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A Biomimetic Total Synthesis of (+)-Ainsliadimer A

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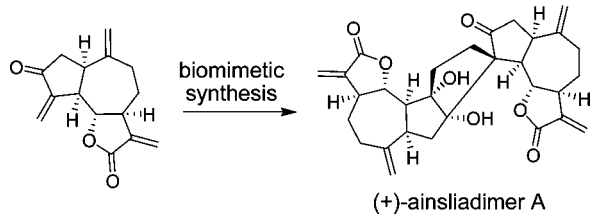
ABSTRACT



A protecting group free and biomimetic total synthesis of (+)-ainsliadimer A has been accomplished in 14 steps from α-santonin. The synthesis relies on a hydrogen bonding promoted [4 + 2]-hetero-Diels−Alder dimerization to afford the key homodimer intermediate, which demonstrates the feasibility of using nonenzymatic conditions to achieve the proposed biosynthesis.

Structurally unique and complex natural products have historically presented challenges to the art and science of organic synthesis.[1] Biomimetic synthesis toward these natural products can provide numerous advantages,[2] such as high yield, good stereo- and chemoselectivity, and exclusion of protecting groups.[3] Recently, Zhang and co-workers discovered a new sesquiterpene lactone dimer, (+)-ainsliadimer A (**1**) (Figure 1), with an unprecedented carbon skeleton from *Ainsliaea macrocephala*, which is used in traditional Chinese medicine for the treatment of various diseases, including angina and rheumatoid arthritis.[4] The structure of **1** was confirmed by spectroscopic analysis as well as X-ray crystallography. Its unique heptacyclic ring system includes 11 contiguous stereogenic centers and a highly functionalized cyclopentane ring with three quaternary carbons connecting the two monomeric sesquiterpene lactone units. These unique architectural features combined with potent inhibitory effect against the production of NO in RAW264.7 stimulated by lipopolysaccharide LPS (IC_{50} = 2.41 μg/mL) render **1** an ideal target for total synthesis. Herein, we report the first total synthesis of (+)-ainsliadimer A based on a concise and biomimetic approach.

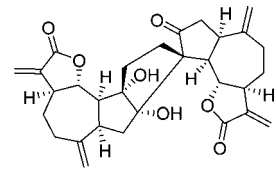


Figure 1. (+)-Ainsliadimer A.

According to the biosynthetic hypothesis,[4] a key [4 + 2]-hetero Diels−Alder cycloaddition of the naturally occurring monomeric sesquiterpene lactone dehydrozaluzanin C (**2**) may be responsible for the formation of the homodimer **3** (Scheme 1).[5] Hydrolysis of the 3,4-dihydro-2*H*-pyran moiety under acidic conditions should afford compound **4**. Subsequent intramolecular aldol reaction would eventually produce the natural

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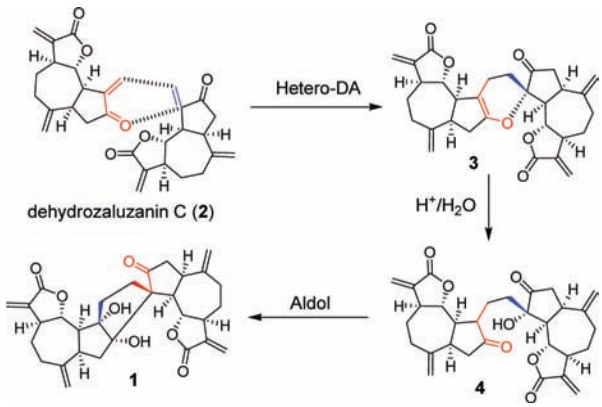
Scheme 1. Proposed Biosynthesis of (+)-Ainsliadimer A



product (+)-ainsliadimer A. It was suggested that the central hetero-Diels−Alder cycloaddition might be catalyzed by a Diels−Alderase.[6] Recently, the enzymatic catalysis of the Diels−Alder reaction in the biosynthesis of natural products has been attracting increasing attention.[7] Therefore, it is appealing to investigate this topic in the biosynthesis pathway of **1**. Inspired by this biosynthesis proposal, we set out to synthesize monomer **2** and to study its dimerization to **3**.

