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Asymmetric Total Synthesis of Dragonbloodins A1 and A2

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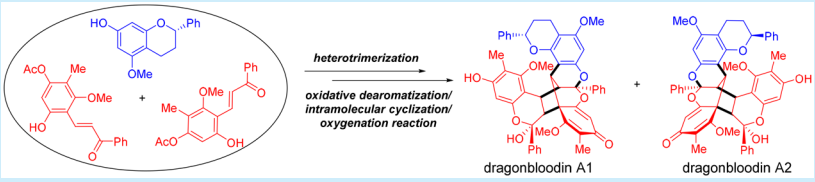
Supporting Information



ABSTRACT: The first asymmetric total synthesis of dragonbloodins A1 and A2, a pair of unprecedented chalcone-flavan heterotrimmers, has been achieved through a series of rationally designed or bioinspired transformations. Key elements of the synthesis include a highly efficient heterotrimerization reaction to assemble the two chalcone units and one flavan unit in one pot and a tandem oxidative dearomatization/cyclization/oxygenation reaction to forge the polycyclic core of dragonbloodins A1 and A2. The present synthesis unambiguously confirms the biogenetic relationship and absolute stereochemistry of dragonbloodins A1 and A2.

Dragon's blood, also known as Draconis Resina, is a renowned traditional medicine widely used in different cultures of the world.[1] In Chinese medicine, Dragon's blood is the major component of the hemostatic preparation "Yun-Nan-Bai-Yao", a popular wound-healing agent and a coagulant. Extensive phytochemical investigations have been carried out on Dragon's blood, leading to the discovery of various compounds that showed diverse biological effects, including antitumor, antiviral, analgesic, and anti-inflammatory activities.[1,2] Structurally, the major constituents identified from Dragon's blood belong to the flavonoid family, existing in either monomeric or oligomeric forms.[3] As a paradigm, two unprecedented flavan trimers, namely dragonbloodins A1 (**1**) and A2 (**2**), were isolated by Wu and co-workers from the genus *Daemonorops draco* in 2016 (Figure 1).[4] It was suggested that dragonbloodins A1 and A2 share a common polycyclic backbone, only differing in the stereochemistry at the C2″ chiral center. Interestingly, it was reported that dragonbloodins A1 and A2 were rather unstable and readily advanced to some unidentified compounds upon separation from each other.[4] By comparison, the samples consisting of a 1:1 ratio of dragonbloodins A1 and A2 turned out to be relatively stable, presumably due to the stabilizing effect of the intermolecular hydrogen bonding between the two molecules. Notably, preliminary biological study revealed that dragonbloodins A1 and A2 exerted an inhibitory effect on human neutrophil superoxide anion generation in a dose-dependent manner. In addition, they could also inhibit neutrophil elastase release (IC_{50} = 6.53 μM), which renders them potential leads for the development of anti-inflammatory agents.[4]

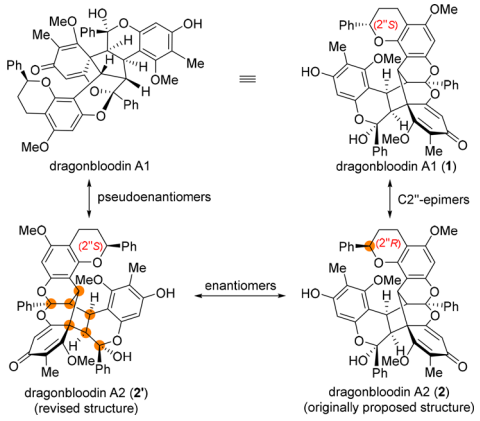


Figure 1. Structures of dragonbloodins A1 and A2.

