

# A Biomimetic Synthesis of *des*-Hydroxy Paecilospirone

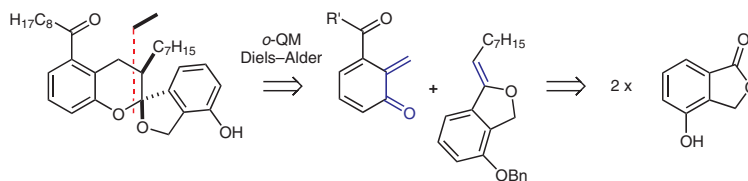
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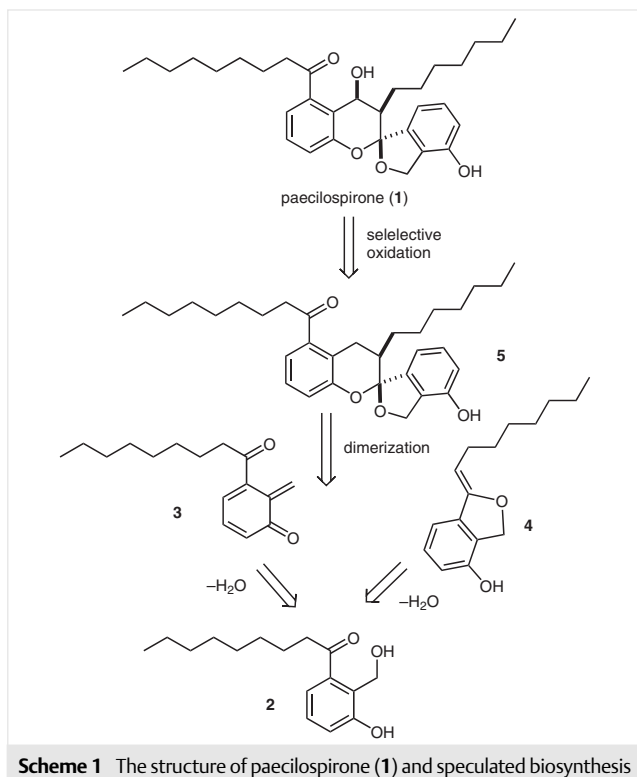
**Abstract** The carbon framework of *des*-hydroxy paecilospirone was rapidly synthesized using a biomimetic approach whereby an enol ether and an *ortho*-quinone methide (*o*-QM), each derived from the same lactone, were combined to arrive at the complete carbon skeleton of paecilospirone.

**Key words** *ortho*-quinone methide, Diels–Alder, paecilospirone, benzylic oxidation, enol ether

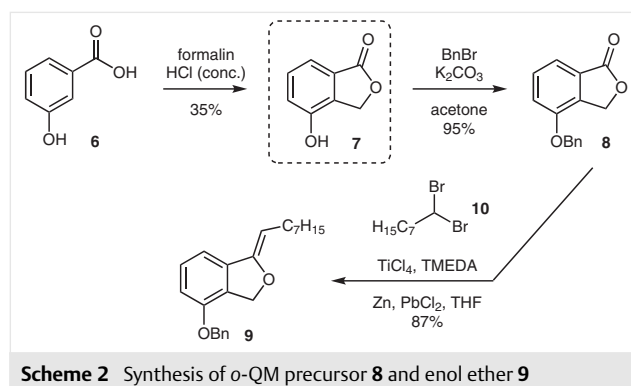
Paecilospirone was first collected from the marine fungus *Paecilomyces* sp. near Yap Island.<sup>1</sup> It was determined to have a rather unique spiro[chroman-2,1'(3'*H*)-isobenzofuran] structure that reportedly inhibited microtubule assembly. In 2011, Brimble and coworkers reported a total synthesis of (+)-paecilospirone in 19 steps.<sup>2</sup>

Our synthetic curiosity in this natural product emerged from an appreciation of its putative biosynthesis, which we propose (Scheme 1). We suppose that salicylic alcohol **2** extrudes water by different mechanisms to either form the *o*-quinone methide (*o*-QM) **3** or the enol ether **4**. Nature then combines these two entities to arrive at the tetracycle **5**, which undergoes further site selective benzylic oxidation to afford paecilospirone A (**1**). We decided to attempt to replicate this efficient process in the laboratory.