Our retrosynthetic analysis for the synthesis of monomer dehydrozaluzanin C (**2**) is depicted in Figure 2. According to the previously reported method, dehydrozaluzanin C could

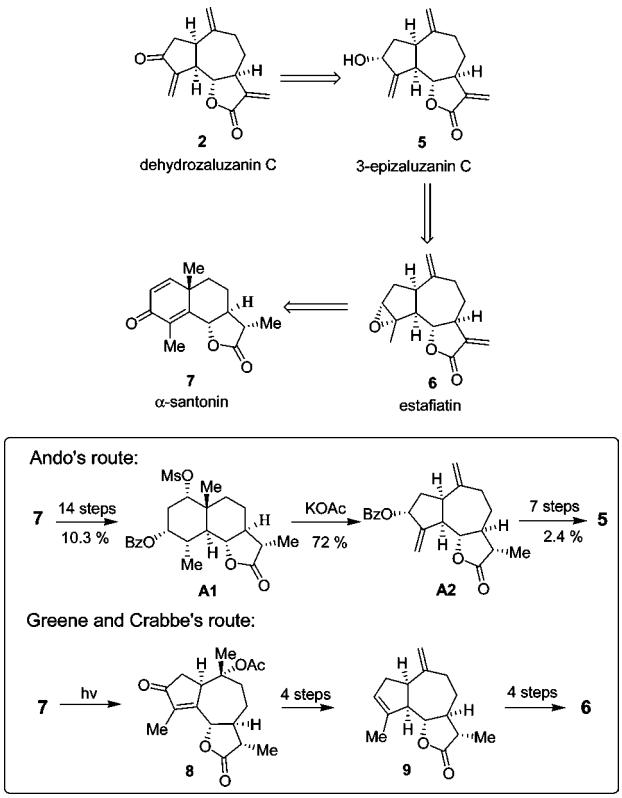
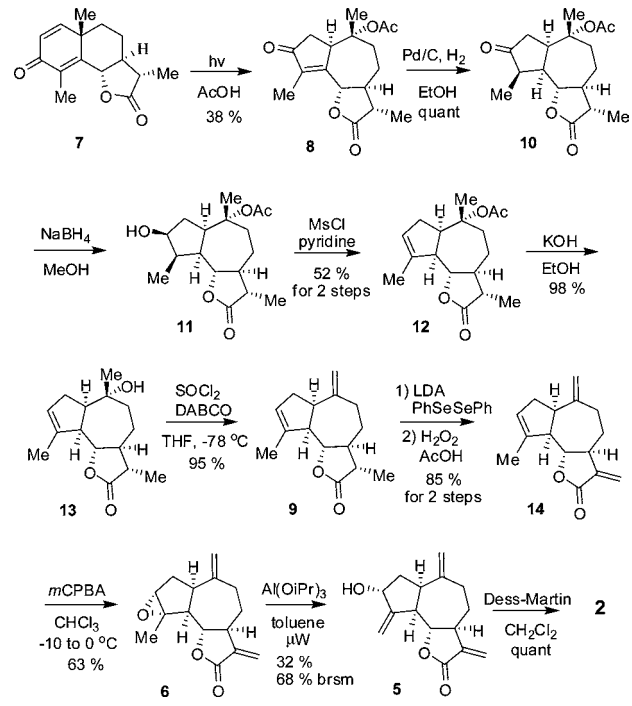


Figure 2. Retrosynthetic analysis of dehydrozaluzanin C.

be prepared from the structurally related natural product 3-epizaluzanin C (**5**) through direct oxidation.[8] 3-Epizaluzanin C (**5**) could be derived from estafiatin (**6**).[9] Accordingly, both **5** and **6** have been previously synthesized from another sesquiterpene natural product α-santonin (**7**). Ando and co-workers have reported a long synthetic route to access **5** from **7**.[9] The key intermediate **A1** was prepared from **7** in 14 steps. A base-mediated rearrangement of **A1** afforded **A2**, which was further transformed to **5** in seven steps. In another case, Greene and co-workers have reported an interesting and much more concise route to generate **6** starting from the direct rearrangement of **7** by photoirradiation to afford *O*-acetylisophotosantonic lactone (**8**).[10] However, this route included several problematic steps, especially the challenge to install the trisubstituted alkene moiety on the key intermediate **9**. In order to efficiently and rapidly access monomer dehydrozaluzanin C (**2**) from α-santonin (**7**), we decided to further optimize the synthetic sequence as well as several reaction conditions based on these two previous studies.[11]

The synthesis of dehydrozaluzanin C (**2**) began with α-santonin (**7**), a commercially available material (Scheme 2). Photolysis of **7** with a high-pressure Hg lamp (500 W)

