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

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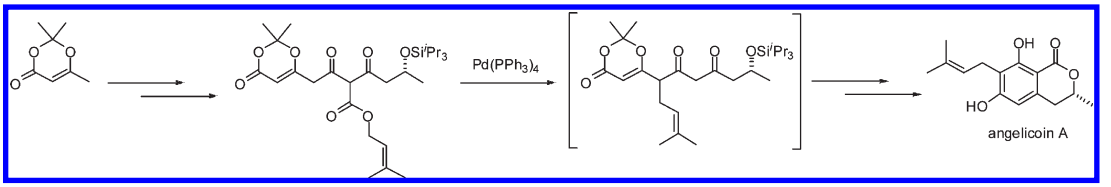
ABSTRACT



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.[1] 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 δ-lactone.[2] 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.[3] However, the majority of these approaches required multistep sequences with the need for phenol protection. Inspired by the elegant work of Harris,[4] Hyatt,[5] and Boeckmann,[6] we have developed an alternative strategy for the synthesis of resorcylate natural products employing a late-stage biomimetic aromatization of oligo-keto-esters.[7−9]

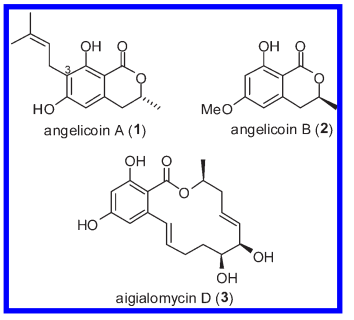


Figure 1. Angelicoin A (**1**) and B (**2**) and aigialomycin D (**3**).

(1) Unuyal, S. K.; Awasthi, A.; Rawat, G. S. *Curr. Sci.* **2005**, *82*, 1246.

(2) Shibano, M.; Naito, H.; Taniguchi, M.; Wang, N.-H.; Baba, K. *Chem. Pharm. Bull.* **2006**, *54*, 717.

(3) (a) Winssinger, N.; Barluenga, S. *Chem. Commun.* **2007**, *1*, 22. (b) Garbaccio, R. M.; Stachel, S. J.; Baeschlin, D. K.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2001**, *123*, 10903. (c) Fürstner, A.; Thiel, O. R.; Kindler, N.; Bartkowska, B. *J. Org. Chem.* **2000**, *65*, 7990. (d) Stob, M.; Baldwin, R. S.; Tuite, J.; Andrews, F. N.; Gillette, K. G. *Nature* **1962**, *196*, 1318.

(4) (a) Harris, T. M.; Harris, C. M. *Tetrahedron* **1977**, *11*, 2159. For further information, see:(b) Barrett, A. G. M.; Morris, T. M.; Barton, D. H. R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2272. (c) Birch, A J. *Fortschr. Chem. Org. Naturst.* **1957**, *14*, 186. (d) Birch, A. J.; Donovan, F. W. *Austral. J. Chem.* **1953**, *6*, 360.

(5) Hyatt, J. A.; Feldman, P. L.; Clemens, R. *J. Org. Chem.* **1984**, *49*, 5105.

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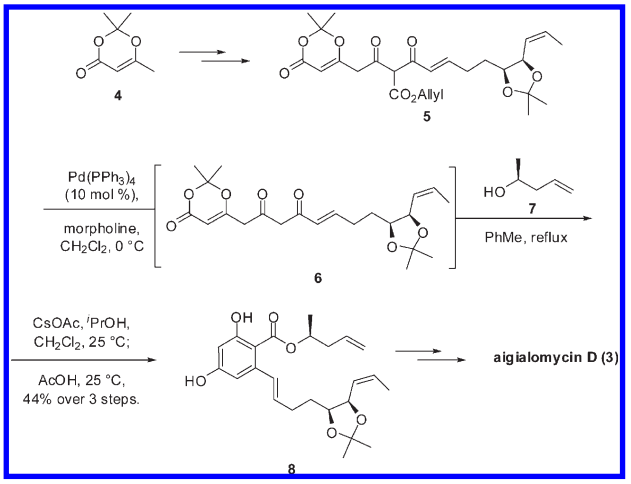
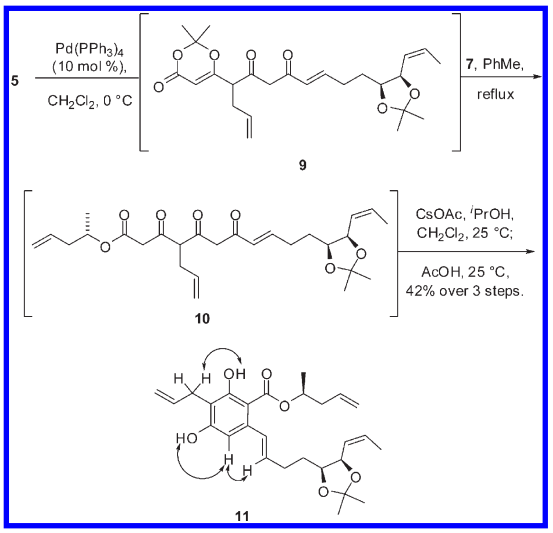
Recently, as part of these studies, we reported the total synthesis of aigialomycin D (**3**) (Figure 1). Our approach featured a key Pd(0)-catalyzed deallylation and decarboxylation of allyl ester **5**, employing morpholine as a nucleophilic palladium π-allyl cation scavenger,[10] to provide the ketene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

