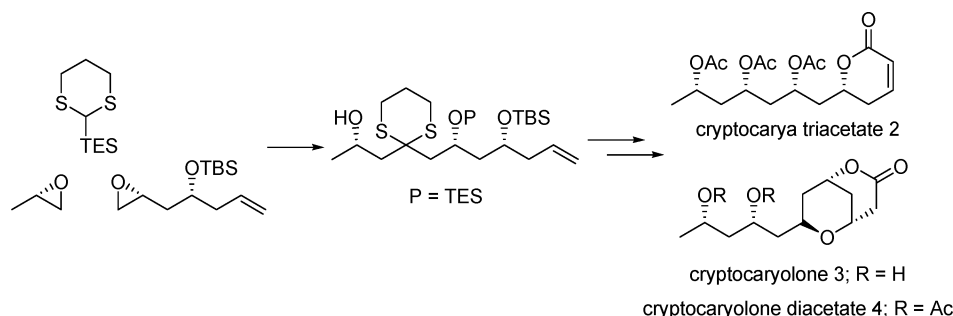


Efficient Asymmetric Total Syntheses of  
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and Cryptocaryolone DiacetateXiaolei Wang,<sup>†</sup> Wenkuan Wang,<sup>†</sup> Huaiji Zheng,<sup>†</sup> Yingpeng Su,<sup>†</sup> Tuo Jiang,<sup>†</sup>  
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## ABSTRACT



**Concise and efficient asymmetric total syntheses of three substituted  $\alpha$ -pyrone-type natural products have been accomplished via 7–9 steps from 5b in high overall yields, which involve linchpin coupling, ring-closing metathesis, and a tandem sequence of deacetylation and intramolecular oxa-Michael addition as the key steps.**

Cryptocarya triacetate **2**, cryptocaryolone **3**, and cryptocaryolone diacetate **4** were isolated from the bark of a South African plant, *Cryptocarya latifolia*.<sup>1</sup> Related investigations showed that they have significant biological activities and medical properties, ranging from the treatment of headaches and morning sickness to that of cancer, pulmonary diseases, and various bacterial and fungal infections.<sup>2</sup> The absolute and relative stereochemistries of cryptocarya acetates **1** and **2** were determined by a combination of Mosher's ester and <sup>13</sup>C NMR/acetonide analysis.<sup>3</sup> The characteristic biological activities and the interesting architectures have stimulated

synthetic efforts directed toward their total syntheses.<sup>4</sup> The first total syntheses of cryptocarya acetates **1** and **2** were accomplished by Nakata in 16 and 24 steps, respectively.<sup>5</sup> Subsequently, other synthetic approaches of **2**, **3**, and **4** were

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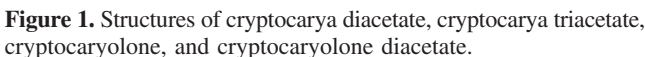
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$5a(b)$  +  $7$   $\xrightarrow[\text{solvent}]{n\text{-BuLi, HMPA}}$   $8a(b)$  and  $9a(b)$

$5a$  R = MOM  
 $5b$  R = TBS  
 P = TES

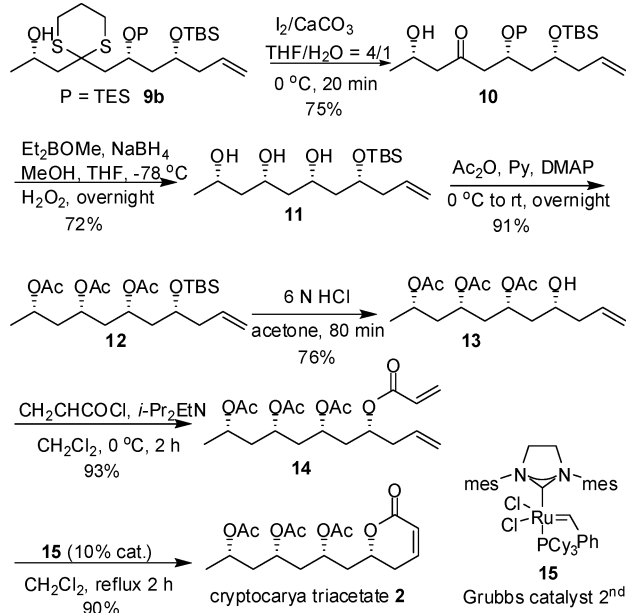
<sup>a</sup> a: -78 °C, 1 h; **5**, then -40 °C, 1 h; -50 °C, HMPA, 15 min; **7**, -78 °C to rt, overnight. b: 0 °C, 10 min; **5**, then -35 °C, 1 h; -50 °C, HMPA, 15 min; **7**, -78 °C to rt, overnight. c: 0 °C, 10 min; **5**, then -35 °C, 1 h; HMPA and **7**, -50 °C to rt, overnight.

