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Total syntheses of the proposed structures of cuevaene A

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ABSTRACT

Two proposed structures of cuevaene A were synthesized and the NMR spectra of both structures are proved to be inconsistent with those of the natural product. The structure of cuevaene A is still unclear and needs to be revised.

In 2000, the Gräfe group reported the isolation of cuevaenes A and B, both of which displayed moderate antibacterial activity against Gram-positive bacteria.[1] Very interestingly, two structurally related compounds, named JBIR-23 and -24, were reported by the Takagi and Shin-ya group in 2009. JBIR-23 and -24 were isolated from the same species, but showed highly cytotoxic effects against several malignant pleural mesothelioma (MPM) cell lines.[2] All of these natural products embrace a tricyclic core and a polyene side chain with an enol methyl ether inside. Such type of triene fragment is novel in natural products and has never been reported before, to the best of our knowledge. However, the structure of cuevaene A was originally proposed as compound **1**, the Takagi and Shin-ya group suggested to revise it to compound **2** by altering the connective position of the polyene side chain to the same site on the cyclohexane ring as that in JBIR-23 and -24, based on the extensive NMR correlations of JBIR-23 and -24 and the possible biosynthetic relationship between them and cuevaene A (Fig. 1). Allured by the novel but uncertain structure of cuevaene A and to lay a foundation for the total synthesis of JBIR-23 and -24, we were interested and involved in the total synthesis and structural confirmation of cuevaene A. Herein, we would like to present our endeavors on the total syntheses of compounds **1** and **2**.

Convinced by the intimate relationship of the structure and biosynthesis between cuevaene A and JBIR-23 and -24, we decided to initiate the total synthesis of compound **2**. The retrosynthesis of compound **2** is depicted in Scheme 1, following a linear strategy. Accordingly, the triene side chain of the target molecule could be

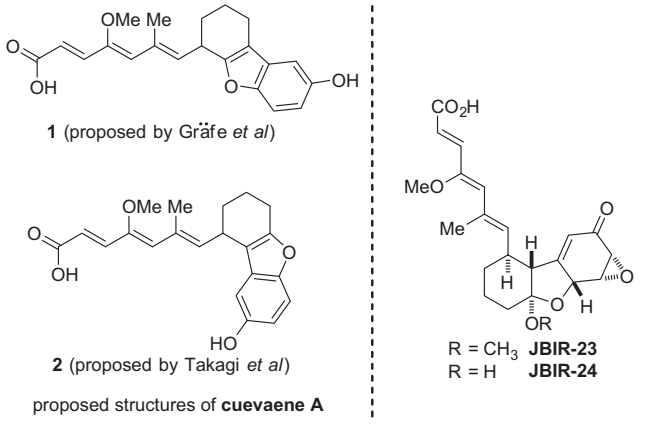
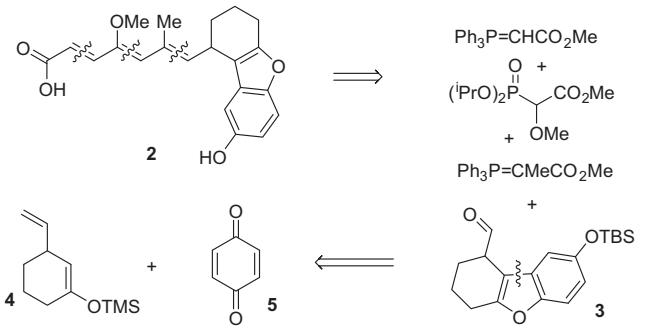


Figure 1. Proposed structures of cuevaene A and JBIR-23 and -24.



Scheme 1. Retrosynthetic analysis of compound **2**.

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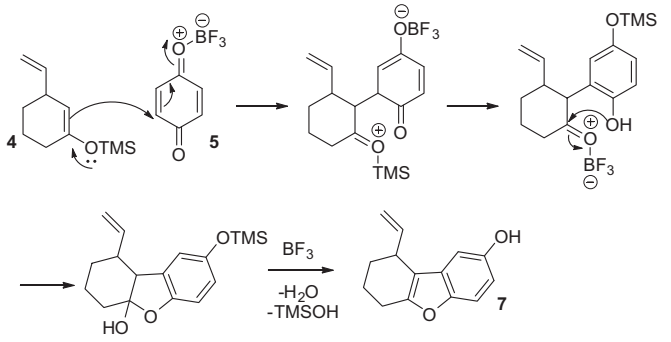


Scheme 2. Formation of compound **7**.

