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Total synthesis and biological evaluation of dracaenins A and B

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ABSTRACT

The first total synthesis of dracaenins A and B is achieved in four steps. The synthesis features the convergent coupling of three readily available fragments with minimized use of protecting groups. The chemical synthesis enables the discovery of their activity in stimulating platelet aggregation, and thus, sheds light on the possible origin of the hemostatic effect of dragon's blood.

Dragon's blood refers to the red resinous exudations from plant species and has been used as herbal medicine for more than 1500 years across many cultures. Modern pharmacological studies of dragon's blood have revealed a wide array of bioactivities [1]. Among them, it has been highlighted to have bidirectional regulatory effect of stimulating both blood circulation and coagulation. The clarification and identification of active components that account for these contrasting activities are crucial for the in-depth studies of this important herbal medicine. In this context, several phenolic compounds [2–4], such as loureirin B (**5**) and cochinchinenin A (**6**), isolated from dragon's blood, have been shown to have the activity of promoting blood circulation (Fig. 1). However, the active components that could stimulate blood coagulation (hemostatic effect) remain to be discovered.

Dracaenins A (**1**) and B (**2**) were isolated from the Chinese dragon's blood, *Dracaena cochinchinensis* (Lour.) S.C. Chen, by Zhang and co-workers in 2012 (Fig. 1) [5]. Structurally, they feature the unusual chalcane-anthocyanidin dimers. Several anthocyanidins, such as dracorhodin (**3**) and nordracorhodin (**4**), have been isolated from dragon's blood and are known to account for its intense red color (Fig. 1). The related dihydrochalcones **5** and **6** have been reported to be able to inhibit platelet aggregation. Thus, the generation of such chalcane-anthocyanidin dimers by nature would be inspiring and useful as chemical probes to study the related biological activities.

The isolation yield of dracaenin A from dragon's blood is very low (23 mg dracaenin A was isolated from 3.0 kg of dragon's blood). In addition, this herbal medicine is very expensive due to its beneficial values to human health, the wide usage and the shortage of natural sources. Total synthesis has long been a powerful tool in facilitating the biological studies of natural products by providing enough materials particularly when the nature supply is limited or not accessible [6]. In addition, once the therapeutic potential of a natural product is identified, efficient chemical synthesis could offer a sustainable alternative for its production, thus alleviating the pressure on natural resource. While the structural complexity of dracaenins A and B is moderate, the concise assembly of these structures is not trivial. Attention should be paid to the electrophilicity of the anthocyanidin part in a synthetic design as demonstrated by the transformation of **3** to other more complex natural products by the group of Trauner [7]. Moreover, there are 7 phenolic oxygens with varied substitution patterns and oxidation state. The successful introduction of them with minimal reliance on protecting groups is crucial for synthetic efficiency [8]. Site-selectivity regarding the formation of the anthocyanidin part and chalcane-anthocyanidin connection are further concerns. Herein, we report our efforts to address these synthetic issues, which lead to the concise and convergent total synthesis of dracaenins A and B on only four steps. The chemical synthesis further enables the discovery of their activity in stimulating platelet aggregation, and thus, sheds light on the possible origin of the hemostatic effect of dragon's blood.