**B**

(entries 3 and 4). While TBS-protected substrate **5b**,<sup>11</sup> which can be prepared from 1,6-heptadien-4-ol via 4 steps, was used in linchpin coupling with **6** and **7**, disubstituted dithiane **9b** was successfully obtained in 74% yield (entry 5).

With the advanced intermediate **9b** in hand, removal of the dithiane, followed by hydroxyl-directed reduction of the resulting ketone **10**,<sup>12</sup> gave triol **11** in 72% yield (Scheme 2). Triol **11** was easily peracetylated to provide triacetate olefin

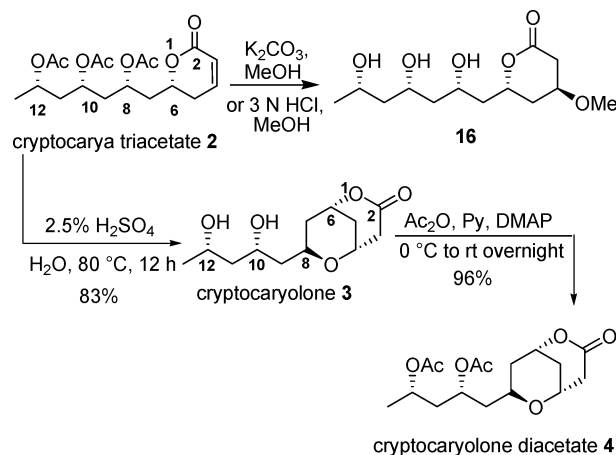
**Scheme 2.** Synthesis of Cryptocarya Triacetate **2**



**12** in 91% yield. Cleavage of the *O*-TBS protection of **12** under the treatment of 6 N aqueous HCl<sup>13</sup> resulted in alcohol **13**, while also a small amount of an acyl-migrated compound was observed. Coupling between alcohol **13** and acrylyl chloride proceeded smoothly to afford acrylate **14** in 93% yield, which underwent ring-closing metathesis utilizing the second-generation Grubbs' catalyst **15**<sup>14</sup> to furnish cryptocarya triacetate **3** in 90% yield.

According to our retrosynthetic analysis, a crucial tandem process combining deacylation and 1,4-oxa-Michael addition required considerable effort to facilitate the formation of the desired cryptocaryolone **3**. Under either basic or acidic conditions in organic protic solvent, such as K<sub>2</sub>CO<sub>3</sub>/MeOH and HCl/MeOH, MeOH performed as the *O*-nucleophile and

**Scheme 3.** Syntheses of Cryptocaryolone **3** and Cryptocaryolone Diacetate **4**



only lactone triol **16** was identified (Scheme 3). To our delight, when subjected to H<sub>2</sub>O with a catalytic amount of H<sub>2</sub>SO<sub>4</sub>, cryptocarya triacetate **2** experienced global deacylation simultaneously followed by a spontaneous oxa-Michael addition of the free hydroxyl group at the C-8 position to the unsaturated lactone moiety to provide cryptocaryolone **3**. Cryptocaryolone **3** was then treated by Ac<sub>2</sub>O/py to afford cryptocaryolone diacetate **4** in 96% yield. The analytical and spectral data of synthetic **2**, **3**, and **4** were in good agreement with those previously reported for cryptocarya triacetate **2**, cryptocaryolone **3**, and cryptocaryolone diacetate **4**.<sup>1,6</sup>

In summary, we have finished the concise and efficient asymmetric total syntheses of cryptocarya triacetate **2**, cryptocaryolone **3**, and cryptocaryolone diacetate **4** in 7–9 steps with 23%, 18%, and 18% overall yields, respectively. The stereogenic centers at C-8 and C-12 positions were economically constructed by a three-component linchpin coupling, while ring-closing metathesis (RCM) was also employed as a feasible choice for the formation of an unsaturated lactone moiety. Syntheses toward these three natural products further demonstrate the value of linchpin technology, substantiating the biosynthetic hypothesis raised by Drewes and allowing significant stereochemical flexibility to initiate structure–activity relationship studies.<sup>1</sup>

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**Supporting Information Available:** Complete experimental procedures and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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