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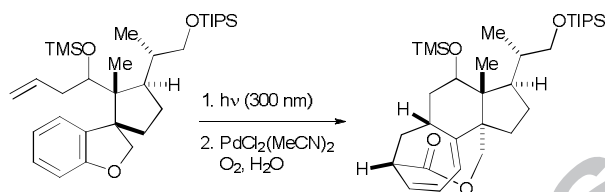
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Graphical Abstract

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Construction of the 5,6,7-tricyclic skeleton of lancifodilactone F

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ABSTRACT

We report herein the synthesis of a fully functionalized B,C,D-ring system of lancifodilactone F. The key transformations involve an arene–olefin *meta*-photocycloaddition reaction and a palladium-catalyzed oxidative C–C cleavage reaction to establish its B,C-rings.

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Lancifodilactone F (**1**) is a structurally unique triterpenoid isolated from the leaves and stems of Chinese herb *Schisandra lancifolia* (Fig. 1).^{1,2} Its 5,6,7-tricyclic skeleton that bears two all-carbon quaternary centers at the 5,6-ring junction (C13 and C14) has presented significant synthetic challenges.^{3–11} Previously, we reported a synthetic strategy for the establishment of this unique molecular framework using a [2+2] cycloaddition reaction and an arene–olefin *meta*-photocycloaddition reaction.¹² We also questioned the original assignment of its C8-configuration based on biosynthetic analysis.¹³ We report herein methods for the unmask of its seven-membered B-ring from the photocycloaddition reaction using sequential oxidative C–C cleavage reactions.

In our previous report, we showed that the construction of the molecular framework of **1** could be achieved by irradiating **2** with UV light to induce an arene–olefin *meta*-photocycloaddition reaction. This photoreaction gave a mixture of **3** and **4** after desilylation (Fig. 1). The C12-trimethylsilyl group of **2** facilitated the photocycloaddition by gearing the olefin group toward the arene. Although the two C12-diastereomers of **2** were readily separable and reacted with equal efficiency, the diastereomeric mixture of **2** could be used directly. A Dess–Martin oxidation followed by a sodium borohydride reduction readily converted **3b/4b** into **3a/4a**. Therefore, we focused on the synthesis of the seven-membered B-ring with **3a** and **4a**.

The arene–olefin *meta*-photocycloaddition reaction has been used by Wender and others to build various polycyclic ring systems.^{14–22} However, its use for the establishment of a seven-membered ring is rare.^{23,24} In particular, selective cleavage of the C–C bonds bridging the cycloheptenyl ring is challenging.²⁵ We aimed to cleave the C1–C5 linkage of **3a** and the C1–C7 linkages

of **4a** under the same reaction conditions, and reveal the seven-membered B-ring with the subsequent cleavage of the C1–C8 linkage without separate operations on **3a** and **4a**.

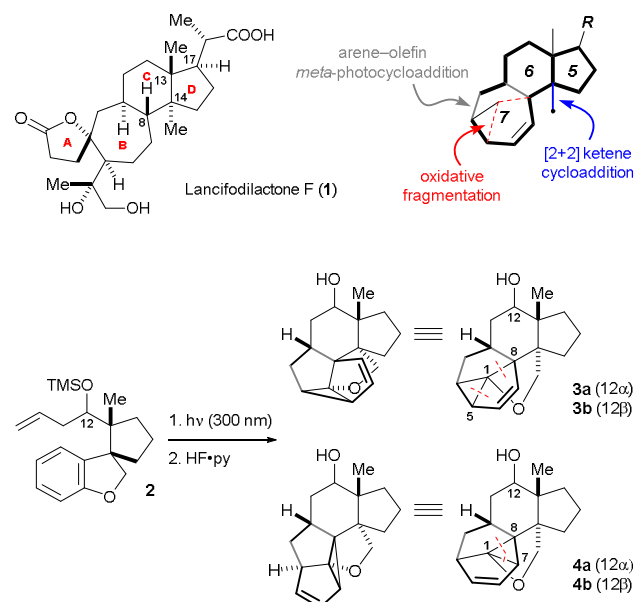


Figure 1. Structure of lancifodilactone F (**1**) and our synthetic strategy.