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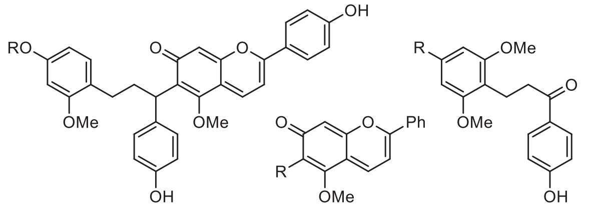
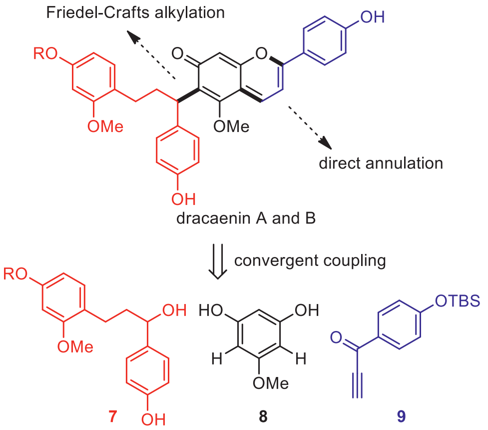
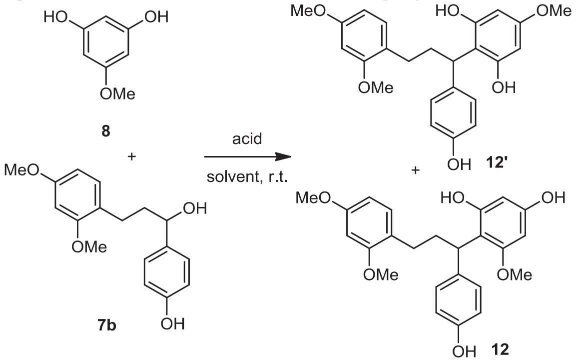

dracaenin A (1); R = H dracorhodin (3); R = Me loureirin B (5); R = OH
dracaenin B (2); R = Me nordracorhodin (4); R = H cochinchinenin A (6); R = H

Fig. 1. Dracaenins A and B and related natural products from dragon's blood.



Scheme 1. Synthetic plan to dracaenins A and B.

Table 1
Optimized conditions for the Friedel-Crafts coupling.



Entry	Acid (equiv.)	Solvent	**12:12′**[b]	Yield of **12** (%)[c]
1	HCl (4.0)	MeOH	–	< 5
2	*p*-TsOH (0.4)	CH_3CN	–	< 5
3	$BF_3 \cdot Et_2O$ (0.12)	CH_2Cl_2	–	< 5
4[a]	$BF_3 \cdot Et_2O$ (0.12)	CH_2Cl_2	1.6:1	48
5	$(PhO)_2POOH$ (0.2)	CH_2Cl_2	1.1:1	40
6	$(PhO)_2POOH$ (0.2)	CH_3CN	1.1:1	48

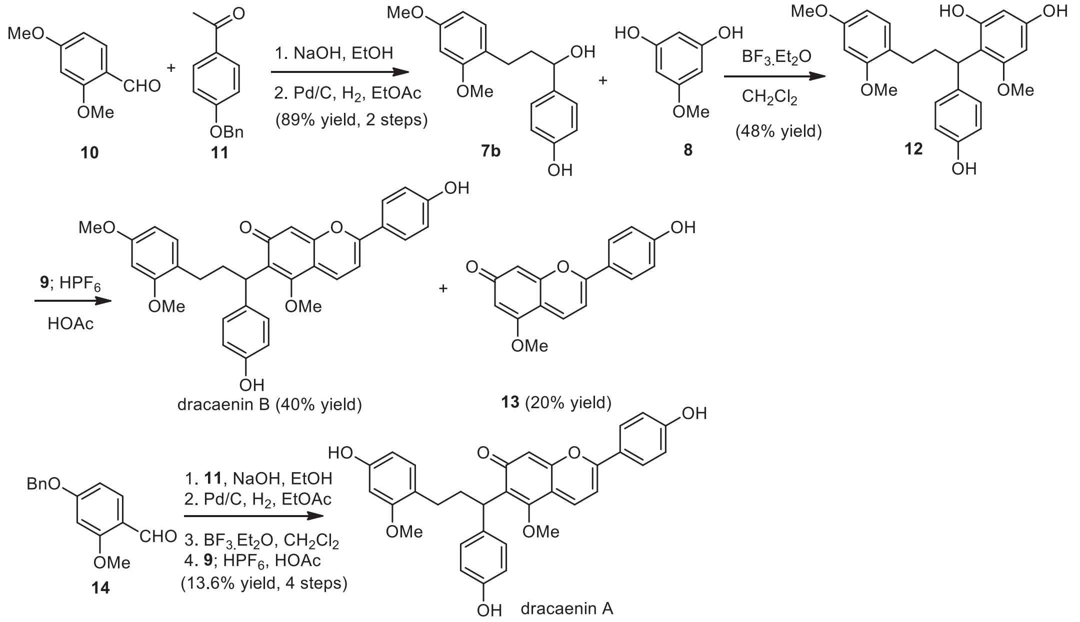
[a] At −10 °C.
[b] Determined by ^1H NMR.
[c] Isolated yield.