We suspected that the unprotected salicylic alcohol **2** might prove particularly unstable and highly reactive under chromatographic conditions, and thus it would not be a prudent choice of starting material. We therefore chose to begin our investigation with the phthalide **7**, which we imagined to be more easily harnessed for our synthetic purposes (Scheme 2). Compound **7** was prepared in a regioselective manner as first shown by Buehler.<sup>3</sup> Benzoic acid (**6**) and formalin were combined at ambient temperature for 24 hours in the presence of concentrated hydrogen chloride. These slightly modified conditions afforded the stable lac-

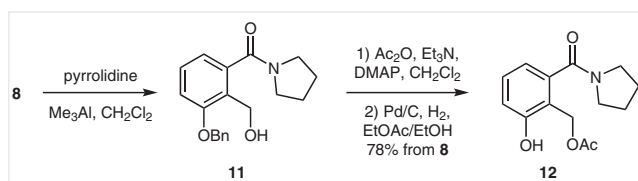


**Scheme 1** The structure of paecilospirone (**1**) and speculated biosynthesis



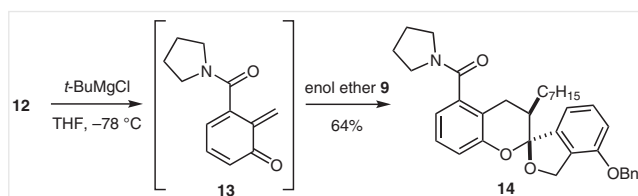
**Scheme 2** Synthesis of *o*-QM precursor **8** and enol ether **9**

tone **7** in a respectable 35% yield. The lactone **7** displays three  $sp^2$  atoms, positioning its five-membered ring into a nearly planar arrangement, which positions RC(=O)–O bond orthogonal to the aromatic  $\pi$ -system. Thus, when the phenol is deprotonated, it is not expelled as carboxylate to form the corresponding *o*-QM, affording stability to this intermediate. For this reason, phenol **7** underwent smooth benzylation under standard basic conditions to afford the benzyl ether **8** in a 95% yield. The carbonyl of the lactone **8** was subsequently found to form the heretofore unknown enol ether **9** as a single geometric isomer in an 87% yield by application of Takai's method with the dibromide **10**.<sup>4–7</sup> Compound **9** thus served as a surrogate of intermediate **4** postulated in the biosynthesis (Scheme 1).



**Scheme 3** Synthesis of a more manageable *o*-QM precursor from **8**

To construct a more manageable *o*-QM precursor leading to something resembling compound **3** in the proposed biosynthesis, the lactone ring in **8** would be opened, an appropriate electron-deficient leaving group installed on the benzylic alcohol, and the phenol protecting group then cleaved (Scheme 2). This proposition was accomplished in three steps by exposure of compound **8** to pyrrolidine and trimethylaluminum to form benzyl alcohol **11**, subsequent acetylation, and careful debenylation under as neutral conditions as possible to provide the phenol **12** in 78% overall yield (Scheme 3).

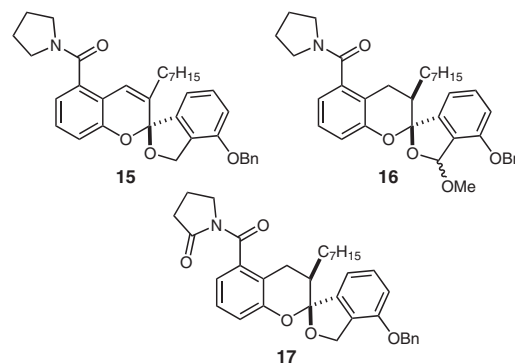


**Scheme 4** Base-triggered *o*-QM generation and cycloaddition

As anticipated from our earlier work with base-promoted generation of *o*-QMs,<sup>8,9</sup> we found that when an ethereal mixture of phenol acetate **12** and enol ether **9** was treated at  $-78^\circ\text{C}$  with *tert*-butylmagnesium chloride, the spiroketal **14** was formed in 64% yield (Scheme 4). We presume this smooth reaction is due to the controlled generation of the *o*-QM intermediate **13** by base-mediated elimination of the acetate, and subsequent inverse demand cycloaddition with the enol ether **9**.

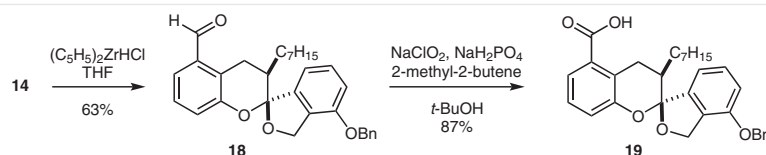
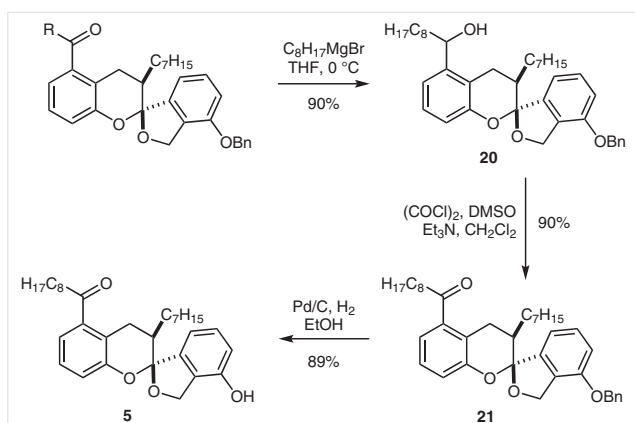
**Table 1** Oxidation of Amide **14**

| Entry | Conditions   | Main product |
|-------|--|--------------|
| 1     | DDQ, H <sub>2</sub> O, DCM   | <b>15</b>    |
| 2     | DDQ, AcOH, DCM   | <b>15</b>    |
| 3     | DDQ, MeOH  | <b>16</b>    |
| 4     | NaIO <sub>4</sub> , RuCl <sub>3</sub> ·H <sub>2</sub> O, CCl <sub>4</sub> , H <sub>2</sub> O, MeCN | <b>17</b>    |