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



During these studies, we observed that reaction of allyl ester **5** with $Pd(PPh_3)_4$ in the absence of morpholine in CH_2CI_2 underwent a modified Carroll rearrangement[12] 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[11] provided resorcylate **11** in 42% yield over 3 steps. The regiochemistry of arene **11** was confirmed by NOE analysis in the ^1H NMR spectrum.[13] Herein we report for the first time this transformation and further studies on the total synthesis of resorcylates 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**[9] with acyl chloride **13** provided diketoester-dioxinone **14**. One pot palladium(0)-catalyzed deallyation-decarboxylation-ketene trapping-aromatization gave the desired resorcylate **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.[2]

Acylation of dioxinone **4** with acyl benzotriazole **17** gave ketoester **18** in 93% yield.[9,14] Subsequent Claisen condensation reaction of ketoester **18** with acid chloride **19**,[9] in the presence of magnesium chloride and pyridine, gave diketoester **20** in 81% yield. Decarboxylation of diketoester **20** in the presence of $Pd(PPh_3)_4$ (10 mol %) gave a separable mixture of dioxinone **21** and resorcylate **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**.

(6) (a) Boeckman, R. K., Jr.; Pruitt, J. R. *J. Am. Chem. Soc.* **1989**, *111*, 8286. (b) Boeckman, R. K., Jr.; Barta, T. E.; Nelson, S. G. *Tetrahderon Lett.* **1991**, *32*, 4091. (c) Boeckman, R. K., Jr.; Weidner, C. H.; Perni, R. B.; Napier, J. J. *J. Am. Chem. Soc.* **1989**, *111*, 8036. (d) Boeckman, R. K., Jr.; Shao, P.; Wrobleski, S. T.; Boehmler, D. J.; Heintzelman, G. R.; Barbosa, A. J. *J. Am. Chem. Soc.* **2006**, *128*, 10572. (e) Boeckman, R. K., Jr.; Goldstein, S. W. *Total Synth. Nat. Prod.* **1988**, *7*, 1. (f) Boeckman, R. K., Jr.; Perni, R. B. *J. Org. Chem.* **1986**, *51*, 5486. (g) Boeckman, R. K., Jr.; Starrett, J. E., Jr.; Nickell, D. G.; Sum, P. E. *J. Am. Chem. Soc.* **1986**, *108*, 5549. For application of intramolecular capture of acyl-ketenes in natural product synthesis, see the review by: (h) Reber, K. P.; Tilley, S. D.; Sorensen, E. J. *Chem. Soc. Rev.* **2009**, *38*, 3022.

(7) (a) Basset, J.-F.; Leslier, C.; Hamprecht, D.; White, A. J. P.; Barrett, A. G. M. *Tetrahedron Lett.* **2010**, *51*, 783. (b) Miyatake-Ondozabal, H.; Barrett, A. G. M. *Org. Lett.* **2010**, *12*, 5573. (c) Mikatake-Ondozobal, H.; Barrett, A. G. M. *Tetrahedron* **2010**, *66*, 6331.

(8) The diketo-dioxinones and triketo-compounds exist as keto−enol mixtures. For simplicity, all are drawn in the all keto-form.

(9) Navarro, I.; Basset, J. -F.; Hebbe, S.; Major, S. M.; Werner, T.; Howsham, C.; Brackow, C. J.; Barrett, A. G. M. *J. Am. Chem. Soc.* **2008**, *130*, 10293.

(10) Aubry, N.; Plante, R.; Déziel, R. *Tetrahderon Lett.* **1990**, *31*, 6311.

