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Synthesis of Illisimonin a Skeleton by Intramolecular Diels–Alder Reaction of *Ortho*-Benzoquinones and Biomimetic Skeletal Rearrangement of *Allo*-Cedranes

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Abstract: Illisimonin A is a new sesquiterpene isolated from *Illicium simonsii*, and it possesses a novel 5/5/5/5/5 pentacyclic skeleton. The tricyclic skeleton of illisimonin A, tricyclo[5.2.1.$0^{1,5}$]decane, is presumed to be biosynthesized from *allo*-cedranes via a skeletal rearrangement. Herein, we report the concise synthesis of highly oxidized *allo*-cedranes by an intramolecular Diels–Alder reaction using *ortho*-benzoquinones and demonstrate the biomimetic transformation of *allo*-cedranes by a retro-Claisen/aldol pathway.

Keywords: biomimetic synthesis; Diels–Alder reaction; illicium sesquiterpene; natural product synthesis; skeletal rearrangement

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1. Introduction

Illicium sesquiterpenes are a family of natural products, many of which show activities on the central nervous system, such as GABA receptors [1–3]. The structures of illicium sesquiterpenes, such as anisatin (**1**), jiadifenolide (**2**), tashironin (**3**), and merrilactone A (**4**), feature highly oxidized carbon frameworks containing consecutive tetra-substituted carbon centers (Figure 1). In the biosynthesis, *allo*-cedrane is a common ancestor of these sesquiterpenes by oxy-functionalization and C-C bond cleavage/formation. The C6-C11 bond cleavage affords *seco*-prezizaanes (e.g., **1** and **2**), while the C6-C7/C10-C11 cleavages and the C6-C10 bond formation produce anislactones (e.g., **4**) [4–9]. Due to their biological activity and complex molecular structure, these compounds have attracted the interest of synthetic chemists. Numerous total syntheses and synthetic studies of these compounds have been reported, especially in the last decade [10–23]. Illisimonin A (**5**), isolated from *Illicium simonsii* in 2017, is a new sesquiterpene that has a neuroprotective effect on oxygen–glucose deprivation-induced cell injury [24]. Unlike the other illicium sesquiterpenes, **5** possesses a novel 5/5/5/5/5 pentacyclic skeleton, 6,12-dioxapentacyclo[6.6.0.$0^{1,5}$.$0^{5,10}$.$0^{9,13}$]tetradecane, including three five-membered carbon rings, a five-membered lactone, and a five-membered lactol. Further, the carbon flamework of **5**, tricyclo[5.2.1.$0^{1,5}$]decane, is unprecedented as a natural product and possesses seven consecutive asymmetric tetra-substituted carbons. The elegant total synthesis of **5** by Rychnovsky's group [25] has revised the absolute stereochemistry, as shown in Figure 1. Therefore, we postulated that the biosynthesis of **5** is mediated by the cleavage of the C6–C7 bond and the formation of the C6-C8 bond from the *allo*-cedrane skeleton. In this study, we investigated the biomimetic transformation from the highly oxidized *allo*-cedranes to the carbon framework of **5**. Herein, we report the concise synthesis of the highly

oxidized *allo*-cedranes by an intramolecular Diels–Alder (IMDA) reaction using *ortho*-benzoquinones. Further, we demonstrate the biomimetic transformation of *allo*-cedranes via a retro-Claisen/aldol pathway.