Attracted by the novel chemical structures and promising biological profiles of dragonbloodins A1 and A2, we initiated a program with the aim of achieving their total synthesis. However, we were surprised to find that the original isolation paper was retracted shortly after their disclosure.[4] According to the author's declaration, the structure of dragonbloodin A2 was incorrectly assigned due to the misinterpretation of the X-ray crystal data, although the structure of dragonbloodin A1 should be correct. While this interlude casted a shadow on our synthetic program, we quickly realized that a total synthesis of these targets could provide more conclusive evidence for their structural assignment. Notably, while our project was ongoing, an elegant biomimetic total synthesis of dragonbloodins A1 and A2 was disclosed by the Trauner group.[5] In this seminal work, the structure of dragonbloodin A2 was revised from **2** to **2′** on the basis of the biogenetic consideration as well as the comparison of their CD spectra. Compared to dragonbloodin A1, **2′** bears the same (*S*)-configuration at the C2″ chiral center

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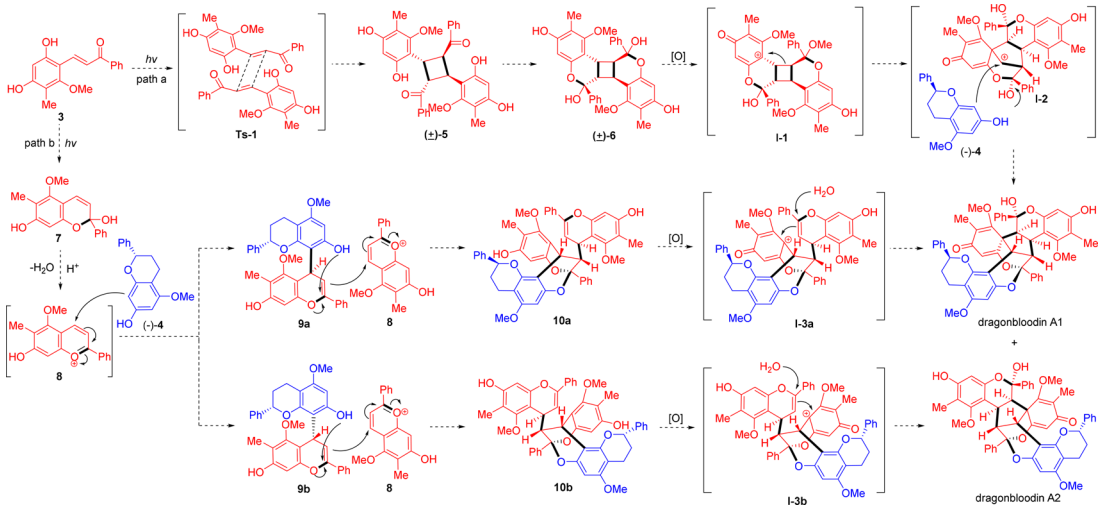
Scheme 1. Proposed Biomimetic Synthetic Strategies for Dragonbloodins A1 and A2



but differs in seven other stereocenters. In this context, dragonbloodin A2 represents the pseudoenantiomer of dragonbloodin A1 instead of the originally proposed C2″-epimier. While such rationalization appears to be reasonable, a more convincing evidence to verify the identity of dragonbloodins A1 and A2 could be obtained only through an asymmetric synthesis, which allows for the direct comparison of the specific rotation of synthetic and natural samples.

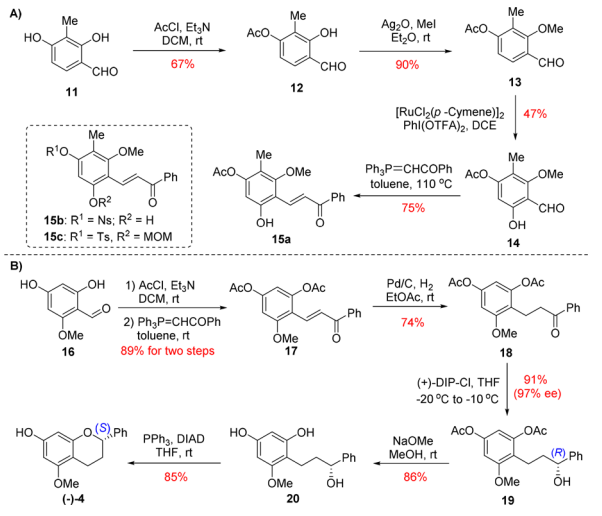
It is worth noting that although Trauner and co-workers achieved the asymmetric synthesis of a key intermediate en route to dragonbloodins A1 and A2, they did not complete the asymmetric total syntheses. Keeping this in mind, we continued to push our project forward, which has culminated in the first asymmetric total synthesis of dragonbloodins A1 and A2. On the basis of this work, we unambiguously verified the identity of dragonbloodins A1 and A2, particularly regarding their absolute configuration.