(11) Calo, F.; Richardson, J.; Barrett, A. G. M. *Org. Lett.* **2009**, *11*, 4910.

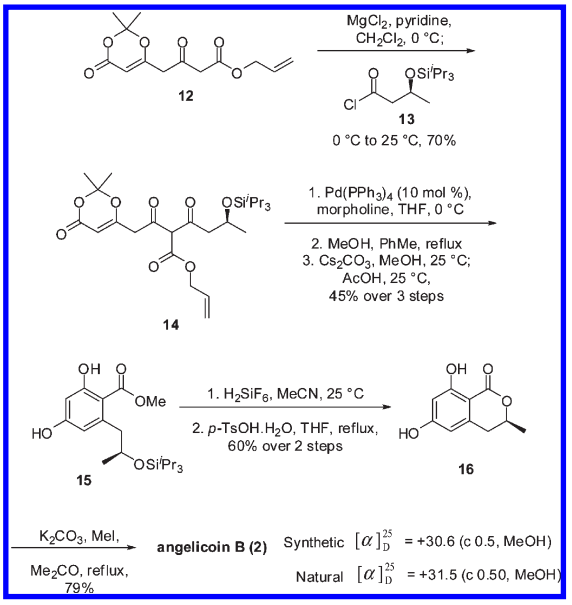
(12) (a) Carroll, M. F. *J. Chem. Soc.* **1940**, 704. (b) Shimizu, L.; Yamada, T.; Tsuji, J. *Tetrahderon Lett.* **1980**, *21*, 3199. (c) Tsuda, T.; Chujo, Y.; Nishi, S; Tawara, K.; Saegusa, T. *J. Am. Chem. Soc.* **1980**, *102*, 6381.

(13) Calo, F. PhD Thesis, Imperial College London, 2010.

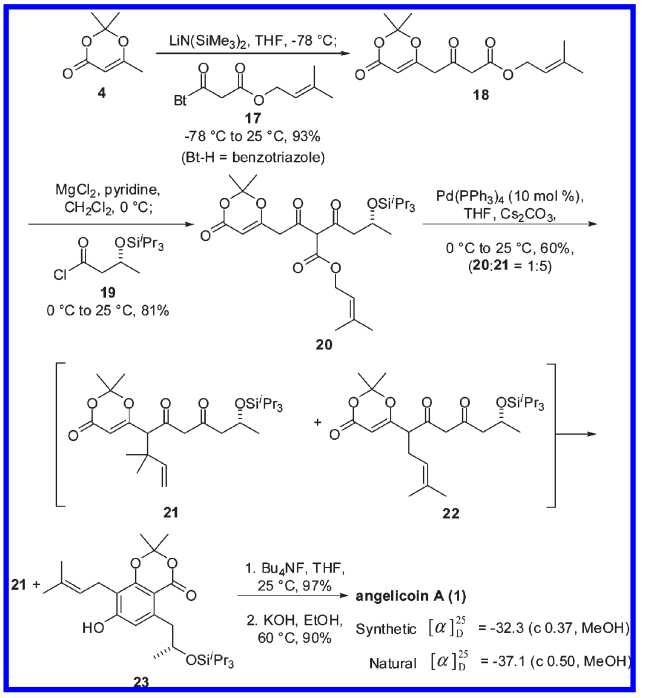
(14) Katritzky, A. R.; Wang, Z.; Wang, M.; Hall, C. D.; Suzuki, K. *J. Org. Chem.* **2005**, *70*, 4854.

(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**)

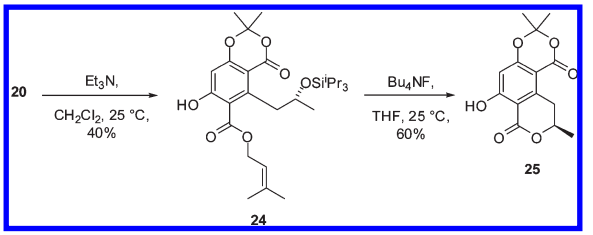


Scheme 4. Synthesis of Angelicoin A (**1**)



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.[15] 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.[16] 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.

(16) (a) Sherden, N. H.; Behenna, D. C.; Virgil, S. C.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6840. (b) Behenna, D. C.; Stoltz, B. M. *J. Am. Chem. Soc.* **2004**, *126*, 15044. (c) Mohr, J. T.; Behenna, D. C.; Harned, A. M.; Stoltz, B. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 6924. (d) Mukherjee, H.; McDougal, N. T.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2011**, *13*, 825.