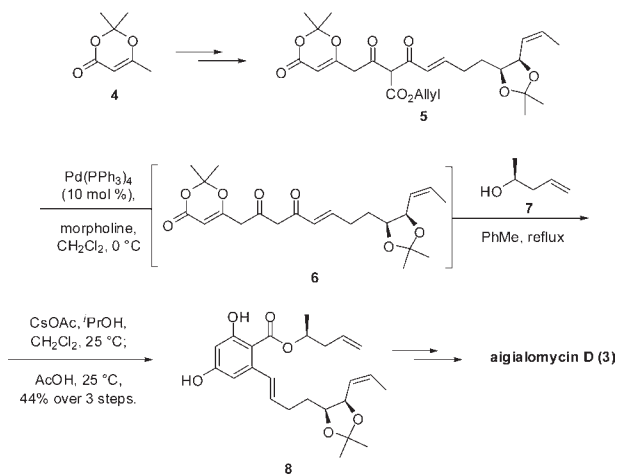
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Recently, as part of these studies, we reported the total synthesis of aigialomycin D (**3**) (Figure 1). Our approach featured a key Pd(0)-catalyzed deallylation and decarboxylation of allyl ester **5**, employing morpholine as a nucleophilic palladium  $\pi$ -allyl cation scavenger,<sup>10</sup> to provide the ketene precursor **6**. Subsequent aromatization of diketo-dioxinone **6** gave resorcyate **8** as a single regioisomer (Scheme 1).<sup>11</sup>

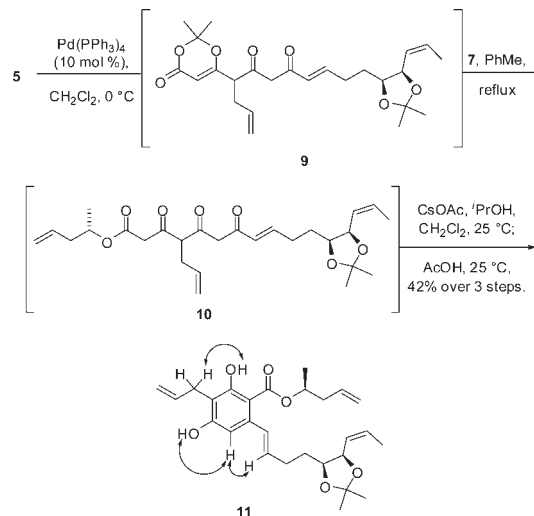
**Scheme 1.** Synthesis of Aigialomycin D (**3**)



During these studies, we observed that reaction of allyl ester **5** with Pd(PPh<sub>3</sub>)<sub>4</sub> in the absence of morpholine in CH<sub>2</sub>Cl<sub>2</sub> underwent a modified Carroll rearrangement<sup>12</sup> affording diketo-dioxinone **9** (Scheme 2). Subsequent ketene trapping with alcohol **7** gave triketoester **10**. Aldol cyclization using cesium acetate followed by acid-mediated aromatization<sup>11</sup> provided resorcyate **11** in 42% yield over 3 steps. The regiochemistry of arene **11** was confirmed by

NOE analysis in the <sup>1</sup>H NMR spectrum.<sup>13</sup> Herein we report for the first time this transformation and further studies on the total synthesis of resorcyates via diketo-dioxinones and the application of decarboxylative rearrangement of prenyl esters in the total syntheses of angelicoins **B** (**2**) and **A** (**1**).

**Scheme 2.** Decarboxylation-Allylation



Application of our dioxinone methodology to the total synthesis of angelicoin **B** (**2**) is shown in Scheme 3. Acylation of ketoester **12**<sup>9</sup> with acyl chloride **13** provided diketoester-dioxinone **14**. One pot palladium(0)-catalyzed deallylation-decarboxylation-ketene trapping-aromatization gave the desired resorcyate **15** in 45% yield over 3 steps. Deprotection of the silyl ether **15** followed by acid catalyzed cyclization gave lactone **16** in 60% yield over 2 steps. Finally, regioselective methylation of phenol **16** provided angelicoin **B** (**2**), which had identical physical and spectroscopic data with those previously reported.<sup>2</sup>

Acylation of dioxinone **4** with acyl benzotriazole **17** gave ketoester **18** in 93% yield.<sup>9,14</sup> Subsequent Claisen condensation reaction of ketoester **18** with acid chloride **19**,<sup>9</sup> in the presence of magnesium chloride and pyridine, gave diketoester **20** in 81% yield. Decarboxylation of diketoester **20** in the presence of Pd(PPh<sub>3</sub>)<sub>4</sub> (10 mol %) gave a separable mixture of dioxinone **21** and resorcyate **23** in a combined yield of 60% (Scheme 4). In these transformations, the linear substituted diketo-dioxinone **22** underwent aromatization faster than its branched isomer **21**. Deprotection of the silyl ether **23** followed by lactonization under basic conditions provided angelicoin **A** (**1**) in an overall yield of 27% over 5 linear steps from dioxinone **4**.

