



# Synthesis of five natural butanolides

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## ARTICLE INFO

### Article history:

Received 20 March 2018

Received in revised form

12 April 2018

Accepted 13 April 2018

Available online 18 April 2018

### Keywords:

Photosensitization

Baylis–Hillman reaction

Natural product

Cycloaddition

Lactones

## ABSTRACT

Litseadioxanins A and B, the so far only known natural products with a dihydrodioxine ring at the terminal of a side chain, were synthesized for the first time. The peroxy functionality was installed via a photo [4 + 2] cycloaddition of O<sub>2</sub> to a multifunctional terminal 1,3-diene, a subtype of the reaction that has only a limited number of simple precedents (mostly monofunctional/with a much shorter alkyl chain) in the literature to date. LED was found to be superior to traditional mercury or tungsten lamps, not only giving better yields but also significantly simplifying the operations. The diene precursors (also natural products) to litseadioxanins were also synthesized for the first time. With the aid of the synthetic samples the previously unknown concentration/time–dependence of [α]<sub>D</sub> of these dienes was revealed.

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## 1. Introduction

Litseadioxanins A and B (**1** and **2**, Fig. 1), two of those lactones isolated<sup>1a</sup> from the stem bark of *Litsea akoensis* (a medium-sized ever green tree), appeared to be rare examples of natural butanolides. Unlike all other γ-lactones isolated from this plant previously, **1** and **2** carried a dihydrodioxine ring at the terminal of a long side chain (the only known cases in natural products to date). Most oxygen atoms in natural products (e. g., those in carbonyl, carboxylic and hydroxyl groups) are derived from dioxygen via trapping of <sup>3</sup>O<sub>2</sub> by carbon-centered radicals, ene reaction or [4 + 2] cycloaddition of <sup>1</sup>O<sub>2</sub> with alkenes or 1,3-dienes, respectively. Given dienes **3**<sup>1b</sup> and **4**<sup>1c</sup> were also found in the stem bark of the same plant, the dihydrodioxine ring in **1** and **2** strongly suggested that their biosynthesis involved a cycloaddition of dioxygen to the dienes.

However, photosensitized [4 + 2] cycloaddition<sup>2</sup> of dioxygen to linear terminal 1,3-dienes are rare (all performed under “classic” conditions with either mercury or tungsten lamp as the light sources) and only limited to those monofunctional/structurally simple ones with a rather short chain (mostly of only one or two CH<sub>2</sub> units); the precedents involving a terminal 1,3-diene located at

the terminal of a long alkyl chain do not seem to have ever been reported to date (to the best of our knowledge). Thus, demonstration of smooth access to **1** and **2** from **3** and **4** by chemical synthesis would not only verify the structures and configurations of the dihydrodioxine-containing butanolides, but also provide supporting evidence that in these cases the peroxy oxygen atoms biogenically were indeed from dioxygen via the cycloaddition reaction.<sup>3</sup>

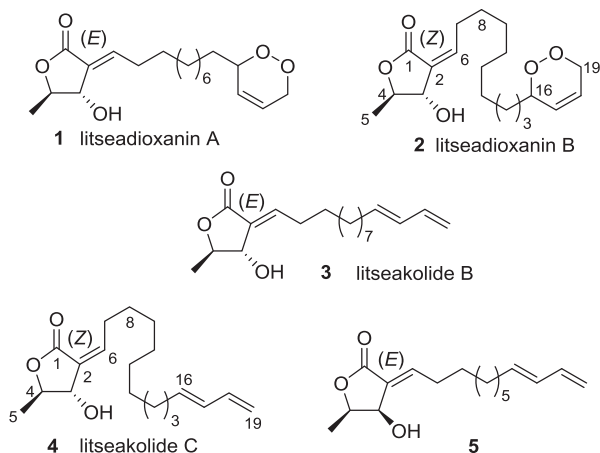
## 2. Results and discussion

To minimize the uncertainty caused by the photo [4 + 2] cycloaddition of dioxygen to linear terminal dienes, at the outset of this work we used a model compound derived from 10-undecenoic acid (through converting the terminal C–C double bond to a 1,3-diene) to probe this reaction. The result clearly showed that such peroxy heterocycles were not very stable (tending to decompose even during storage) and the cycloaddition of terminal dienes located at the end of a long alkyl chain was indeed much more difficult than cyclic dienes or internal linear dienes. To avoid complications, it appeared wise to place the installation of the dihydrodioxine ring at the end of the synthesis.

The synthesis of the long chain with a terminal conjugated diene began as described in Scheme 1. Ozonolysis of the known **6**<sup>4</sup> (readily prepared from the corresponding alcohol by TBS protection) followed by reductive workup with Ph<sub>3</sub>P gave known<sup>5</sup>

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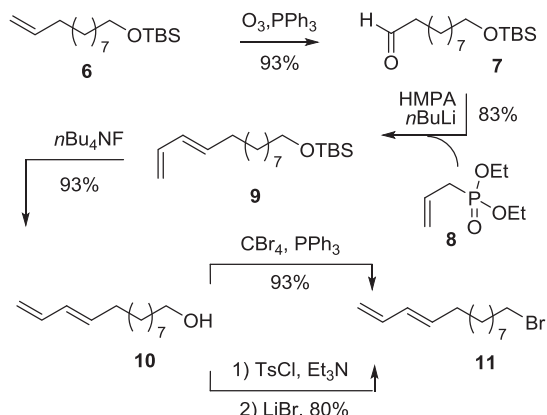