Initially, we envisioned that the cleavage of the allylic bonds of **3a** and **4a** could be best achieved by oxidation of their double bonds (Fig. 2). Indeed, reaction of **3a/4a** with *meta*-chloroperbenzoic acid (mCPBA) gave the corresponding

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epoxides, which were treated with hydrochloric acid to induce the cleavage of the C1–C5 linkage of **3a** and the C1–C7 linkage of **4a** to give **5** and **6**, respectively. Subsequent reaction of **5/6** with zinc chloride promoted the cleavage of their C1–C8 linkages to afford diene **7**. The lactone ring of **7** was then cleaved and the resulting hydroxyl groups were protected to provide **8**.

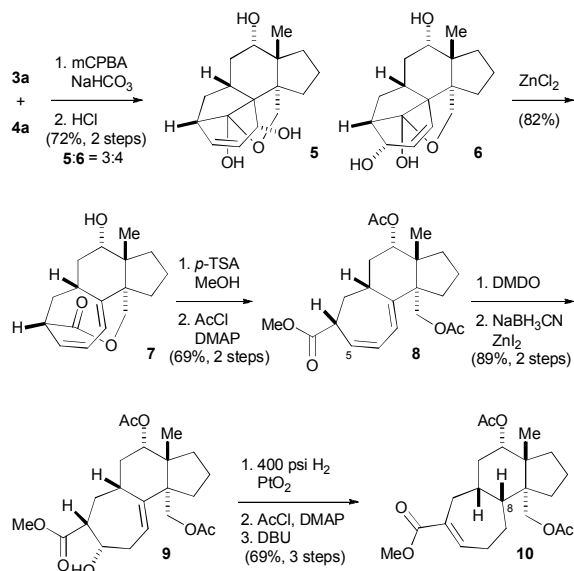


Figure 2. Model studies for the establishment and functionalization of the carbon skeleton of lancifodilactone F (**1**).

The selective functionalization of the C5-position of **8** was accomplished by oxidation of the diene with dimethyldioxirane (DMDO) to generate a vinyl epoxide that was subsequently reduced by sodium cyanoborohydride in the presence of zinc iodide to give homoallylic alcohol **9**. Saturation of the sterically hindered tri-substituted olefin of **9** was challenging but could be achieved by hydrogenation in the presence of platinum oxide under a high pressure of hydrogen affording the correct C8 stereochemistry. Acetylation of the hydroxyl group followed by treatment with a strong base promoted the elimination of the C5-acetate group to yield **10**.

With a working plan for the B-ring synthesis in hand, we turned our attention to the incorporation of the side-chain on the D-ring. This C17 side-chain was introduced by the conjugate addition of isopropenyl cuprate to enone **11** (Fig. 3). The resulting ketone **12** was converted into enol triflate **13** with good regioselectivity. Subsequent Suzuki coupling of **13** and 2-hydroxyphenylboronic acid provided **14** smoothly. Hydroboration of the 1,1-disubstituted olefin proceeded with excellent stereoselectivity, giving **15** as the only diastereomeric product after oxidation and protection of the resulting primary hydroxyl group. Alkylation of the phenol of **15** with *tert*-butyl bromoacetate followed by hydrolysis of the *tert*-butyl ester group afforded **16**. Treatment of **16** with *p*-toluenesulfonyl chloride in the presence of triethylamine generated a ketene that underwent an intramolecular [2+2] cycloaddition reaction with the tetra-substituted olefin. The ketene approached from the less hindered face of the olefin to give cyclobutanone **17** as the only diastereomer. This reaction established the C13 and C14 all-carbon quaternary centers with the desired *trans*-relative stereochemistry.

To construct the B,C-rings of **1**, the cyclobutanone of **17** was cleaved by a Haller–Bauer reaction to give a carboxylic acid that was then converted into aldehyde **18**. Reaction of **18** with the

allyl Grignard reagent gave **19** as a 1.6:1 separable mixture of C12-diastereomers. As the C12 stereocenter of the β -diastereomer could be inverted after photolysis, we only describe in the following sections the elaboration of the major diastereomer **19a**. After protection of the hydroxyl group of **19a** with a trimethylsilyl group, irradiation of TMS-**19a** with UV light (250–375 nm, λ_{max} 300 nm) led to the smooth formation of a 1:1 mixture of two regioisomers **20a** and **20b**. This transformation allowed for the establishment of the B,C-rings of **1** in a single step. Consistent with our previous observation with **2**,¹² the photocycloaddition reaction of **19** failed completely. The bulky trimethylsilyl group helped restrict the conformation of the olefin-containing side-chain and push the olefin toward the aromatic ring to facilitate this otherwise difficult arene–olefin *meta*-photocycloaddition reaction.