It could be envisioned from the outset that a successful synthesis would afford dracaenins A and B in short synthetic sequence, in a convergent manner [9] and with the minimized use of protecting groups [8]. To fulfill these standards, our synthetic plan was depicted in Scheme 1. We surmised that the chalcane-anthocyanidin connection of dracaenins A and B could be furnished by the direct Friedel-Crafts coupling of alcohol **7** and phloroglucinol derivative **8**. It was hoped that the coupling could proceed without any protecting groups on the phenolic oxygens. Regarding the synthesis of the anthocyanidin part, several known methods have been reported [7,10,11]. The most common approach requires the prefunctionalization of the precursor, for example the coupling products of **7** and **8**, with an aldehyde group as the synthetic handle. We envisioned that such stepwise operations would pose significant challenges in controlling the chemoselectivity without using protecting groups. Thus, we turned to a direct annulation approach developed by the group of Chassaing using ethynyl ketone **9** [12,13]. In our synthetic plan, only ethynyl ketone **9** was protected as the TBS ether, which was introduced during its preparation and could be concomitantly cleaved under the acidic annulation conditions. In addition, our synthetic design features the convergent coupling of three fragments **7**–**9**, which could allow for the synthesis of structural analogs, if necessary, by the facile variation of these fragments.

We first selected dracaenin B as our synthetic target (Scheme 2). The coupling partner **7b** was successfully synthesized in 2 steps by the Aldol type condensation of **10** and **11** followed by hydrogenation of the resulting chalcone. The coupling of **7b** and phloroglucinol derivative **8** turned out to be challenging. Different acids that could potentially promote the Friedel-Crafts alkylation were screened (Table 1). In the presence of HCl or *p*-TsOH, the formation of the desired product was not observed. The switch to $BF_3 \cdot Et_2O$ [14,15] at −10 °C led to the production of **12** in synthetically useful yield (48%; entry 4), albeit companied with its regio-isomer **12′** (**12:12′** = 1.6:1). The use of diphenyl phosphate as the acidic promotor in acetonitrile gave similar yield of **12** with slightly lower site-selectivity (entry 6). In the current investigation, we chose to use the $BF_3 \cdot Et_2O$ condition for the synthesis of **12**.

Finally, we turned to the direct annulation of **12** and **9** to afford the anthocyanidin moiety. The literature conditions using stoichiometric amount of HPF_6 gave less than 5% formation of the PF_6^- salt of dracaenin B [12,13]. After further examination of the reaction mixture, the formation of **13** was observed as the major by product, indicating that the *retro*-Friedel-Crafts type cleavage occurred under the strong acidic conditions. While this side reaction pathway could be potentially inhibited by the appendant of suitable protecting groups, we did not prefer such a strategy as it would hurt the step economy of the synthesis [16]. After systematic investigation of the amount of HPF_6 and the reaction concentration, we found dracaenin B could be formed in 40% yield in the presence of 12 mol% HPF_6 and at diluted concentration. Analogously, dracaenin A was produced from **14** in four steps in 13.6% overall yield. While the reaction yields of the coupling steps were not optimal at this moment, the rapid assembly of dracaenins A and B in only four steps, in a highly convergent manner and in good overall yields is noteworthy.

Dragon's blood has been highlighted to have the bidirectional regulatory effect of stimulating both blood circulation and coagulation. The active components that could stimulate blood coagulation (hemostatic effect) remain to be discovered. With enough materials synthesized, the effects of dracaenins A and B on adenosine diphosphate (ADP), arachidonic acid (AA) or collagen induced platelet aggregation were evaluated by the light transmission method (Fig. 2). As shown in **1b**, ADP (2.5 µmol/L) mediated platelet aggregation was obviously stimulated by dracaenin B in a concentration-dependent manner, with average increasing rates of 8.02%, 9.15%, 13.87%, 19.76% and 114.18% at concentrations of 0.98, 2.9, 8.8, 26.3 and 79 µmol/L, respectively. Dracaenin B also showed marked stimulating effects in a concentration dependent manner with the increasing rates of 7.17%, 12.71%, 28.52%, 35.94% and 51.29% on collagen induced platelet aggregation, and 0.24%, 1.10%, 2.22%, 43.95% and 71.04% increasing rates on AA induced platelet aggregation at concentration range from 0.98 µmol/L to 79 µmol/L (**2b** and **3b**). The stimulating effect on platelet aggregation was also observed using dracaenin A (**1a-3a**), albeit less potent than that of dracaenin B. These results revealed the effects of dra-



