

Biomimetic Total Synthesis of  
*ent*-Penilactone A and Penilactone B

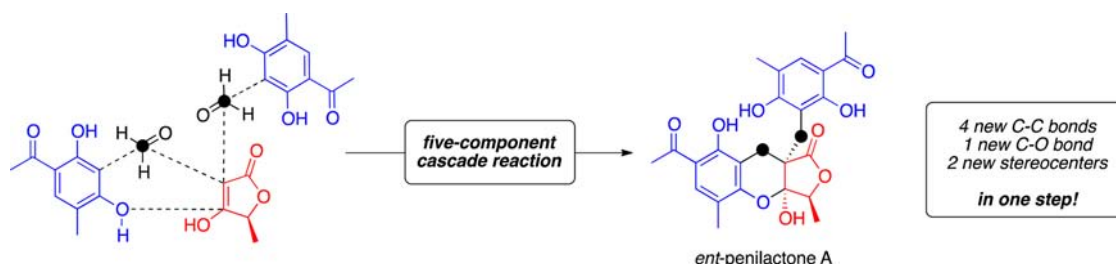
Justin T. J. Spence and Jonathan H. George\*

School of Chemistry and Physics, University of Adelaide, Adelaide, SA 5005, Australia

jonathan.george@adelaide.edu.au

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## ABSTRACT



The total synthesis of *ent*-penilactone A and penilactone B has been achieved via biomimetic Michael reactions between tetronic acids and *o*-quinone methides. A five-component cascade reaction between a tetronic acid, formaldehyde, and a resorcinol derivative that generates four carbon–carbon bonds, one carbon–oxygen bond, and two stereocenters in a one-pot synthesis of penilactone A is also reported.

Extremophiles (i.e., microorganisms that grow optimally under extreme conditions of temperature and pressure, or in an unusual chemical environment) are a valuable source of structurally diverse natural products.<sup>1</sup> In particular, deep sea microorganisms grow in darkness at low temperature and high pressure, and have therefore evolved biosynthetic pathways that produce unique secondary metabolites.<sup>2</sup> For example, penilactones A (**1**) and B (**2**) (Figure 1) are two unusual polyketide natural products isolated from *Penicillium crustosum* PRB-2, a fungus found in an Antarctic deep sea sediment.<sup>3</sup> The structures of **1** and **2** were elucidated using NMR and X-ray studies, revealing a novel tricyclic ring system. Furthermore, CD spectra showed that **1** and **2** possess opposite absolute configurations, which suggested to us that they might be formed in Nature by predisposed, nonenzymatic cascade reactions. They are therefore attractive targets for biomimetic synthesis.

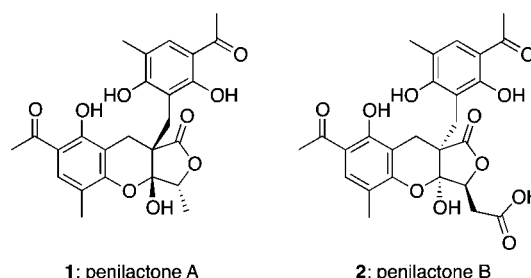


Figure 1. Penilactones A and B.

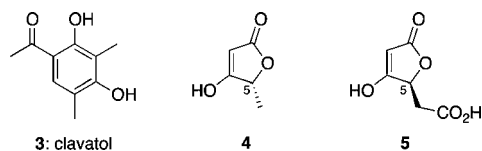
We have previously used biosynthetic speculation as a guide for the development of biomimetic cascade reactions that have been applied in very short syntheses of complex natural products.<sup>4</sup> Such an approach can inspire syntheses that rapidly install the molecular architecture of the natural product target with minimal protecting group operations and functional group interconversions.