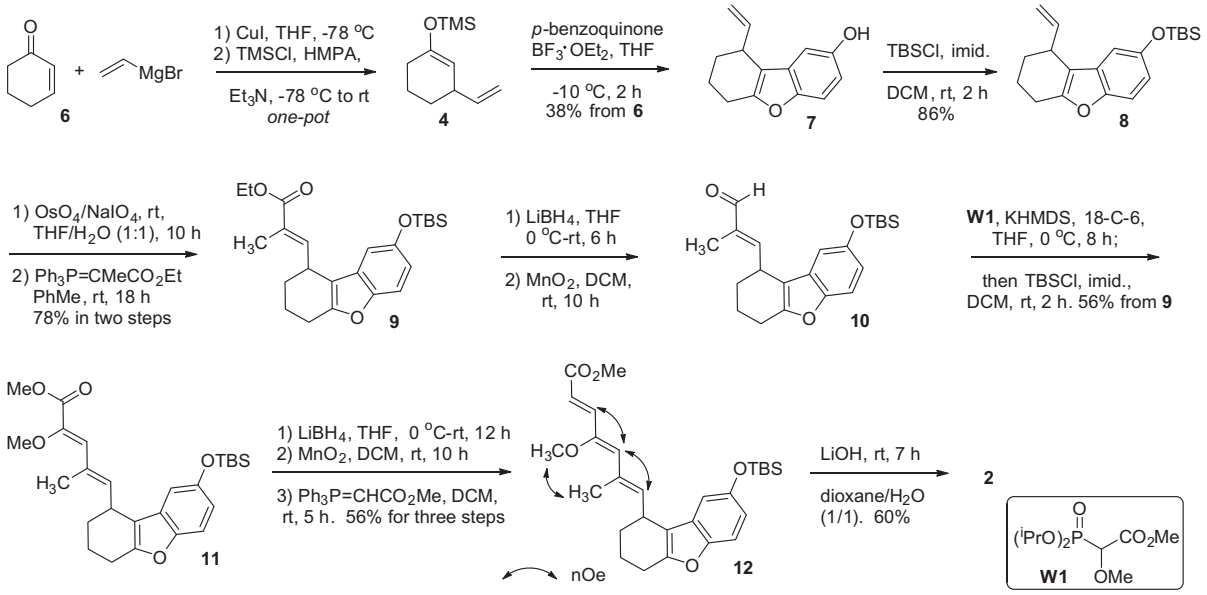
installed by Wittig reactions and HWE reaction sequentially. Retrosynthetically, we envisioned the 6–5–6 fused tricyclic motif arising from a Lewis acid-promoted cascade methodology, and coupling with enol silyl ether **4** and *para*-benzoquinone **5**.

According to the known procedure,[3] compound **4** was facilely prepared via Michael addition of vinyl Grignard reagent with 2-cyclohexen-1-one in the presence of copper (I) iodide, which was followed by a cascade reaction promoted by boron trifluoride, affording compound **7**. Actually, the formation of benzofuran from cyclohexenyloxytrimethyl-silane and *para*-quinone in the presence of lithium perchlorate had been described in the literature.[4] However, we found that the application of lithium perchlorate did not facilitate the workup process for the cascade reaction in a preparative scale, while using boron trifluoride instead achieved comparable yield (Scheme 2).

