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Biomimetic Synthesis of Complex Flavonoids Isolated From *Daemonorops* "Dragon's Blood"

Matthias Schmid[a] and Dirk Trauner*[a,b]

Abstract The dragonbloodins are a pair of complex flavonoid trimers isolated from the palm tree *Daemonorops draco*, one of the sources of the ancient resin known as "Dragon's Blood". We present a short synthesis that clarifies their relative configuration and sheds light on their origin in Nature. It features biomimetic cascade reactions that involve both ionic and radical intermediates. The biogenetic relationships between dracorhodin, the dracoflavans C, and the dragonbloodins A1 and A2 are discussed.

"Dragon's Blood" is an intensely colored red resin that has been used in medicine since ancient times and across many cultures.[1] It can stem from several different plant sources, which has led to some confusion regarding its composition and its pharmacology. A variety obtained from the palm tree *Daemonorops draco* has recently received renewed attention as a source of bioactive molecules. It was shown to have antiviral[2] and anticancer[3] effects, as well as activity against osteoporosis,[4] diabetes,[5] inflammation[6] and platelet aggregation.[7] Detailed investigations into its chemical components yielded a range of flavonoids of varying complexity (Figure 1). They comprise monomeric flavonoids, such as (2*S*)-5-methoxyflavan-7-ol (**1**) and (2*S*)-5-methoxy-6-methylflavan-7-ol (**2**). Their oxidized congeners nordracorhodin (**3**) and dracorhodin (**4**), respectively, which are shown here as the anhydrobases, are largely responsible for the intense red color of Dragon's Blood. The monomeric flavonoids can dimerize in various ways to give rise to nordracorubin (**5**) and dracorubin (**6**),[8] daemonorol A (**7**) and C (**8**),[9] dracooxepine (**9**),[10] and the diastereomeric dracoflavans C1 (**10a**) and C2 (**10b**).[11]

Recently, the group of Wu isolated the first flavonoid trimers from Dragon's Blood – dragonbloodin A1 (**11a**) and A2 (**11b**).[12] These highly complex molecules feature a unique skeleton with a central spiro[4.5]deca-8-oxo-6,9-diene core. The original report was retracted shortly after its publication because of doubts regarding the structure of dragonbloodin A2 and the proposed biosynthesis based on this structure. The monomeric and dimeric flavonoids in Figure 1 all feature the (*S*)-configuration in their chromane moieties, which is consistent with their biosynthesis catalyzed by chalcone isomerase.[13] This and the CD spectra of **11a** and **11b** lead us to hypothesize that the dragonbloodins are not epimers but pseudoenantiomers differing in seven of eight stereocenters except the (2*S*) center of the chromane moiety. We now wish to report our own studies on the dragonbloodins, which clarify the relationship between dragonbloodin A1 and A2, and provided an effective synthetic entry through an oxidative biomimetic cascade.