As originally proposed by Li et al. in their isolation paper,<sup>3</sup> we believe that the biosynthesis of penilactones A (**1**) and B (**2**) involves reactions between *o*-quinone methides<sup>5</sup> and tetronic acids. This is supported by the coisolation of penilactones A and B with an oxidized

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(4) (a) George, J. H.; Hesse, M. D.; Baldwin, J. E.; Adlington, R. M. *Org. Lett.* **2010**, *12*, 3532–3535. (b) Pepper, H. P.; Lam, H. C.; Bloch, W. M.; George, J. H. *Org. Lett.* **2012**, *14*, 5162–5164.  
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derivative of clavatul (3),<sup>6</sup> a possible *o*-quinone methide precursor (Figure 2). Tetronic acids such as 4 and 5 are also common fungal metabolites,<sup>7</sup> and they are therefore reasonable biosynthetic precursors of penilactones A and B. Indeed, closely related tetronic acids to 4 and 5 have recently been isolated alongside clavatul (3) from *Penicillium griseoroseum*.<sup>8</sup>

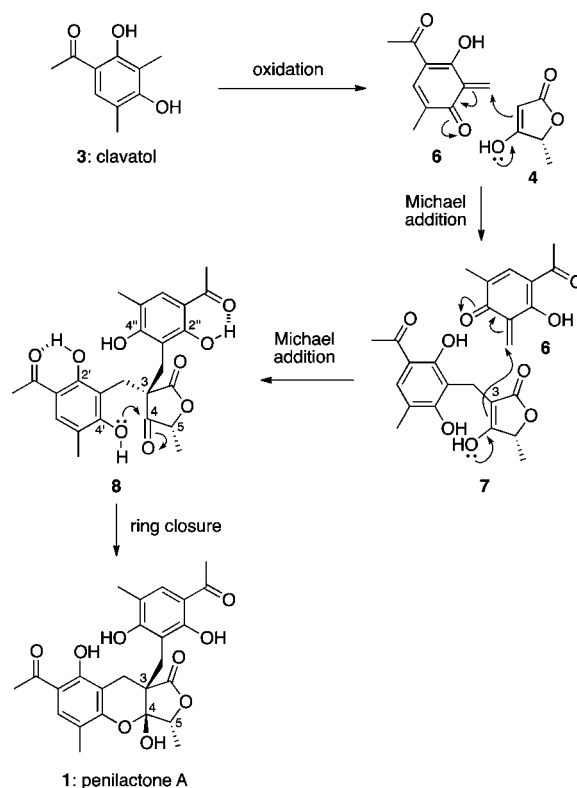


**Figure 2.** Plausible biosynthetic precursors of the penilactones.

A possible mechanism for the biosynthesis of penilactone A (1) is outlined in Scheme 1. Oxidation of clavatul (3) could give *o*-quinone methide 6. A sequence of two Michael addition reactions between tetronic acid 4 and two molecules of 6 would form ketone 8 via the enol 7, with formation of a quaternary carbon center at C-3. Ketone 8 could then undergo intramolecular nucleophilic attack of the C-4' hydroxy group at the C-4 carbonyl group to form penilactone A (1). This final cyclization step must be a selective process, since 8 possesses four distinct phenols that could potentially add to the C-4 ketone. However, the C-2' and C-2'' phenolic hydroxy groups are presumably deactivated by hydrogen bonding to the adjacent acetate groups, while the C-5 stereocenter might direct addition of the C-4' phenol rather than that attached to C-4''. A similar mechanism could account for the formation of penilactone B (2) from tetronic acid 5, with the C-5 stereocenter in this case dictating the formation of a molecule with the opposite absolute configuration to penilactone A (1).

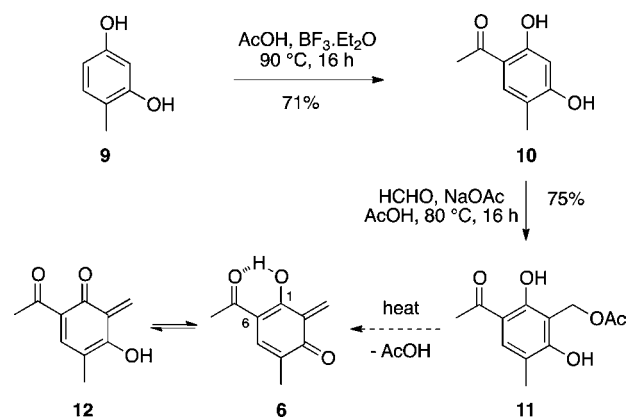
In order to gain insight into the biosynthetic mechanism outlined above, we planned to conduct a short biomimetic synthesis of the enantiomer of penilactone A (*ent*-1). This target was chosen, as (*S*)-5-methyl tetronic acid (*ent*-4) is readily synthesized from (*S*)-lactic acid.<sup>9</sup> We also needed to synthesize a suitable precursor of *o*-quinone methide 6, and 2-methyleneacetoxymethyl-4-methyl-6-acetylresorcinol (11) was targeted, as similar species have been shown to generate *o*-quinone methides under thermal conditions (Scheme 2).<sup>10</sup> Friedel–Crafts acylation of commercially available 4-methylresorcinol (9) gave 4-methyl-6-acetylresorcinol 10, which was reacted with HCHO, NaOAc, and AcOH to give 11 in good yield.<sup>11</sup> This compound could potentially generate two tautomeric *o*-quinone methides, 6 and 12, via thermal elimination of AcOH. Selective formation of