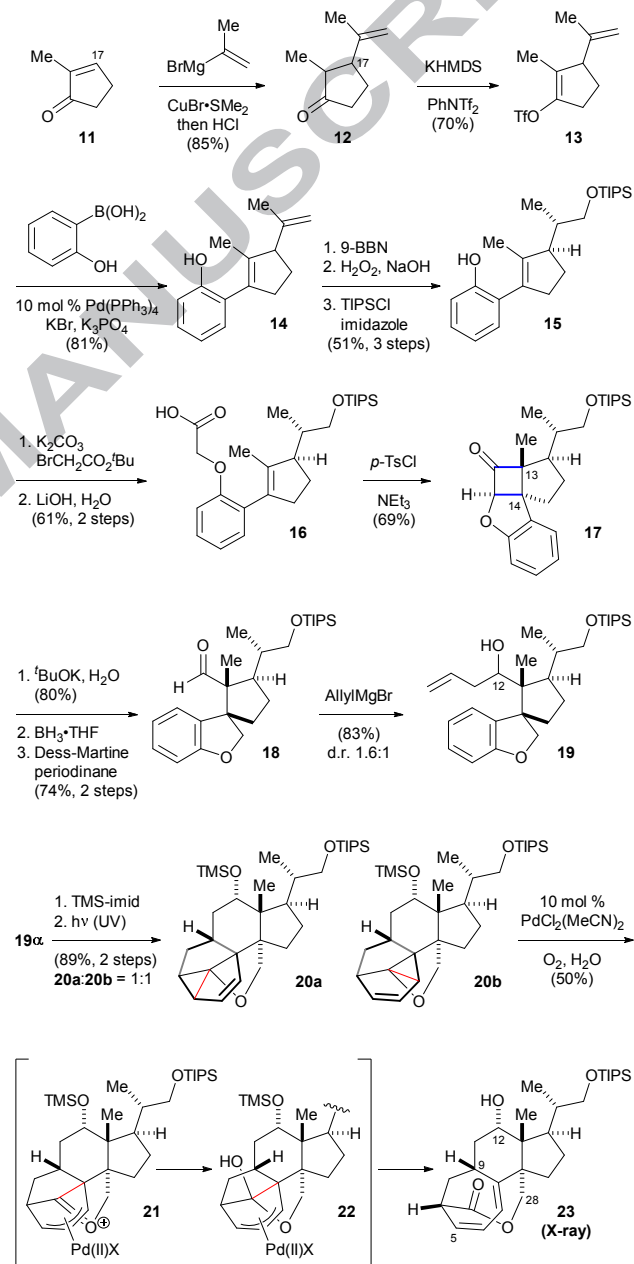


Figure 3. Construction of the B,C,D-ring system of lancifodilactone F (**1**).

In our model study with **3/4**, we used a three-step oxidative method involving one oxidation and two acid-induced C–C

cleavage reactions to reveal the B-ring of **1** from the photocycloaddition products. We envisioned that a palladium(II) salt could function as both an oxidant and a Lewis acid to cleave the C1–C5 and the C1–C8 linkages of **20a** and the C1–C7 and the C1–C8 linkages of **20b** concurrently. Indeed, treatment of **20a/b** with a catalytic amount of palladium(II) chloride in the presence of oxygen and water induced the cleavage of the C1–C5 linkage of **20a** and the C1–C7 linkage of **20b** to give the palladium π -allyl complex **21**. The oxonium ion of **21** was then trapped by water to yield **22**. Subsequent cleavage of the C1–C7 linkage of **22** afforded diene **23**. The trimethylsilyl group was also removed during this reaction.

In summary, we have developed a strategy for the efficient synthesis of the fully functionalized B,C,D-ring of lancifodilactone F (**1**). A [2+2]-photocycloaddition was first used to establish the C13/14 adjacent all-carbon quaternary centers. An arene–olefin *meta*-photocycloaddition followed by a palladium-promoted oxidative C–C bond cleavage reaction was then used to construct the B,C-ring. The remaining tasks required for the completion of the synthesis of **1** include the installation of the A-ring and the C5 side-chain, inversion of the C9 stereochemistry, and C12/28 deoxygenation.

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