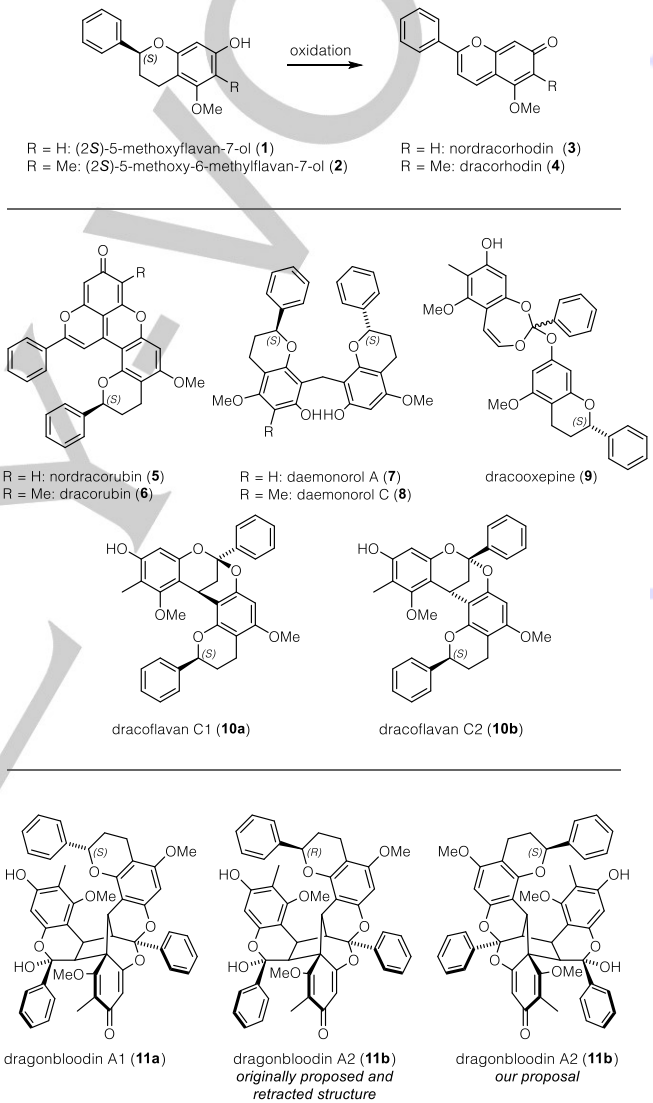

Figure 1. Natural flavonoids isolated from Dragon's Blood.

Our proposed biosynthetic pathway that links the monomers with the di- and trimers is shown in Scheme 1. A 1,6-addition of flavan-7-ol **1** to dracorhodin (**4**) would lead to the two diastereomeric intermediates **12a** and **12b**. This process is not catalyzed by an enzyme and occurs with low diastereoselectivity. The benzo-4*H*-pyrans **12a** and **12b** possess a nucleophilic vinyl ether moiety that can react with other various electrophiles, the simplest of which is a proton. Accordingly, protonation of **12a** would yield oxocarbenium ion **13a**. Closure of the acetal would then afford dracoflavan C2 (**10b**). The analogous reaction

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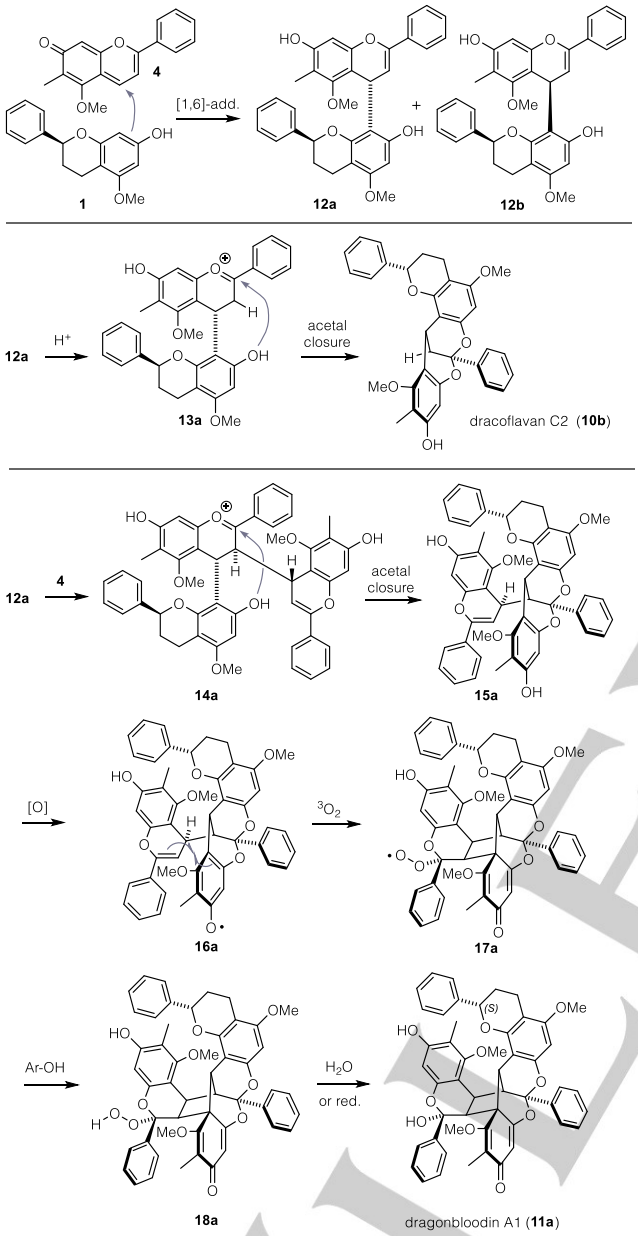
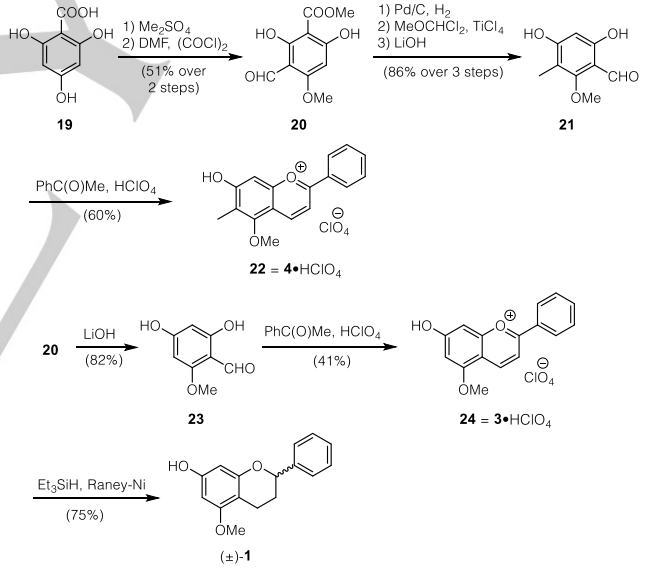
(not shown) would yield dracoflavans C1 (**10a**) from **12b**. Alternatively, enol ether **12a** could react with dracorhodin (**4**) as an electrophile, which would yield oxocarbenium ion **14a**. This second nucleophilic attack onto **4** can be expected to occur with a high degree of diastereoselectivity *trans* to the existing chromanol moiety. Closure of the acetal then yields **15a**, which still retains an enol ether moiety.