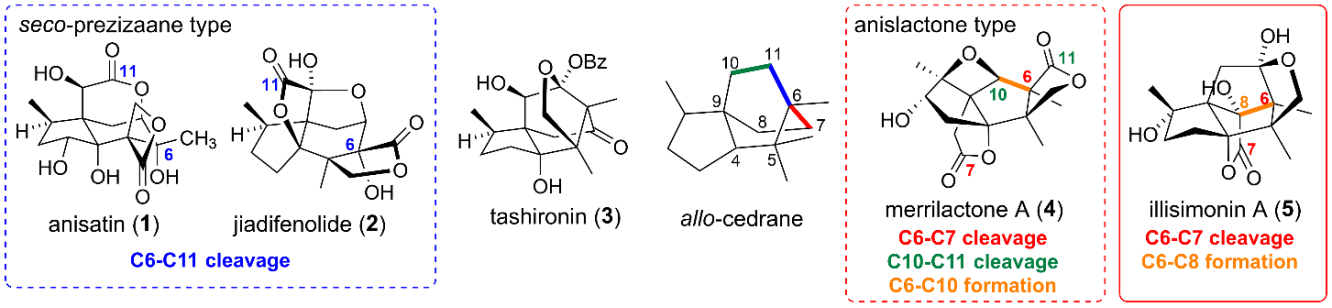
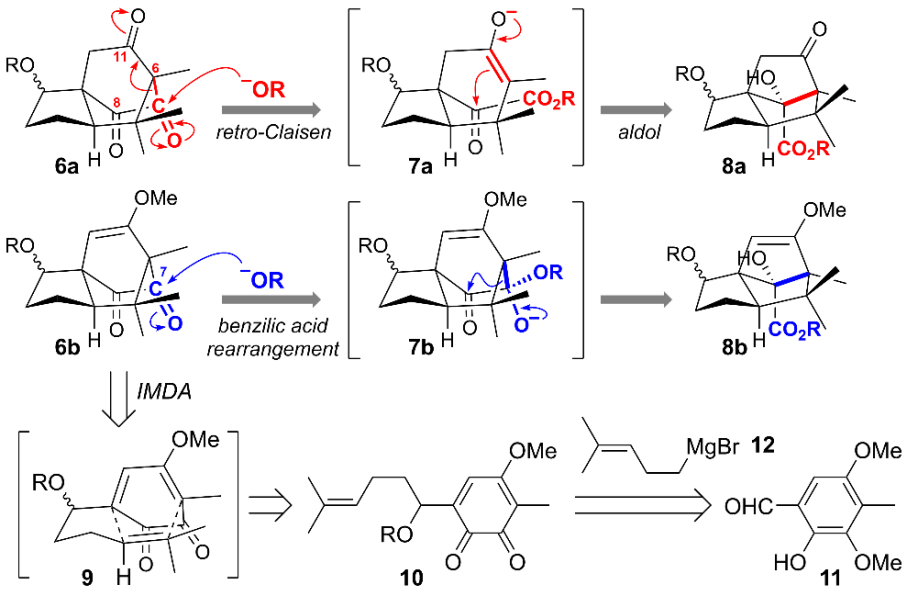


Figure 1. Illisimonin A and its related compounds.