From a structural point of view, dragonbloodins A1 and A2 consist of two units of chalcone **3** and one unit of flavan **4**. Apparently, the most efficient way to access these targets should build on a biomimetic heterotrimerization reaction. Keeping this in mind, we designed two distinct strategies (Scheme 1). The first one features a [3 + 3 + 4]-mode (path a). In this scenario, the chalcone **3** could undergo homodimerization through a photoinduced [2 + 2]-cycloaddition[9] to give the cyclobutane derivative (±)-**5** that would readily advance to (±)-**6** through hemiketalization. Upon treatment with suitable oxidant, (±)-**6** could undergo tandem oxidative dearomatization/cyclobutane ring-expansion[10] to generate the carbon cation **I-2**. Finally, **I-2** could be trapped with (−)-**4** through sequential nucleophilic attack and ketalization to give dragonbloodins A1 and A2.

Alternatively, we assumed that the heterotrimerization reaction could also proceed through a [3 + 4 + 3]-mode (path b). Thus, the chalcone **3**, upon irradiation or treatment with acidic conditions, could undergo sequential double-bond isomerization and hemiketalization to give the bicycle **7**.[6] The hemiketal **7** readily advances to the benzopyrylium intermediate **8** through dehydration, and the latter could further undergo nucleophilic addition with flavan (−)-**4** to from two diastereomeric heterodimers **9a** and **9b**.[7] Both **9a** and **9b** could react with the second unit of benzopyrylium **8** through sequential nucleophilic addition and ketalization, thus giving rise to the corresponding bridged compounds **10a** and **10b**. Upon exposure to suitable oxidant, **10a** and **10b** could undergo tandem oxidative dearomatization/cyclization/hemiketalization to afford dragonbloodins A1 and A2, respectively.[8]

Our synthesis commenced with the preparation of the chalcone unit (Scheme 2A). Thus, selective acetylation of 2,4-dihydroxy-3-methylbenzaldehyde **11**[11] afforded **12** in 67% yield, which after methylation, provided the fully protected aldehyde **13**. To introduce the third phenolic hydroxyl, we resorted to an interesting method developed by Ackermann and co-workers, that is, the aldehyde-assisted Ru(II)-catalyzed C−H oxygenation reaction.[12] Gratifyingly, the transformation proceeded smoothly, providing the desired product **14** in a reasonable yield. Of note, the reaction could be improved by replacing the acetyl group to sulfonyl group (Ts- or Ns-) (Table S1). Finally, treatment of **14** with (triphenylphosphoranylidene)acetophenone in refluxing toluene provided the chalcone derivative **15a** smoothly. In parallel, **15b** and **15c**, two other protected chalcone derivatives, were also prepared on the basis of the above procedure (for details, see the SI).

Scheme 2. Syntheses of the Chalcone and Flavan Units



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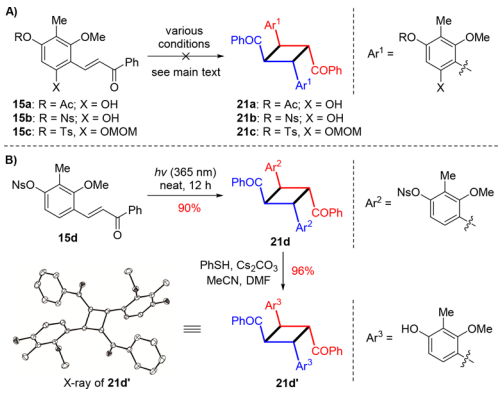
With the requisite chalcone unit in hand, we moved to achieve the asymmetric synthesis of the flavan unit (Scheme 2B). To this end, the aldehyde **16**[13] was first converted to the chalcone **17** through acetylation, followed by Wittig olefination. Next, reduction of **17** through catalytic hydrogenation gave the ketone **18**. Subsequently, an asymmetric reduction was effected with the chiral reagent (+)-DIP chloride, which gave the secondary alcohol **19** with excellent yield (91%) and enantioselectivity [(*R*)-configuration, 97% ee].[14] Finally, removal of the acetyl group followed by intramolecular Mitsunobu reaction afforded the desired flavan unit (−)-**4** smoothly, with the C2 stereochemistry being inverted to (*S*)-configuration.[15]