Scheme 1. Proposed biogenesis of the dracoflavans and dragonbloodins.

To account for the formation of the dragonbloodins we propose an autoxidation mechanism. The phenolate corresponding to **15a** is initially oxidized to the phenoxy radical **16a**. Intramolecular addition to the enol ether moiety generates the *spiro* cyclohexadienone and gives a stabilized benzylic radical (not shown) that reacts with triplet oxygen to yield the hydroperoxy radical **17a**. This intermediate abstracts a hydrogen atom from the next phenol, completing the radical chain (see SI for details). The resultant hydoperoxide **18a** is either reduced or, more likely, undergoes hydrolysis to generate dragonbloodin A1 (**11a**). An analogous oxidative cascade starting from **12b** would yield the *pseudo*-enantiomeric trimer dragonbloodin A2 (**11b**).

To test our hypothesis experimentally, we first synthesized the flavonoid monomers **1** and **4**. Dracorhodin (**4**) and its simple congeners have been the subject of many previous studies and our optimized approach largely follows an established route.[14] Thus, 2,4,6-trihydroxybenzoic acid (**19**) was converted into aromatic aldehyde **20** *via* selective methylation and formylation. Reduction of the formyl group with palladium on charcoal, Rieche formylation, and ester cleavage followed by decarboxylation then gave aldehyde **21** in excellent yield. We found that the use of LiOH instead of NaOH prevented deformylation, which was otherwise a significant side reaction. Condensation of **21** with acetophenone promoted by perchloric acid cleanly afforded dracorhodin as the flavylium perchlorate salt **22**. Racemic 5-methoxy-flavan-7-ol (**1**) was also synthesized from aldehyde **20**, which could be hydrolyzed and decarboxylated to afford **23**. An analogous condensation with acetophenone gave surprisingly low yields of nordracorhodin perchlorate **24** when compared to dracorhodin perchlorate **22**. Hydrogenation of the flavylium salt **24** with PtO_2 or Pd/C as a catalyst also gave only poor yields of **1**. By contrast, reduction with Raney-Nickel and triethylsilane proved to be effective affording racemic **1** in high purity. Interestingly, substitution of the perchlorate anion with hexafluorophosphate lead to a dramatic drop in yield in the course of this reduction.



Scheme 2. Synthesis of flavonoid building blocks dracorhodin perchlorate (**22**) and 5-methoxyflavan-7-ol (**1**).