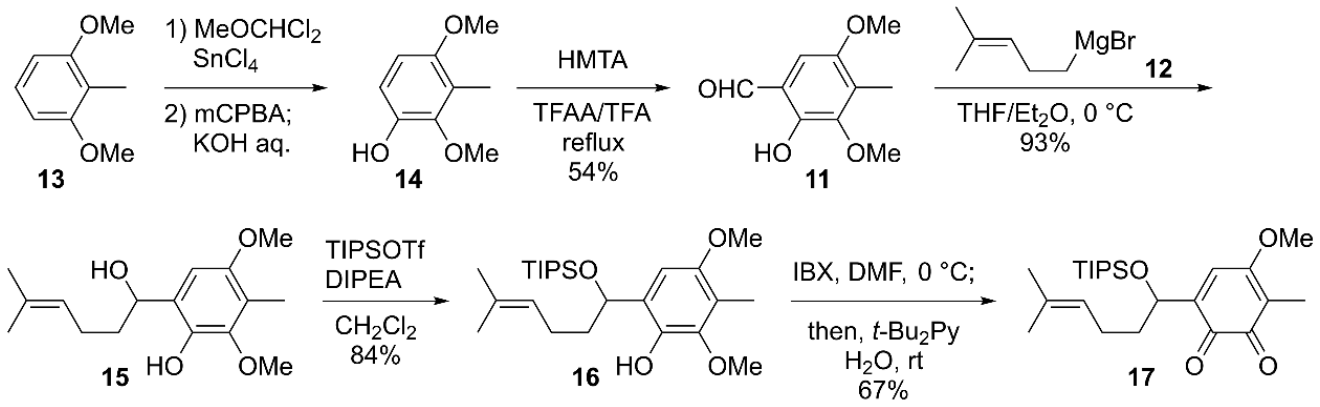
2. Results and Discussion

The synthetic route is shown in Scheme 1. We postulated that the following two pathways are possible for the skeletal rearrangement from *allo*-cedrane to the tricyclic core of **5**: (i) a retro-Claisen condensation/aldol reaction and (ii) a benzilic acid rearrangement (BAR) [26]. The treatment of triketone **6a** with an oxygen nucleophilic reagent led to the C6-C7 bond cleavage, thereby affording **7a**. A subsequent addition reaction from the resulting enolate to C8 ketone led to the formation of a C6-C8 bond, affording a 5-5-5 tricyclic core (**8a**). Furthermore, the addition of an oxygen nucleophilic reagent to the C7 ketone of **6b** produced a tricyclic core (**8b**) via the BAR pathway. However, the BAR of bicyclo[2.2.2]octan-1,2-dione is rare, with only one example reported by the Ghatak group in 1993 [27]. The biosynthesis may involve a retro-Claisen/aldol pathway; however, the BAR pathway is synthetically challenging. Therefore, we decided to investigate both synthetic pathways. *Allo*-cedrane derivatives **6a** and **6b** would be synthesized by the IMDA reaction of benzoquinone **10** via transition state **9** [28,29]. Benzoquinone **10** can be prepared by the addition reaction of Grignard reagent **12** to aldehyde **11**, followed by the oxidation of the resulting *o*-methoxyphenol. Notably, there are few reported examples of the IMDA using *ortho*-benzoquinones and the BAR of bicyclo[2.2.2]octandiones; the characteristics of these reactions, especially stereoselectivities, are unpredictable.



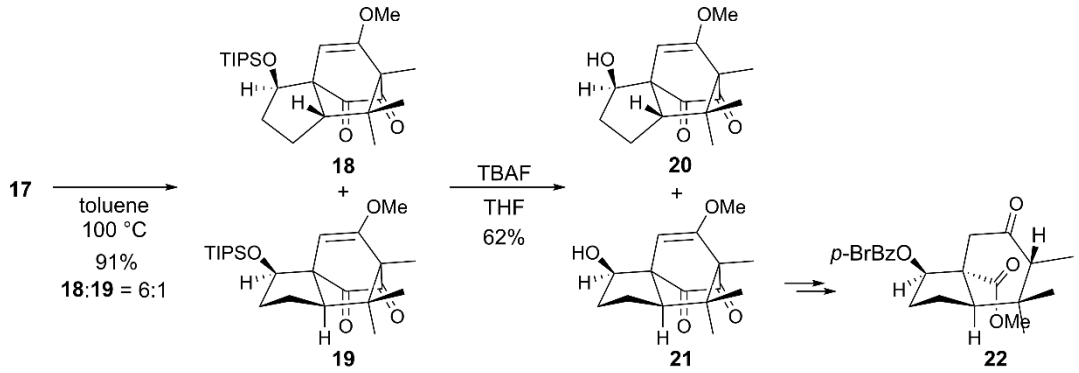
Scheme 1. Synthetic strategy toward the illisimonin A skeleton.

The preparation of *ortho*-benzoquinones commenced with the $SnCl_4$-mediated formylation of commercially available **13** and the following Dakin oxidation, according to the literature [30] (Scheme 2). The resulting phenol **14** was subjected to site-selective formylation with hexamethylenetetramine (HMTA) in trifluoroacetic acid (TFA)/trifluoroacetic anhydride (TFAA) to afford benzaldehyde **11** [31] in a 54% yield. Further, the addition reaction of **12** to **11** afforded diol **15** in a 93% yield. The selective protection of the hydroxyl group at the benzylic position was achieved using triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) and *N*,*N*-diisopropylethylamine (DIPEA) to afford phenol **16** in an 84% yield. Oxidative dearomatization using *o*-iodoxybenzoic acid (IBX) [32] and the hydrolysis of the resulting quinonium cation afforded *ortho*-benzoquinone **17** in a 67% yield.



Scheme 2. Preparation of IMDA precursor **17**.

