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Concise Total Synthesis of Albaflavenone Utilizing Sequential Intramolecular Aldol Condensation: Determination of Absolute Configuration

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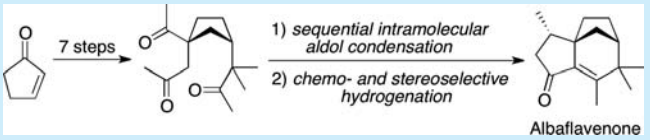
Supporting Information

ABSTRACT: The first total synthesis of albaflavenone, a novel antibiotic sesquiterpene, has been accomplished via the concise construction of its zizaene skeleton utilizing sequential intramolecular aldol condensation followed by chemo- and diastereoselective reduction of the conjugated carbon−carbon double bond. This synthetic work was completed in nine steps from 2-cyclopenten-1-one as a starting material without the use of protecting groups and with high stereocontrol. In addition, the absolute configuration of naturally occurring albaflavenone was determined to be 1*R*,2*S* and 8*S*.



In 1994, Gülter and co-workers reported the isolation of a novel antibiotic sesquiterpene, albaflavenone **1**, from the Gram-positive soil bacteria *S. albidoflavus*.[1] Albaflavenone **1** possesses a unique tricyclo[6.2.1.0^{1,5}]undecene skeleton, the zizaene skeleton, and bears three stereocenters including an all-carbon quaternary center (Figure 1). Studies on the biosynthetic pathway of albaflavenone **1**, which was realized as an oxidized *epi*-isozizaene **2** metabolite, and related oxidized metabolites, albaflavenols **3a**, **3b** and 4,5-epoxy-2-*epi*-zizaan-6*β*-ol **4**, have been recently disclosed.[2−5] The structure and the biosynthetic importance of **1** are of interest to organic chemists. One group has succeeded in the enzymatic formation of albaflavenone **1**,[3] but no total synthesis or synthetic study of **1** has been reported to date. In addition, the absolute configuration of albaflavenone **1** has not yet been determined.

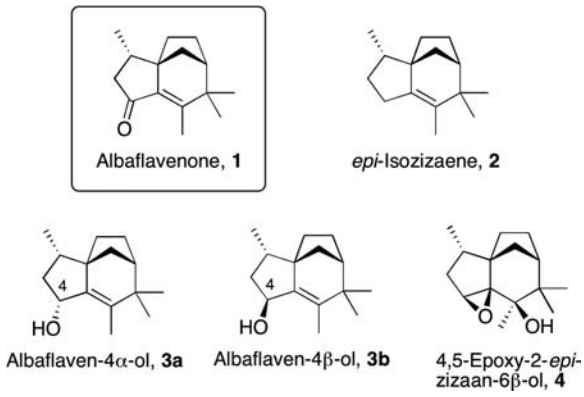


Figure 1. Structure of albaflavenone and related compounds.

This compact but challenging tricyclic terpenoid core attracted our interest, and a synthetic study of albaflavenone **1** was initiated. Our goal was to develop an efficient synthetic procedure to access natural products possessing the zizaene skeleton and to extend the asymmetric synthesis. Herein, we describe the concise and highly stereocontrolled total synthesis of albaflavenone **1** in nine steps without the use of protecting groups, involving the direct construction of the tricyclic skeleton through sequential intramolecular aldol condensation, and the determination of the absolute configuration of albaflavenone **1**.

The synthetic strategy for albaflavenone **1** is outlined in Figure 2. The target molecular **1** could be synthesized by chemo- and diastereoselective reduction of the conjugated carbon−carbon double bond of compound **5**. The tricyclic compound **5** would be derived from triketone **6** directly utilizing sequential intramolecular aldol condensation. Triketone **6** would be obtained by double Wacker oxidation of the two vinyl groups of ketone **7**. Compound **7** would be

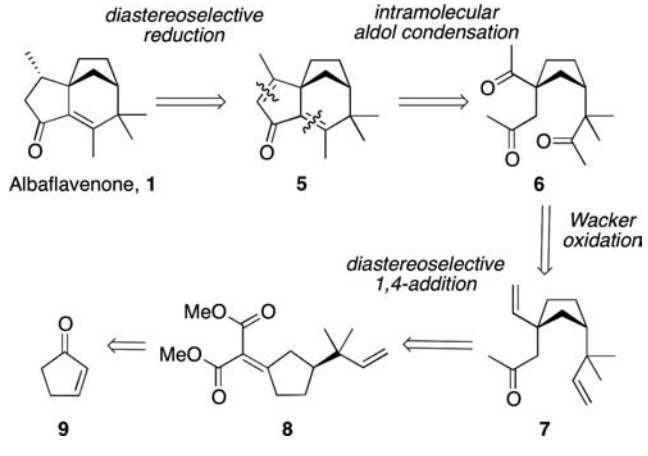


Figure 2. Synthetic strategy toward albaflavenone.