With both monomeric flavonoid building blocks in hand, we proceeded to synthesize the dimeric dracoflavans **10a**/**b** (Scheme 2). Taking inspiration from the work of Pettus[15], we dissolved a mixture of flavylium salt **22** and racemic flavanol **1** in aqueous phosphate buffer (pH 5.8) and methanol and heated the mixture to 110 °C in a closed vial. This directly afforded the dracoflavans **10a** and **10b** in a 56:44 ratio, which is virtually identical to the ratio in which the two diastereomers have been found in Nature. We were never able to isolate the putative intermediates **12a/b** (Scheme 1) but we consistently found traces of

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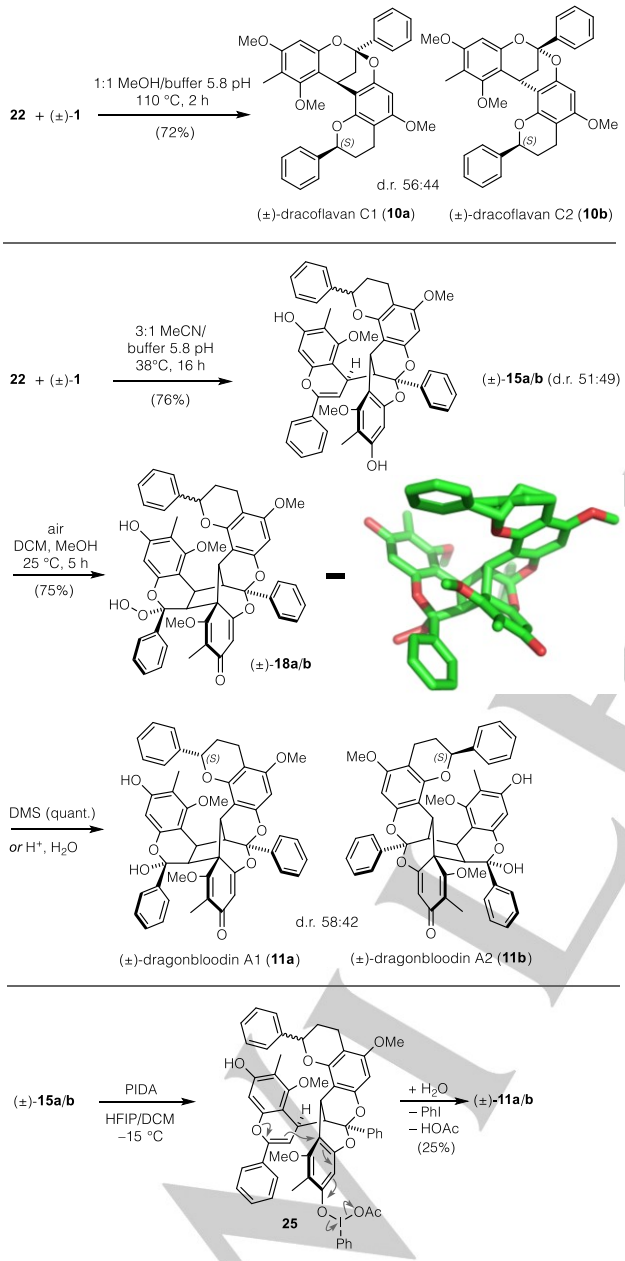
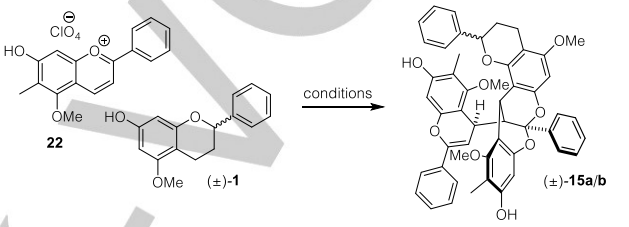
trimeric byproducts that clearly stemmed from one equivalent of chromanol **1** and two equivalents of anhydrobase **4**. These were ultimately identified as **15a**/**b** (dr 51:49) in accordance with our biogenetic hypothesis (Scheme 1). Extensive screening of solvents and condition screening increased the combined yield of the trimers to 76% (see Table 1). Interestingly, a large excess of **1** was required to obtain good yields although it is the minor building block in the formation of the trimers. **15a**/**b** proved to be highly sensitive and we quickly realized that they were unstable toward air during attempts of separation and purification. We therefore exposed them deliberately to oxygen. When **15a**/**b** was stirred in a solution of DCM with 3% MeOH in the presence of air we could isolate large quantities of a material that was stable toward silica gel chromatography. A crystal suitable for X-ray structure analysis revealed it to the hydroperoxy hemiacetal (±)-**18a**/**b**. It is important to note that this crystal contains four distinct molecules, *viz*. two enantiomers of both *pseudo*-enantiomeric diastereomers.[16] The structure depicted in Scheme 3 shows an average of the hydroperoxides corresponding to natural dragonbloodin A1 and the unnatural enantiomer of dragonbloodin A2. The hydroperoxides **18a**/**b** could be cleanly reduced with dimethyl sulfide (DMS) to provide the dragonbloodins **11a**/**b**. Perhaps more relevant to the biosynthesis, we noted that during HPLC purification the hydroperoxide **18a**/**b** underwent clean hydrolysis to provide the dragonbloodins **11a** and **11b**. The spectra of our racemic molecules matched those obtained from the natural products by Wu *et al*.[12]