Having both chalcone and flavan units secured, we turned to explore the bioinspired heterotrimerization reaction. Initially, the [3 + 3 + 4]-mode (path a, Scheme 1) was attempted. On the basis of our design, the first step is to realize the homodimerization of the two chalcone units through a [2 + 2]-photocycloaddition. To our surprise, although there exist some relevant precedents,[9d−g] such transformation was much more challenging than our expectation. Indeed, we evaluated a number of potential substrates (e.g., **15a**−**c**) under various conditions involving different light sources (Hg lamp, UV lamp, and sunlight), solvents (DCM, THF, acetone, CH_3CN, hexanes, and neat), and additives [$Cu(OTf)_2$ and benzophenone] (Scheme 3). Unfortunately, we failed to get promising

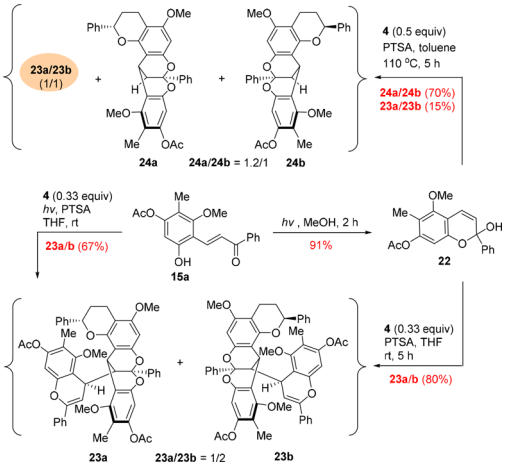
Scheme 3. Attempts to Effect Homodimerization of the Chalcone Units through [2 + 2]-Photocycloaddition



results. In most cases, the starting material remained unchanged. Compared to those precedents,[9] we assume that the poor reactivity in our cases could be attributed to the notable steric effect associated with substrates, which precludes two monomers from approaching each other. Of note, this hypothesis was validated by the following observation: the less substituted chalcone **15d** readily underwent [2 + 2]-photocycloaddition upon irradiation (365 nm) in its solid state,[16] which gave rise to the head-to-tail dimerization product **21d** in 90% yield. Notably, the structure of **21d** was confirmed by the X-ray crystallographic study of its deprotection product **21d′**.

Although the proposed [2 + 2]-photocycloadditions failed to give satisfactory results, we found that **15a**, upon photoirradiation, could undergo sequential double-bond isomerization and hemiketalization to give the bicycle **22** in 90% yield. This discovery paved the way to explore the alternative trimerization reaction through the [3 + 4 + 3]-mode (path b, Scheme 1). Recently, Lee and co-workers reported an acid-catalyzed heterodimerization of 2-hydroxychalcones and resorcinols.[17] Inspired by this work, we attempted to effect the heterotrimerization of **22** and (−)-**4** under identical conditions (PTSA, toluene, 110 °C) (Scheme 4). Gratifyingly,

Scheme 4. Heterotrimerization of Chalcone and Flavan Units



a small amount of the expected heterotrimers **23a**/**23b** (ca. 15% yield) was identified in the reaction, which existed as an inseparable diastereoisomers in a ratio of 1.2:1. Additionally, the heterodimers **24a**/**24b** (1:1) were isolated in 70% combined yield. Encouraged by this result, we performed a comprehensive condition optimization to improve the yield of the heterotrimers (Table S2). It was found that both the solvent effect and reaction temperature played crucial roles in the reaction. Eventually, the best result was obtained when the reaction was performed in THF at room temperature using 3.0 equiv of **6a**, which delivered a mixture of **23a**/**23b** in 80% combined yield, favoring **23b** as the major isomer (**23a**/**23b** = 1:2). More interestingly, based on the above results, a operationally simple one-pot protocol was developed to effect the photoinduced double-bond isomerization/hemiketalization and subsequent acid-promoted heterotrimerization, which enabled the direct access of **23a**/**23b** from **15a** and (−)-**4** in a single operation with high efficiency (67% yield). Notably, no heterotrimerization products could be obtained in the reaction without irradiation.