Next, the IMDA reaction was pursued using **17** (Scheme 3). The reaction under thermal conditions produced two cycloadducts, **18** and **19**, as an inseparable mixture. The removal of the TIPS group using tetra-*n*-butylammonium fluoride (TBAF) afforded a mixture of alcohols **20** and **21**. The analytical amount of **20** derived from the major cycloadduct was isolated, and its X-ray crystallographic analysis revealed that the IMDA reaction favored the undesired facial selectivity (Figure 2 and Supplementary Materials). Notably, since compound **20** also possesses an allo-cedrane skeleton, our synthetic method can be applied to the synthesis of other illicium sesquiterpenes. The Dess–Martin oxidation of the mixture of **20** and **21** retained the diastereomeric ratio of 6:1 in a mixture of the resulting triketone. Thus, the minor cycloadduct **19** possessed the desired stereochemistry. Moreover, the whole stereochemistry of the minor cycloadduct **19** was clearly determined using the X-ray crystallographic analysis of compound **22** derived from **19** by degradation during BAR studies. Our initial expectation was that **TS B**, in which the bulky siloxy group was orthogonal to the quinone plane and the prenyl group was antiperiplanar to the ketone, would be favorable, and that **19** would be the preferred isomer (Figure 3). However, the IMDA reaction afforded isomer **18**, which suggests that the reaction probably proceeded through **TS A**, where the prenyl group was orthogonal to the quinone plane, while the siloxy group and the ketone were antiperiplanar.



Scheme 3. IMDA reaction of *ortho*-benzoquinone **17**.

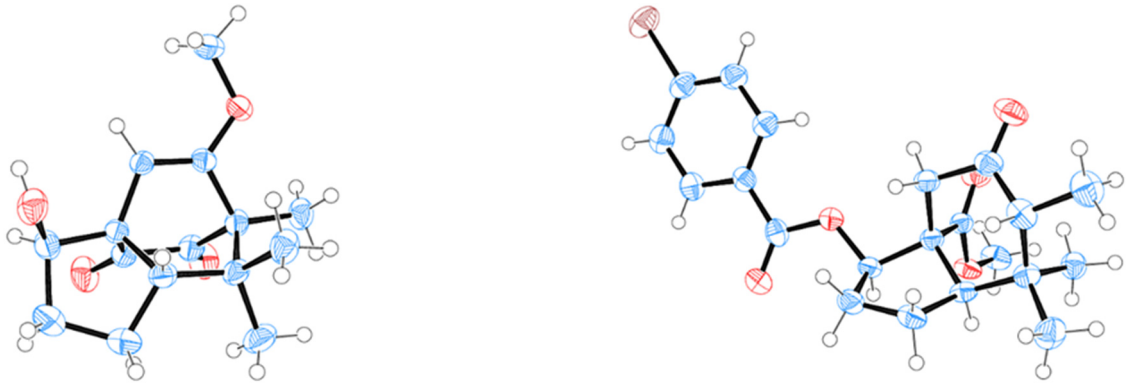


Figure 2. Ortep drawing of **20** and **22**.