**Fig. 1.** The structure and configurations of five natural butanolides verified through synthesis in this work.

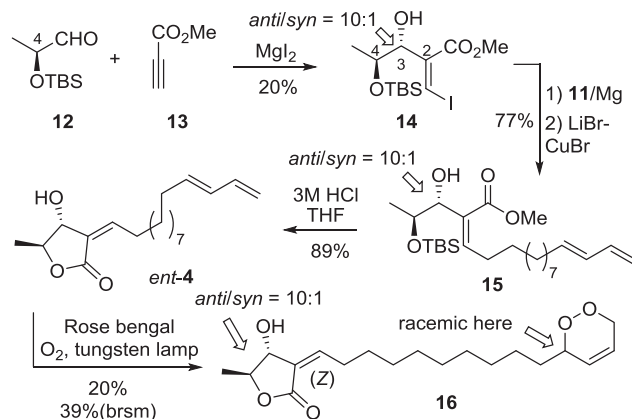
aldehyde **7**. The diene subunit was then installed by a Horner–Wadsworth–Emmons reaction with **8**<sup>6</sup> (deprotonated with *n*-BuLi). The TBS in the resulting **9** was cleaved to give **10**<sup>7</sup> and the newly freed OH was converted into the corresponding bromide **11**<sup>8</sup> with CBr<sub>4</sub>/PPh<sub>3</sub>.

The subsequent steps were then explored using the known<sup>10</sup> aldehyde **12** we had in hand via a Morita–Baylis–Hillman<sup>11</sup> reaction. Under the literature conditions, the best selectivity of the C-3/C-4 diol centers was 0.7:1 of *anti*/*syn* (difficult to separate from each other), with a yield of 20% (10:1 of *anti*/*syn* after chromatography, Scheme 2).

Connection of the Grignard reagent prepared in situ from **11** with the vinyl iodide **14** in the presence of LiBr–CuBr gave **15** in 77% yield. Removal of the TBS protecting group and lactonization occurred under the same conditions (3 M HCl/THF), affording lactone *ent*-**4**. Finally, photosensitized [4 + 2] cycloaddition reaction was performed under O<sub>2</sub> (balloon) to afford the end product **16** (i.e., a 10:1 mixture of **1** and its C-3 epimer). As mentioned above, in initial model reactions, we already observed that the dihydrodioxine ring was not stable. It was particularly obvious when using a 125 W high pressure mercury lamp as the light source (with rose bengal as the sensitizer; the desired dihydrodioxine in the reaction mixture was nearly negligible while using methylene blue instead of rose bengal as the sensitizer led to no reaction at all). Use of a tungsten lamp (external irradiation) as reported by Taylor<sup>2m</sup> gave much better results. The expected cycloaddition product



**Scheme 1.**



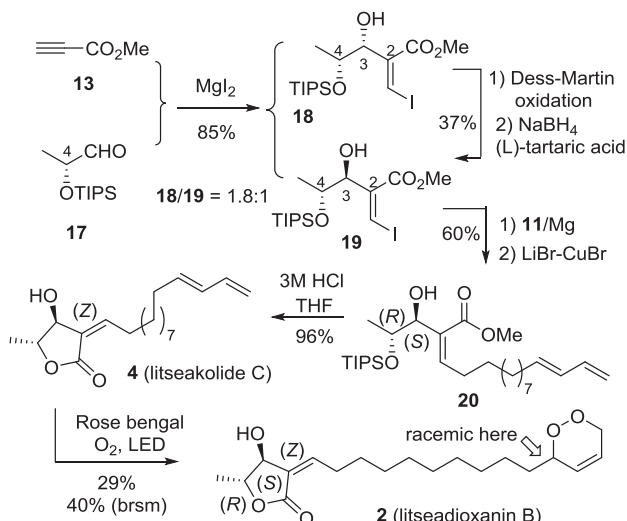
**Scheme 2.**

could be isolated in ca. 20% isolated yield. However, the heat generated by the tungsten lamp (250 W) was still a serious problem, which appeared to be at least partially responsible for the decomposition of the cycloaddition product.

Synthesis of natural **2** was then performed as shown in Scheme 3. In efforts to improve the result of the Morita–Baylis–Hillman reaction, we tested a range of different reactants ratios, temperatures and sequences of additions. However, the undesired *syn* isomer was almost always slightly more than the *anti* isomer, no matter what protecting group on the hydroxyl group was used. The chiral catalyst (effective on aldehydes in conjugate with a C–C double bond) reported by Ryu<sup>3c</sup> failed to give any expected product here. Fortunately, we found that when using TIPS as the protecting group, the two isomers<sup>12</sup> (**18**/**19** = 1.8:1) could be separated cleanly on silica gel (while the corresponding isomers carrying a TES, TBS, TBDPS, PMB or MOM were inseparable). The undesired isomer **18** could be partially recycled via oxidation with Dess–Martin periodinane followed by asymmetric reduction<sup>13</sup> with NaBH<sub>4</sub>/(L)-tartaric acid.

The isolated pure **19** was then treated with the Grignard reagent prepared from **11** in the presence of LiBr–CuBr to afford **20** in 60% yield, which on removal of the silyl protecting group and lactonization (3 M HCl/THF) resulted in **4**.

The <sup>1</sup>H and <sup>13</sup>C NMR of **4** were in full consistent with those



**Scheme 3.**

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