With **23a**/**23b** in hand, we moved to complete the total synthesis of dragonbloodins A1 and A2. For this end, the acetyl group of **23a**/**23b** was removed with the action of NaOMe/MeOH. In agreement with the observation reported by Trauner and co-workers,[5] the resulting products **10a**/**10b** were sensitive to air, and partially converted to the hydroperoxy **25a**/**25b** through auto-oxidation during the course of chromatographic purification. However, we found that the isolated yield of **25a**/**25b** varied in different experiments. After several tries, we developed a more reliable and reproducible protocol to effect the tandem oxidative dearomatization/intramolecular cyclization/oxygenation reaction. Thus, direct treatment of the newly generated **10a**/**10b** with silver oxide under air furnished **25a**/**25b** in 63% yield.[8c] Finally, reduction of **25a**/**25b** with dimethyl sulfide led to the formation of dragonbloodins A1/A2. At this stage, the ratio of dragonbloodins A1 and A2 was 1:2. Interestingly, we found that this sample was inclined to precipitate in EtOAc, forming a precipitate consisting of a 1:1 ratio of dragonbloodins A1 and

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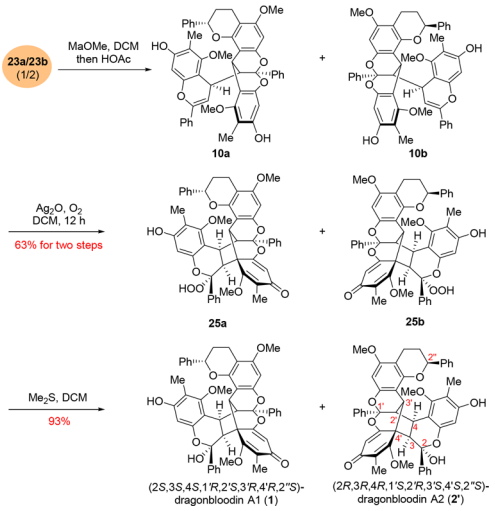
A2. As a result, the mother liquid showed an increased proportion of dragonbloodin A2. After repeating such operation twice, we obtained the pure dragonbloodins A2 for structural characterization. Gratifyingly, the spectroscopic data (^{1}H and ^{13}C NMR) of synthetic dragonbloodins A1 and A2 were identical with those reported for the natural samples. Moreover, the optical rotation of synthetic dragonbloodin A2 ($[\alpha]_D$ −54.72, c = 0.27, $CHCl_3$) was also in good agreement with the reported one ($[\alpha]_D$ −58.08, c = 0.06, $CHCl_3$).[4,18] Thus, the absolute configuration of dragonbloodin A2 could be unambiguously assigned as shown in the structure **2′** (Scheme 5). Naturally, the identity of dragonbloodin A1 (**1**) is confirmed as well.

Scheme 5. Total Synthesis of Dragonbloodins A1 and A2



In summary, we have achieved the first asymmetric synthesis of dragonbloodins A1 and A2, a pair of unprecedented chalcone-flavan heterotrimmers. The key elements of our synthesis include (1) an aldehyde-assisted Ru(II)-catalyzed C−H oxygenation to access the chalcone unit, (2) a bioinspired heterotrimerization to unite the two chalcone and one flavan units together, and (3) a tandem oxidative dearomatization/cyclization/oxygenation reaction to forge the polycyclic core of dragonbloodins A1 and A2. The present synthesis provides unequivocal evidence for the structural determination of dragonbloodins A1 and A2. Given that the structural revision of naturally occurring dragonbloodins A1 and A2 has remained yet to be made by the isolation team, our study may provide valuable information to those synthetic chemists who are now working on these targets.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00315.

Experimental details, characterization; ^{1}H and ^{13}CNMR spectra for all newly synthesized compounds (PDF)

Accession Codes

CCDC 1819926 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(18) The NMR spectroscopic data and optical rotation of natural samples were provided in the Supporting Information of the retracted paper (see ref 4).

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