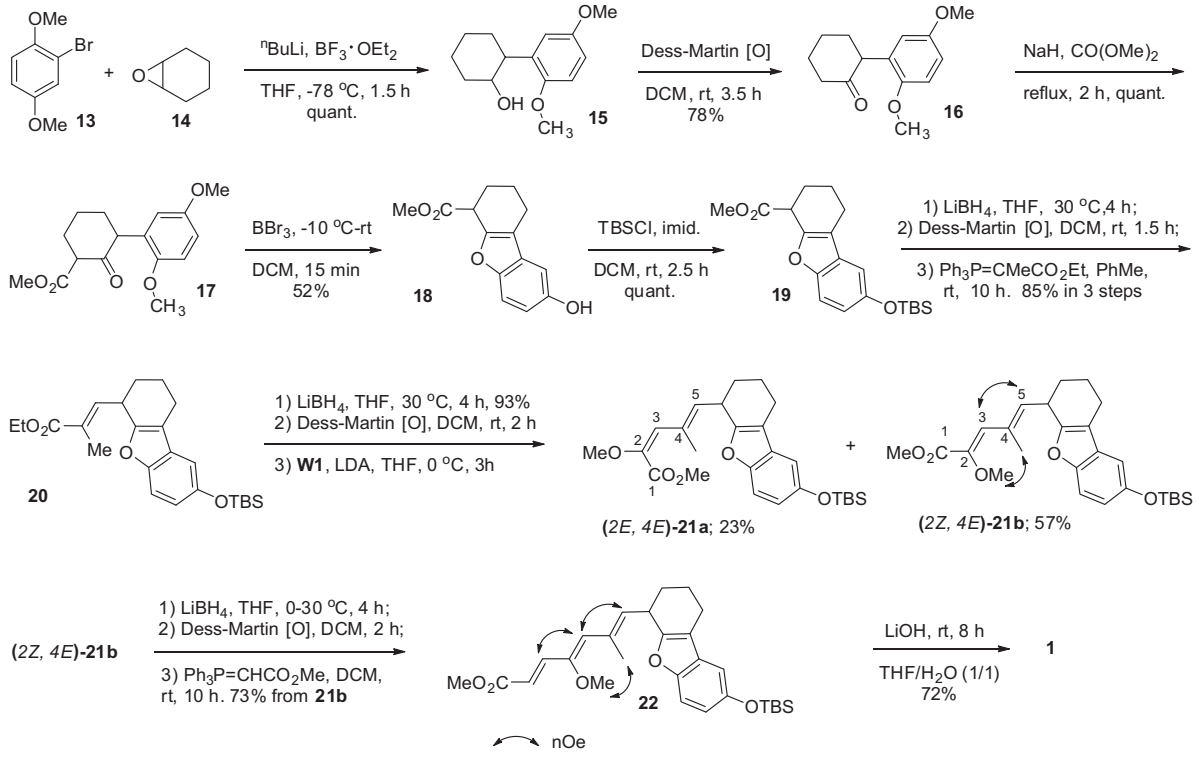
After the protection of the free phenol of compound **7**, the terminal alkene was transformed to an aldehyde via Johnson–Lemieux oxidation ($OsO_4/NaIO_4$), which was subjected to Wittig condition to give compound **9** as the sole detected stereoisomer. After following the routine reduction–oxidation transformation, aldehyde **10** was obtained from ester **9**. Then the second trisubstituted alkene fragment was constructed as the only detected stereoisomer through coupling of aldehyde **10** with reagent **W1**.[5] Since the silyl protective group on phenol was cleaved under the WHE reaction condition, reprotection was made to produce compound **11**. The installation of the last disubstituted alkene was achieved via a reduction–oxidation-Wittig reaction sequence to give ester **12**. The desired stereochemistry of the triene fragment was confirmed by NOESY and NOE difference spectrometry of compound **12**. The proposed structure of cuevaene A, compound **2**, was achieved by removing the TBS protection and hydrolyzing the ester with lithium hydroxide (Scheme 3). However, to our disappointment, the NMR spectra of the synthetic compound **2** do not fit with those of cuevaene A.[6] The major difference between the ^{1}H NMR of cuevaene A and that of compound **2** is the space between the chemical shifts of H5 and H7 on the spectra (0.26 ppm vs 0.07 ppm). Thus we wondered if the structure originally proposed by the Gräfe group be the real one of cuevaene A.

Then we turned our attention to the total synthesis of compound **1**, starting with an epoxide-opening reaction with bromide **13** and epoxide **14**. After compound **15**[7] was obtained in a quantitative yield, it was oxidized to ketone **16** under Dess–Martin condition. The introduction of the side chain of compound **1** began with the installation of an ester at α-position of the ketone, achieving compound **17**.[8] In the presence of boron tribromide,[9] the deprotection of methyl ether and the formation of benzofuran were realized in one-pot in 52% yield to form compound **18**, whose free phenol was protected as TBS ether **19** in a quantitative yield. After the remaining construction of the triene fragment on the side chain by following the same sequence as in Scheme 3, compound **1** was achieved. It is worth noting that two isomers (**21a**/**21b**) were obtained in a ratio of 1:2.5 when compound **20** reacted with the reagent **W1**. The relative configurations of the double bonds of **21** and **22** were confirmed through NOE difference spectrometry or NOESY. The final transformation with lithium hydroxide afforded compound **1** (Scheme 4). Unfortunately, the NMR spectra of the synthetic compound **1** are closely similar to those of the synthetic compound **2**, and still inconsistent with those of the natural cuevaene A.

In summary, we have completed the syntheses of two proposed structures of cuevaene A and both are proved incorrect. The correct structure needs to be further probed.



Scheme 3. Total synthesis of compound **2**.



Scheme 4. Total synthesis of compound **1**.

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Supplementary data

Supplementary data (experimental procedures, characterization data for new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.06.133.

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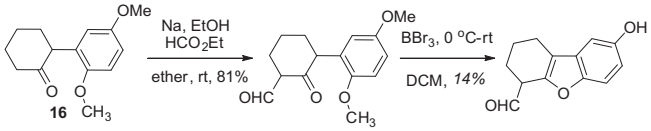
8. Direct introducing a formyl group seems straightforward, making the synthesis more concise; however, the formation of the benzofuran proved problematic only in 14% yield.



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