### Scheme 1. Proposed Biosynthesis of Penilactone A



*o*-quinone methide 6 was expected due to hydrogen bonding between the C-1 OH and the adjacent C-6 acetate group, although addition to either *o*-quinone methide tautomer should be effective in forming the penilactone target molecules.

### Scheme 2. Synthesis of *o*-Quinone Methide Precursor 11



Indeed, when 11 was heated in toluene in the presence of (*S*)-5-methyl tetronic acid (*ent*-4), *ent*-penilactone A (*ent*-1) was formed as a single stereoisomer in excellent yield (Scheme 3) by a mechanism that presumably follows the biosynthetic hypothesis outlined in Scheme 1. This biomimetic cascade reaction formed two carbon–carbon bonds, one carbon–oxygen bond, and two stereocenters in one step. The reaction was highly selective, as the final cyclization of

(7) Boll, P. M.; Sorensen, E.; Balieu, E. *Acta Chem. Scand.* **1968**, 22, 3251.

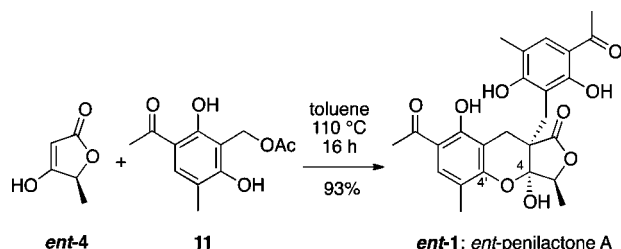
(8) Da Silva, J. V.; Fill, T. P.; Da Silva, B. F.; Rodrigues-Fo, E. *Nat. Prod. Res.* **2013**, 27, 9–16.

(9) (*S*)-5-Methyl tetronic acid was synthesized in two steps from (*S*)-ethyl lactate according to: (a) Fryzuk, M. D.; Bosnich, B. J. *J. Am. Chem. Soc.* **1978**, 100, 5491–5494. (b) Brandange, S.; Flodman, L.; Norberg, A. J. *Org. Chem.* **1984**, 49, 927–928.

(10) Rodriguez, R.; Adlington, R. M.; Moses, J. E.; Cowley, A.; Baldwin, J. E. *Org. Lett.* **2004**, 6, 3617–3619.

(11) This reaction presumably proceeds via the *o*-quinone methide 6.