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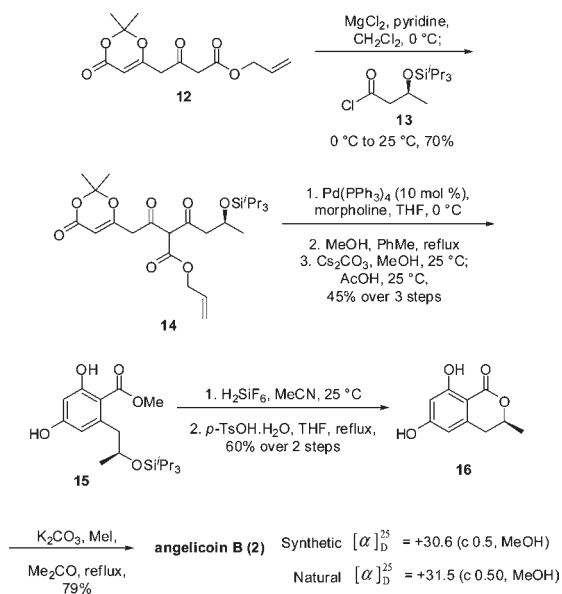
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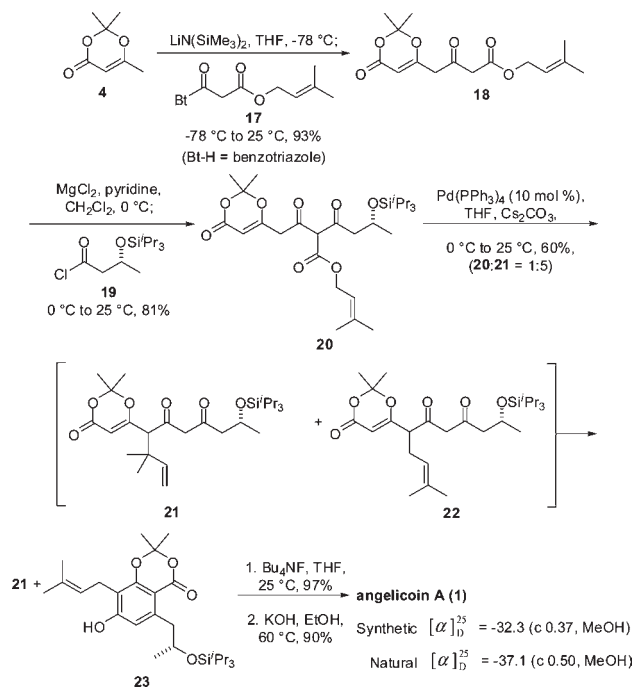
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(15) For X-ray crystal structures, see Supporting Information. Mechanistic studies are currently being carried out and will be reported in due course.

### Scheme 3. Synthesis of Angelicoin B (2)



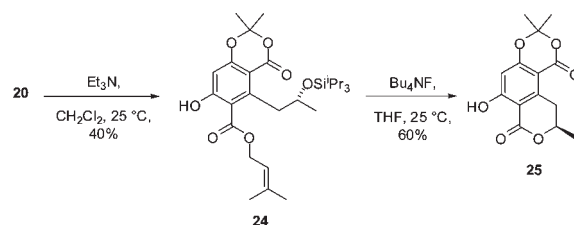
### Scheme 4. Synthesis of Angelicoin A (1)



Cyclization of diketoester-dioxinone **20** under basic conditions followed by deprotection of the silyl ether **24** furnished

phenol **25** in which the prenyl carboxylate ester was retained (Scheme 5). The structures of tricyclic lactone **25** and synthetic angelicoin A (**1**) were both confirmed by X-ray crystallographic studies, thereby confirming that the decarboxylation reaction was accompanied by prenyl migration.<sup>15</sup> This differs from the extensive work of Stoltz and co-workers, which was based upon the palladium-catalyzed enantioselective decarboxylative allylic alkylation reactions of ketone enolates without migration.<sup>16</sup> Our research illustrates that, for these precursors, only migration of the allyl or prenyl fragment is observed.

### Scheme 5. Retention of the Ester Functionality



In summary, we report total syntheses of angelicoin A (**1**) and B (**2**) using biomimetic aromatization reactions with a highly regioselective decarboxylative prenyl transfer reaction with the former natural product. We are further examining oligo-keto-dioxinone aromatization and decarboxylation-allyl rearrangement reactions mechanistically, in the total synthesis of other natural products, and in medicinal chemistry.

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**Supporting Information Available.** Experimental procedures for the synthesis of all new compounds, along with characterization data and spectra and X-ray structural data for compounds **1** and **25**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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