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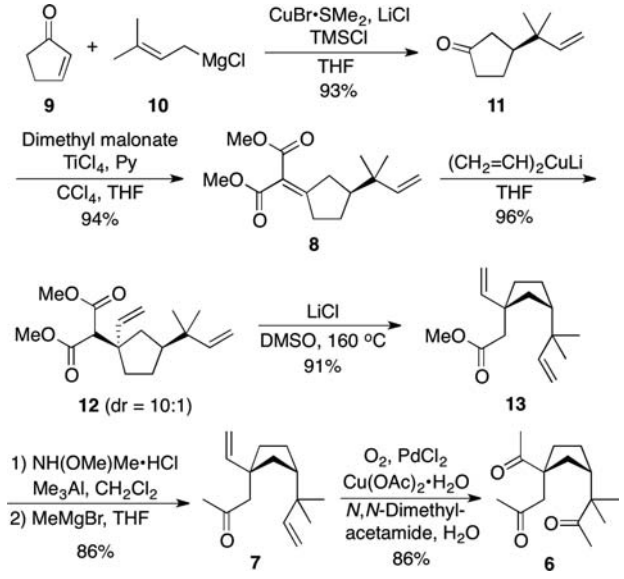
constructed by stereocontrolled 1,4-addition of the α,β-unsaturated diester **8**, which was prepared from 2-cyclopenten-1-one (**9**) in a two-step operation.

Our synthetic study of the racemic form started with the introduction of the isoprenyl group with 2-cyclopenten-1-one (**9**) using Lipshutz's conditions[6] as shown in Scheme 1.

Scheme 1. Synthesis of the Triketone 6



Treatment of **9** with prenyl Grignard reagent **10** in the presence of a copper bromide dimethyl sulfide complex afforded compound **11** in 93% yield. The Knoevenagel condensation of **11** with dimethyl malonate gave the unsaturated diester **8**. The stereoselective 1,4-addition to the unsaturated diester **8** proceeded smoothly to furnish the vinylated product **12** in 96% yield in a 10:1 stereoisomeric ratio. The diester **12** was then transformed to the methyl ketone **7** via a three-step operation including decarboxylation, conversion of the resulting methyl ester **13** to the Weinreb amide, and methylation. The oxidation of the two vinyl groups in **7** was carried out under Wacker oxidation conditions to give the triketone **6** in 86% yield.

With the key intermediate **6** in hand, we next focused on the construction of the tricyclic skeleton through sequential intramolecular aldol condensation. In the first aldol condensation, the spiro compounds **14** and **15** might be produced via enolates **A** and **B** (Figure 3).[7]

Therefore, it is necessary to determine suitable conditions to control the enolate formation and provide the desired spiro compound **14** preferentially. After several trials,[8] we found that compound **14** was formed preferentially using LHMDS as the base at −78 °C. Thus, the first aldol condensation was carried out at −78 °C in methoxycyclopentane. After the consumption of triketone **6**, the reaction mixture was refluxed to promote the second aldol condensation to afford the desired tricyclic compound **5** in 52% yield along with spiro compound **14** (14% yield) and **15** (5% yield) (Scheme 2). Finally, the chemo- and stereoselective hydrogenation of **5** by use of Pd/C in hexane provided target **1** in 95% yield as a single diastereomer.[8] The spectral data of synthetic albaflavenone **1** were identical with those of the natural product.[1]

According to our synthetic route, in order to synthesize optically active albaflavenone **1**, compound **11** must be

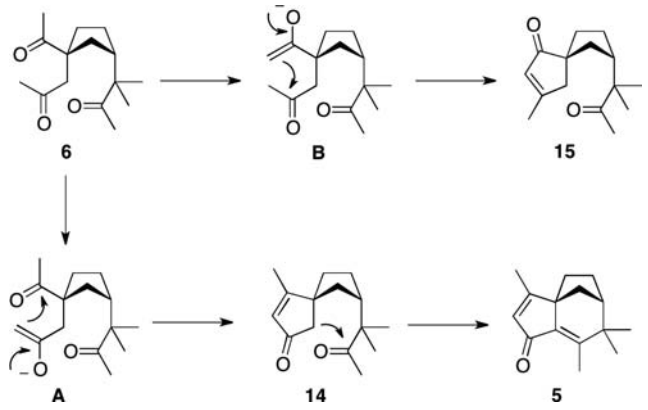
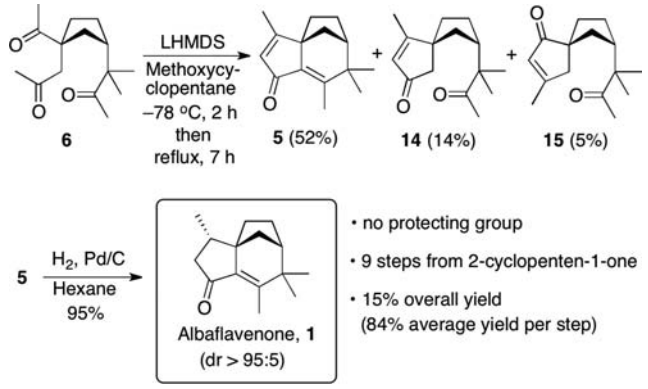