Scheme 2. Synthesis of Dehydrozaluzanin C



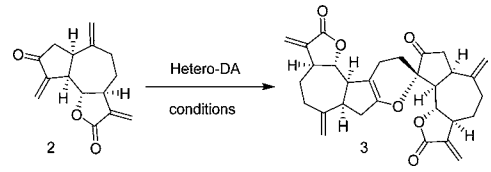
in acetic acid afforded *O*-acetylisophotosantonic lactone (**8**).[12] We have modified the reaction procedure for the large-scale preparation of **8** with consistent yield (38−40%).[11] Hydrogenation of the double bond smoothly provided compound **10** in quantitative yield and excellent diastereoselectivity. Selective reduction of ketone **10**, followed by mesylation of the corresponding hydroxyl group and in situ *anti*-elimina-

tion, afforded alkene **12** (52% over two steps).[13] We also observed a small amount of undesired disubstituted alkene byproduct. Saponification of **12** with 5% aq. KOH in ethanol cleanly generated alcohol **13**. The kinetic dehydration of **13** turned out to be a little challenging. The normal condition using $SOCl_2$ and Et_3N as base at −78 °C generated an inseparable mixture of di- and tetrasubstituted alkenes (4:1), which impeded the further synthesis. Through careful reaction optimization by screening different bases, we were pleased to find that, by using DABCO as base, we could reproducibly access the kinetically controlled dehydrated product disubstituted alkene **9** in greater than 12 to 1 ratio. Selenenylation of **9**, followed by oxidation of the resulting selenide and subsequent selenoxide elimination, led to the formation of the desired α-alkylidene-γ-butyrolactone **14**.[9] Epoxidation of **14** on the convex face afforded estafiatin (**6**) as the major diastereomer.[10] Treatment of **6** with aluminum isopropoxide in toluene under microwave condition gave the α-allylic alcohol 3-epizaluzanin C (**5**), which was further oxidized by Dess−Martin periodinane oxidation to afford dehydrozaluzanin C (**2**).

With monomer **2** in hand, we initiated studies on hetero-Diels−Alder dimerization to test the proposed biosynthesis (Scheme 1). Although spontaneous hetero-Diels−Alder cycloadditions of α-alkylidene ketones have been reported in the literature,[14] we did not observe any desired dimer **3** when monomer **2** was allowed to stand at 20 °C without solvent for 2 weeks.[6b] If the reaction temperature was elevated to 60 °C, we identified a significant amount of decomposed material as well as partially recovered monomer **2**. Next, we examined the feasibility of using Lewis acid catalysis for the hetero-Diels−Alder cycloaddition. Exposure of monomer **2** to several Lewis acids such as Et_2AlCl, $BF_3{\cdot}OEt_2$, $SnCl_4$, $TiCl_4$, $Yb(OTf)_3$, and $Sc(OTf)_3$ in THF or CH_2Cl_2 or under neat condition at various temperatures from −78 to 40 °C led to either no reaction or decomposition.

Hydrogen bonding catalysis that can mimic the action of enzymes or antibodies has recently emerged as an extraordinarily important advancement for organic synthesis.[15] Inspired by the elegant work of Rawal et al. for hydrogen-bond-promoted hetero-Diels−Alder reactions,[16] we began to investigate the potential of hydrogen bond donor catalysis. Initially, the Diels−Alder dimerization was carried out in a number of hydrogen-bonding solvents (CH_3OH, H_2O, DMF, $CHCl_3$, *i*PrOH, *t*BuOH, 0.1 M) at 35 °C for 12 h. We only observed a small amount of the desired dimer **3** in $CHCl_3$.[16d] We also observed that the addition of triethylamine or a catalytic amount of HCl did not accelerate the dimerization, which ruled out the possibility of involvement of HCl as a catalyst. However, prolonged reaction time or elevated reaction temperature only led to more decomposition. Encouraged by this result, we further examined several commonly used hydrogen bond donor catalysts (Table 1).

Table 1. Hydrogen Bonding Promoted HDA Dimerization



entry	catalysts	conversion (%)[a]	yield (%)[b]
1	CSA	decomposed	
2	1,1′-binaphthyl-2,2′-diylhydrogenphosphate	trace	
3	*N*,*N*′-dimethylurea	trace	
4	*N*,*N*′-dimethylthiourea	trace	
5	*N*,*N*′-diphenylguanidinium BArF salt	trace	
6	TADDOL	trace	
7	phenol	trace	
8	4-bromophenol	trace	
9	*β*-naphthol	80	18
10	(±)-BINOL	79	64
11	(+)-BINOL	86	71
12	(−)-BINOL	85	70

[a] 1.0 equiv of catalyst (BINOL 0.5 equiv), neat, 50 °C, 60 h. The reaction mixture was analyzed by HPLC-MS, and the conversion was calculated by the integration of UV peaks. [b] All yields are isolated yields.