### Scheme 3. Biomimetic Synthesis of *ent*-Penilactone A

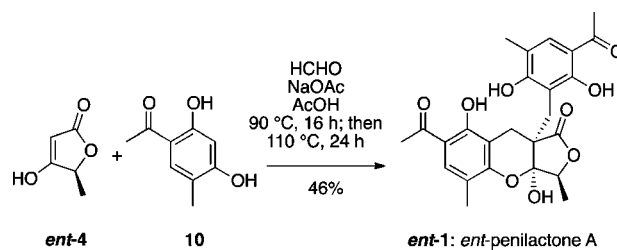


the intermediate ketone **8** must occur by preferential attack of the C-4' hydroxyl at the C-4 carbonyl group. If the reaction was stopped prematurely or run with an excess of the tetronic acid *ent*-4, the monoadduct **7** could be isolated, which adds further support to the biosynthetic proposal. The  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of *ent*-1 in  $\text{DMSO}-d_6$  showed the existence of a single compound and perfectly matched the published data of Li et al.<sup>3</sup> However, the NMR spectra of *ent*-1 in  $\text{CDCl}_3$  and  $\text{C}_6\text{D}_6$  showed a 7:1 mixture of two species, with the major compound being penilactone A and the minor compound being an as yet unidentified diastereomer of penilactone A. We believe this shows that the final cyclization to form the C-4 hemiacetal was under equilibrium, with penilactone A being the exclusively favored compound in DMSO. NOESY spectra revealed that the major diastereomer in  $\text{CDCl}_3$  and  $\text{C}_6\text{D}_6$  was the same diastereomer *ent*-1 as in  $\text{DMSO}-d_6$  and in the crystal structure of Li et al. Importantly, the optical rotation of *ent*-1,  $[\alpha]_{\text{D}}^{25} +37.8$  ( $c$  0.98, MeOH), showed good correlation with the literature value for **1**,  $[\alpha]_{\text{D}}^{20} -45.1$  ( $c$  0.1, MeOH), thus confirming the absolute stereochemical assignment of Li et al.<sup>3</sup>

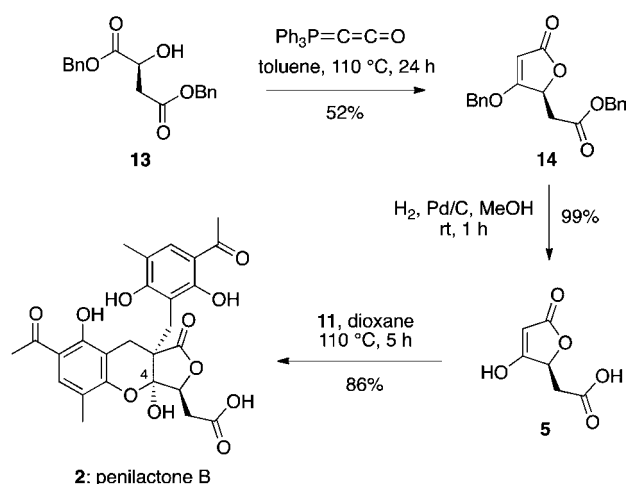
The synthesis of *ent*-penilactone A (*ent*-1) could be further shortened by combining the conversion of **10** to **11** with the subsequent biomimetic addition to tetronic acid *ent*-4 in a one-pot, five-component cascade reaction<sup>12</sup> (Scheme 4). This reaction directly assembles the natural product with the formation of four carbon–carbon bonds, one carbon–oxygen bond, and two stereocenters in a single step.

Synthesis of penilactone B (**2**) required tetronic acid **5**, which was made in two steps (Scheme 5). The first step was a domino addition–Wittig reaction of dibenzyl (*S*)-2-hydroxysuccinate (**13**)<sup>13</sup> with (triphenylphosphoranylidene)-ketene, which gave **14** according to the protocol developed by Schobert.<sup>14</sup> This was followed by debenzylation of **14** under standard conditions to give **5**. Heating **5** with **11** in dioxane then gave penilactone B (**2**) in excellent yield. Again, the  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra of **2** in  $\text{DMSO}-d_6$  showed a single compound that matched the published NMR data for penilactone B,<sup>3</sup> but alternative NMR solvents indicated a mixture of two diastereomers. We therefore suggest that both

### Scheme 4. Synthesis of Penilactone A via a Five-Component Cascade Reaction



### Scheme 5. Biomimetic Synthesis of Penilactone B



penilactones A and B can exist as a mixture of diastereomers due to a solvent-dependent equilibrium of ring opening and ring closure at the C-4 hemiacetal group. The optical rotation of synthetic **2**,  $[\alpha]_{\text{D}}^{25} +27.1$  ( $c$  1.0, MeOH), showed good agreement with the literature data,  $[\alpha]_{\text{D}}^{24} +29.4$  ( $c$  0.1, MeOH).<sup>3</sup>

In conclusion, we have developed a concise synthesis of *ent*-penilactone A (*ent*-1) and penilactone B (**2**) using a strategy guided by biosynthetic speculation. We have confirmed their absolute configurations and shown that the penilactones can exist as a solvent-dependent mixture of diastereomers due to ring opening at the C-4 hemiacetal group. This work also demonstrates the ability of biomimetic synthesis to rapidly generate complex natural products and gives some insight into the possible biosynthesis of the penilactones.

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**Supporting Information Available.** Synthetic procedures and analytical data for compounds *ent*-1, **2**, **5**, **10**, **11**, and **14**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.

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