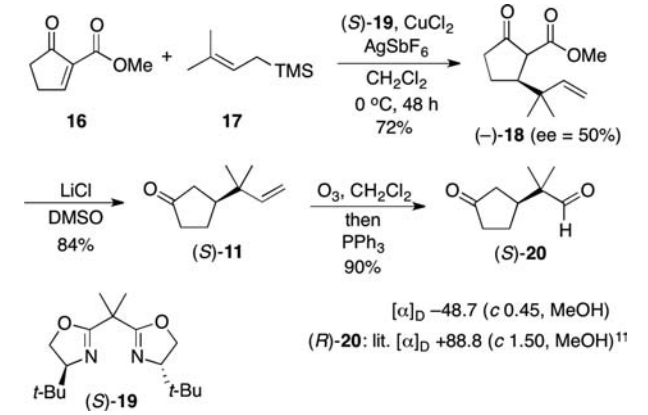
Figure 3. Sequential intramolecular aldol condensation.

Scheme 2. Synthesis of Albaflavenone



obtained in optically active form. The synthesis of optically active **11** was initiated by the asymmetric 1,4-addition of trimethylprenylsilane **17** to unsaturated β-ketoester **16** using modified Snapper conditions[8,9] as shown in Scheme 3. To the

Scheme 3. Synthesis of Optically Active 11



mixture of $CuCl_2$, $AgSbF_6$, and bis(oxazoline) ligand **19** in CH_2Cl_2 were added **16** and **17** at −78 °C, and then the reaction mixture was stirred for 48 h at 0 °C. As a result, the desired compound **18** was obtained in 72% yield with 50% ee.[10] The decarboxylation of **18** provided the optically active **11** in 84% yield. In order to determine the absolute configuration, compound **11** was transformed to known aldehyde **20**[11] via ozonolysis of the vinyl group. The optical rotation of the synthetic aldehyde **20** had the opposite rotation to that

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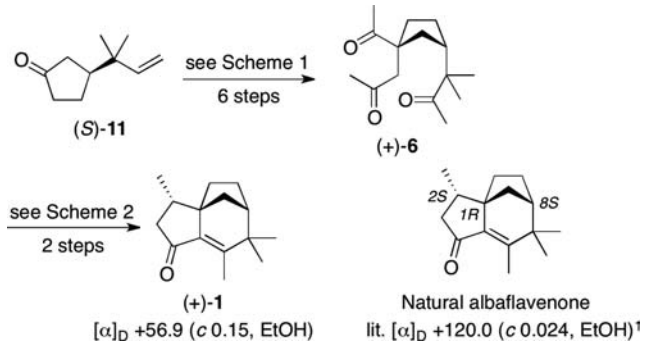
reported in the literature [synthetic **20**: $[\alpha]_D$ −48.7 (*c* 0.45, MeOH); reported (*R*)-**20**: $[\alpha]_D$ +88.8 (*c* 1.50, MeOH)[11]]. Therefore, the absolute configuration of **11** was assigned as the *S* configuration. With the optically active **11** in hand, the asymmetric synthesis of albaflavenone **1** through the established procedure was completed as shown in Scheme 4. Both

Scheme 4. Synthesis of Optically Active Albaflavenone and Determination of Absolute Configuration



the ^{1}H and ^{13}C NMR spectra of synthetic **1** were identical with those of natural albaflavenone **1** and the optical rotation of the synthetic sample had the same rotation as that reported for the natural product [synthetic **1**: $[\alpha]_D$ +56.9 (*c* 0.15, EtOH); natural product **1**: $[\alpha]_D$ +120.0 (*c* 0.024, EtOH)[1]]. Therefore, we determined the absolute configuration of naturally occurring albaflavenone as 1*R*,2*S* and 8*S*.

In summary, we have achieved the first total synthesis of tricyclic sesquiterpene albaflavenone **1** in racemic form in 9 steps from 2-cyclopenten-1-one (**9**). The overall yield was 15% from 2-cyclopenten-1-one (**9**) (84% average yield per step). The key features of our synthesis include a facile construction of the carbon framework of the natural product using a diastereoselective 1,4-addition of vinyl cuprate, double Wacker oxidation, sequential intramolecular aldol condensation, and chemo- and diastereoselective hydrogenation. In addition, the absolute configuration of natural albaflavenone **1** was determined to be 1*R*, 2*S*, and 8*S*. It is noteworthy that our synthetic route does not require the use of any protective groups and in the racemic route only five carbons were wasted (two carbons [**12** → **13**:decarboxylation] and three carbons [**13** → **7**:conversion to methyl ketone from methyl ester via Weinreb amide]). This means that our synthetic procedure is atom economical.[12,13] Our methodology can be extended to the synthesis of structurally related oxidized metabolites. Further investigations are now in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedure and spectroscopic data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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