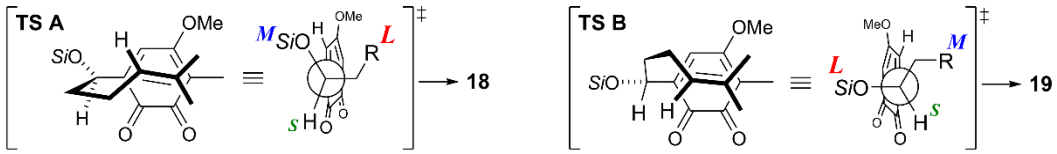
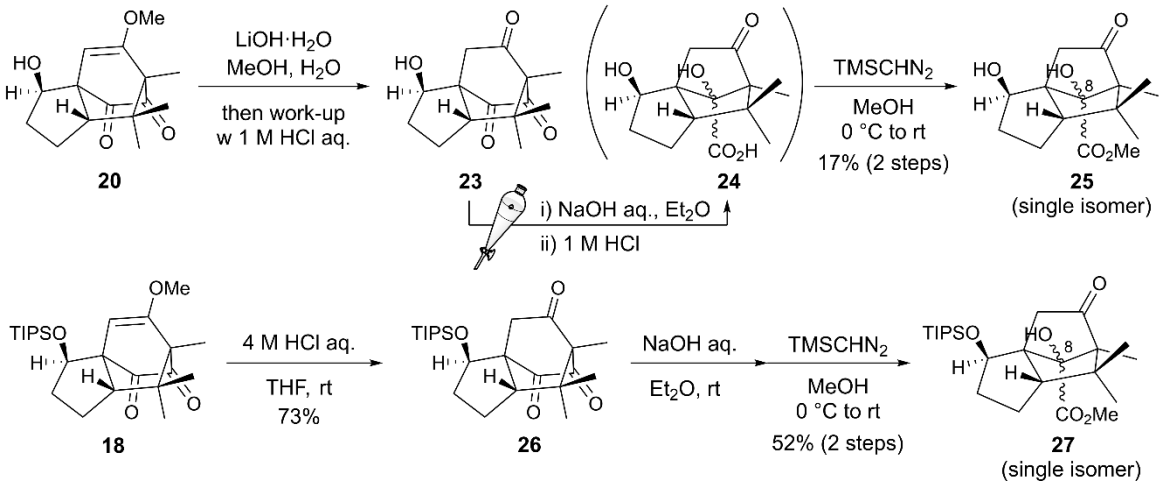


Figure 3. Plausible transition states of the IMDA reaction.

Next, we investigated the BAR using the major product **20** because of the pseudosymmetry of the bicyclo[2.2.2]octane skeleton (Scheme 4). The treatment of **20** with lithium hydroxide and subsequent esterification using trimethylsilyl diazomethane ($TMSCHN_2$) afforded α-hydroxyester **25** in a 17% yield as a single product. After a thorough investigation, we found that the BAR of **20** did not provide the desired intermediate **24**. However, triketone **23** was obtained by hydrolysis because of the 1M hydrochloric acid used for work-up. During the acid-base extraction to obtain a carboxylic acid, the skeletal rearrangement of triketone **23** by a retro-Claisen/aldol process proceeded under the basic conditions to produce α-hydroxycarboxylic acid **24**. Further, triketone **26**, prepared by the hydrolysis of **18**, was treated with NaOH aq. at room temperature and $TMSCHN_2$ to afford α-hydroxyester **27** in a 52% yield as a single product. The structure of **27** was determined using 2D NMR spectroscopy (see Supplementary Materials), except the stereochemistry at the C8 position. Further attempts for structure determination, such as recrystallization of **27** and its derivatives, were unsuccessful. Thus, our results support the fact that the retro-Claisen/aldol reaction can transform highly oxidized *allo*-cedranes to the skeleton of illisimonin A in biosynthesis as well as chemical synthesis.



Scheme 4. Attempts on the skeletal rearrangements of *allo*-cedranes.

3. Conclusions

In conclusion, we constructed the tricyclo[5.2.1.$0^{1,5}$]decane skeleton by an intramolecular Diels–Alder reaction using *ortho*-benzoquinones and a biomimetic skeletal rearrangement. We have achieved a concise synthesis of *allo*-cedranes (seven steps from commercially available 2,6-dimethoxytoluene) by the introduction of a prenyl side chain using the Grignard reaction, the oxidative dearomatization of 2-methoxyphenol, and the intramolecular Diels–Alder reaction of *ortho*-benzoquinone. Although the intramolecular Diels–Alder reaction proceeded with an undesired facial stereoselectivity, we obtained the desired cycloadduct as a minor product. Moreover, we have demonstrated that the skeletal rearrangement of *allo*-cedranes to the tricyclic skeleton of illisimonin A proceeds under basic conditions, not by a benzilic acid rearrangement but via a retro-Claisen/aldol reaction. Based on the results of the present study, further investigations into the total synthesis of illisimonin A are currently underway.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/org2030016/s1, PDF file containing X-ray crystallographic data for compound **20** and **22** and experimental procedures and copies of NMR Spectra (1H and 13C) for all new compounds.

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