With this material in hand, we were now poised to explore selective oxidation of the chroman core (Table 1). One of the reasons that we chose the amide **14** (Scheme 4), instead of something more closely resembling the ketone **5** (Scheme 1), was that the knowledge that amides could serve as surrogates for the respective ketone and acid functionalities. Unfortunately, the amide **14** failed to undergo the desired oxidation. Instead, we found that upon exposure of compound **14** to DDQ in water or acetic acid, the chromene **15** formed in low yield. On the other hand, when the DDQ oxidation was performed in methanol, a methoxy group was installed on the isobenzofuran ring resulting in a diastereomeric mixture of the acetals **16**. Furthermore, we found that application of ruthenium tetroxide caused oxidation of the pyrrolidine ring to afford the corresponding lactam **17**. While the chromene **15** might have proven useful in accessing the desired alcohol, the low yield of the chromene (<20%) dissuade further investigations. In addition, our attempts to remotely deprotonate amide **14** at its  $\gamma$ -position and oxidize the corresponding enolate, or some derivative of it, with DMDO or other suitable oxidants, also failed.

We therefore decided to investigate the conversion of the amide into the corresponding carboxylic acid in the hope that this functional group might facilitate oxidation of the chroman ring. This task was accomplished by a two-step procedure. First, the amide **14** was converted into the aldehyde **18** in 63% yield by its reduction with Schwartz's reagent. Subsequent Pinnick oxidation afforded the acid **19** in 87% yield (Scheme 5).<sup>10</sup> Unfortunately, we were unable to oxidize this material in the desired manner using a variety of procedures, such as hypervalent iodide,<sup>11,12</sup> lead tetraacetate,<sup>13</sup> or Pd(II).<sup>14</sup>

Scheme 5 Synthesis of acid **19**Scheme 6 Synthesis of *des*-hydroxy paecilospirone (**5**)

Unable to facilitate the desired benzylic oxidation of the either the amide **14** or then acid **19** in an acceptable yield the aldehyde **18** was elaborated into *des*-hydroxy paecilospirone (**5**) over three steps (Scheme 6). Nucleophilic addition of octyl magnesium bromide to the aldehyde **18** afforded the alcohol **20** in 90% yield. This material was converted into ketone **21** in 90% yield by a Swern oxidation. Hydrogenolysis of the benzylated phenol group furnished *des*-hydroxy paecilospirone (**5**) in 89% yield.<sup>15</sup>

In summary, a synthetic strategy resembling what we believe to be the biosynthesis of paecilospirone has been completed. Our approach utilizes an *o*-QM and an enol ether synthesized from the same starting material and arrives at *des*-hydroxy paecilospirone (**5**) in just ten steps. The approach may be amenable to enantioselective control through a chiral amide. Perhaps a method for the selective oxidation of such complex systems, as compounds **14**, **19**, and **5** with their numerous benzylic sites, will be discovered that can emulate nature's abilities which routinely surpass our own.

## Funding Information

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## Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/s-0036-1592001>.

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- (15) Compound **5**: <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ = 7.30–7.24 (m, 2 H), 7.16 (t, *J* = 7.9 Hz, 1 H), 6.95–6.90 (m, 2 H), 6.80 (d, *J* = 7.9 Hz, 1 H), 5.30 (s, 1 H), 5.25 (d, *J* = 12.8 Hz, 1 H), 5.07 (d, *J* = 12.8 Hz, 1 H), 3.30 (dd, *J* = 17.6, 5.5 Hz, 1 H), 3.01–2.84 (m, 3 H), 2.36–2.25 (m, 1 H), 1.77–1.67 (m, 2 H), 1.46–1.07 (m, 22 H), 0.87 (t, *J* = 7.0 Hz, 3 H), 0.83 (t, *J* = 7.1 Hz, 3 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>) δ = 204.8, 153.5, 150.0, 141.0, 138.2, 129.8, 126.9, 126.7, 122.4, 121.4, 120.6, 115.7, 114.5, 111.6, 70.6, 41.9, 38.2, 31.8, 31.8, 30.6, 29.6, 29.4, 29.2, 29.1, 26.8, 26.1, 24.6, 22.7, 22.6, 14.1, 14.1. IR ν<sub>max</sub> (neat): 3393, 2925, 2854, 1670, 1607, 1455, 1287, 1258, 927. HRMS (ESI<sup>+</sup>) calcd for C<sub>32</sub>H<sub>44</sub>O<sub>4</sub>Na [M+Na]<sup>+</sup>: 515.3137; found: 515.3126