Scheme 2. Total synthesis of dracaenins A and B.

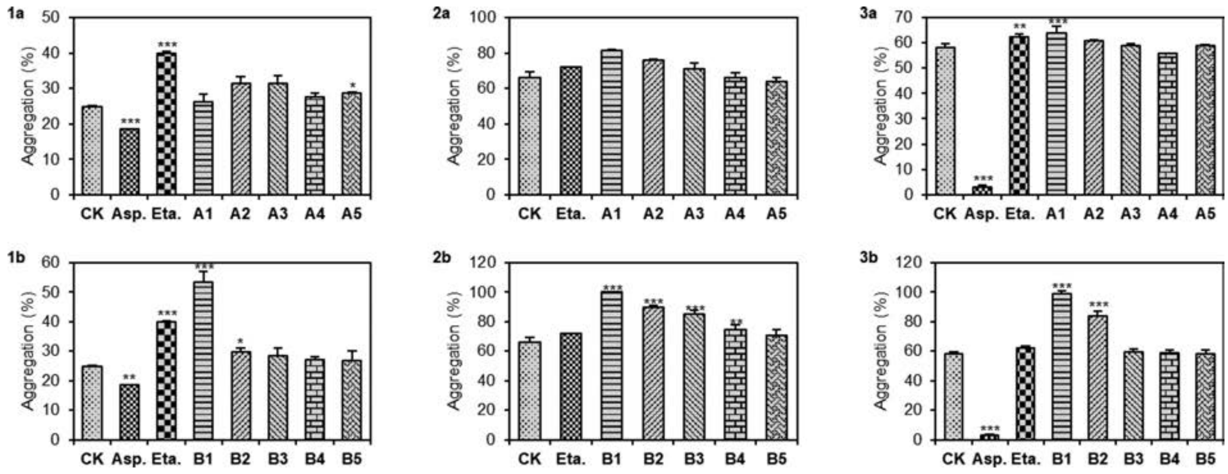


Fig. 2. The effect of dracaenins A and B on ADP, collagen and AA-induced platelet aggregation; control group (CK) was treated with 0.1% DMSO; aspirin (Asp. 17.90 µmol/L) and estamsylate (Eta. 494.30 µmol/L) were used as negative and positive controls. The concentration of dracaenin A for group A1 to A5 is 55, 18.3, 6.1, 2 and 0.68 µmol/L respectively; the concentration of dracaenin B for group B1 to B5 is 79, 26.3, 8.8, 2.9 and 0.98 µmol/L respectively. The platelet aggregation was induced by 2.5 µmol/L ADP (**1a** & **1b**), 3.0 µg/mL collagen (**2a** & **2b**) and 150 µg/mL AA (**3a** & **3b**), respectively. The bar graphs are a summary of each independent experiments; each column shows the mean ± standard deviation of at least three independent experiments. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$ *versus* the control group.

caenins A and B in stimulating platelet aggregation, and shed light on the possible origin of the hemostatic effect of dragon's blood.

In conclusion, dracaenins A and B represent the unusual chalcane-anthocyanidin dimers isolated from dragon's blood. We have achieved the first total synthesis of these natural products in only 4 steps. Our synthesis features the convergent coupling of three readily available fragments with minimized reliance on protecting groups. The chemical synthesis enables the discovery of their activity in stimulating platelet aggregation, and thus, sheds light on the possible origin of the hemostatic effect of dragon's blood.

Declaration of competing interest

The authors declare no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2021.10.067.

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