As the data show, the cycloadditions are accelerated to a much greater extent by using *β*-naphthol or (±)-BINOL (entries 9 and 10, Table 1), in which the OH group is expected to form hydrogen bond to the ketone moiety. We observed that (±)-BINOL represented better activation effect to afford homodimer **3** as a single stereoisomer in 64% yield along with 21% of recovered monomer **2**. The relative stereochemistry of dimer **3** was confirmed by 2D-NMR analysis.[11] The high facial selectivity could be explained by the fact that the bulky seven-membered ring of dienophile blocks the *β*-face, and as a result, the diene approaches to

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the dienophile from the less hindered α-face (Scheme 1). The higher yield using BINOL rather than β-naphthol indicates that the bidentate nature of BINOL may help orient two monomers to facilitate the [4 + 2]-hetero-Diels−Alder cycloaddition. Because monomer **2** is a chiral substrate, it would be of interest to probe if one of the enantiomers of BINOL is a more efficient catalyst. Interestingly, we found either enantiomer of BINOL showed a slightly enhanced activation effect compared with the racemate (entries 10−12, Table 1). This result might be rationalized by the fact that on the solid state racemic BINOL could be composed of the centrosymmetric structure characterized by intermolecular hydrogen bonds formed by a pair of (+)- and (−)- enantiomers, which reduces the hydrogen bonding effect on monomer **2**.[17] Further reaction condition studies showed that prolonged reaction time or elevated reaction temperature only led to more decomposition. These results implicated that this type of dimerization might be catalyzed by an enzyme, such as Diels−Alderase.

It was anticipated that under the thermo conditions for [4 + 2]-hetero-Diels−Alder cycloaddition there might be a degenerate [3, 3]-sigmatropic rearrangement[18] that could occur within dimer **3** between the ketone carbonyl oxygen and the enol ether distal alkene carbon (Figure 3). The

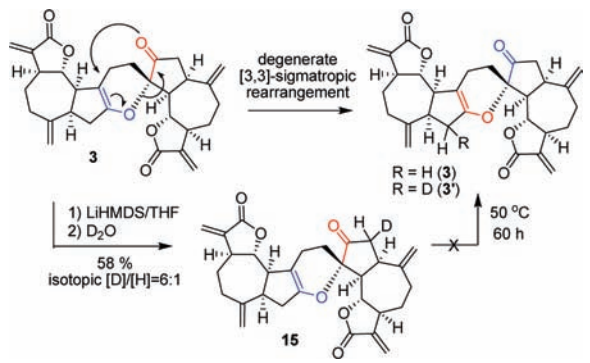
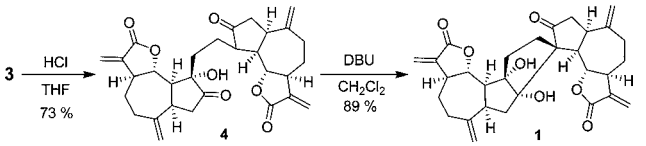


Figure 3. Possible degenerate [3,3]-sigmatropic rearrangement of dimer **3**.

occurrence of degenerate rearrangement may be detectable by isotopic labeling.[19] To gain evidence for this rearrangement and its ease, we prepared a deuterium-labeled compound **15** under basic conditions.[20] When dimer **15** was heated (neat, 50 °C, 60 h), starting material was recovered, and the rearranged product **3′** was not observed. Elevated reaction temperature only led to monomer **2** through retro-Diels−Alder reaction, as well as decomposition. These thermolysis experiments rule out the possible occurrence of degenerate [3,3]-sigmatropic rearrangement.

Completion of the total synthesis of **1** is illustrated in Scheme 3. Hydrolysis of compound **3** under mild acidic

Scheme 3. Total synthesis of (+)-Ainsliadimer A



condition afforded compound **4**. In the final step of the synthesis, the intramolecular aldol reaction of **4** was best accomplished by treatment with a large excess of DBU in dilute CH_2Cl_2 (0.0008 M) at 20 °C, which efficiently generated the final natural product **1** in 89% yield. Synthetic **1** was confirmed to be identical with data reported for natural ainsliadimer A by ^{1}H and ^{13}C NMR spectra,and high-resolution mass spectrum (HRMS). The optical rotation of synthetic **1** was $[\alpha]_D$ +42 (c = 0.002, $CHCl_3$), while natural **1** was $[\alpha]_D$ +47 (c = 0.05, $CHCl_3$), therefore confirming that the absolute configuration of synthetic **1** was consistent with natural **1**.

In conclusion, a protecting group free and biomimetic total synthesis of (+)-ainsliadimer A has been accomplished in 14 steps. The synthesis demonstrates the feasibility of using nonenzymatic conditions to achieve the proposed biosynthesis. The dimerization represents the first example of hydrogen bonding mediated [4 + 2]-hetero-Diels−Alder cycloaddition of both electron-deficient diene and dienophile. The mechanistic basis for this transformation and its synthetic utility are under investigation. Further studies toward the synthesis of additional dimeric sesquiterpene lactones as well as biological evaluation of ainsliadimer A and congeners are in progress and will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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