Scheme 3. Synthesis of the dracoflavans C (**10a** and **10b**) and the dragonbloodins A (**11a** and **11b**). DMS = dimethylsulfide, HFIP = hexafluoro-*iso*-propanol, PIDA = phenyliodine diacetate.

Table 1. Reaction optimization of biomimetic trimerization.



Entry	Ratio **22**:**1**	Additives	Solvent	*T* [°C]	Yield [%][a]
1	1:1.5	Na_3PO_4	MeOH	RT to 65	0
2	1:1.5	Na_3PO_4/. 4Å Mol[17]	Toluene	RT	traces
3	1:6	buffer pH 5.8[c]	MeOH	RT	14%
4	1:4	buffer pH 5.8[c]	HFIP	RT	0
5	1:4	buffer pH 5.8[c]	DMF	RT	traces
6	1:4	buffer pH 5.8[c]	MeCN	RT	60–63%[b]
7	1:4	buffer pH 5.8[c]	MeCN	38	76%[b]
8	1:3	buffer pH 5.8[c]	MeCN	45	32%[b]

[a] Yield calculated by NMR spectroscopy after 15-20 h reaction time [b] Yield of isolated product [c] ratio solvent to aqueous 0.1 M pH 5.8 phosphate buffer 3:1 v/v, c[**22**] = 0.025 M.

Although these results imply the role of molecular oxygen, we also explored further oxidants that would be able to "umpol" the nucleophilic phenol and provide the spiro-cyclohexadienone.[18] Treatment of **23a**/**b** with [bis(trifluoroacetoxy)iodo]benzene (PIFA) failed to yield **11a**/**b** and only cleaved the trimer to afford dracorhodin as main product. Under less acidic conditions using (diacetoxyiodo)benzene (PIDA), however, we could isolate dragonbloodin A **11a**/**b**, albeit in low yield (Scheme 3). The oxidative cyclization presumably proceeds via iodine(III) intermediate **25**, which undergoes intramolecular nucleophilic attack by the enol ether moiety followed by interception with water.

The absolute configuration of the dragonbloodins can be inferred from the (*S*)-configuration of their biosynthetic precursor, compound **1**. Our asymmetric synthesis of this compound is based on the asymmetric hydrogenation of flavones and chromones recently developed by Glorius *et al* (Scheme 4).[19] Selective TBS protection and methylation of the

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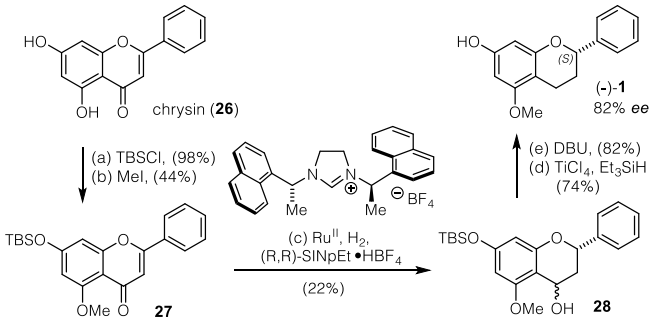
commercially available flavonoid chrysin (**26**) afforded the requisite substrate **27**. Hydrogenation with Ru(cod)(η^3-methylallyl)$_2$ and the NHC ligand (*R*,*R*)-SINpEt·HBF$_4$ as a catalyst afforded the flavan-4-ol **28**, albeit in low yield. Reductive removal of the benzylic hydroxyl group under ionic conditions and deprotection then afforded (2*S*)-(−)-**1** with an *ee* of 82%. Chrysin could also be used as convenient source for (±)-**1** (see Supporting Information).



Scheme 4. Asymmetric synthesis of (*S*)-5-Methoxyflavan-7-ol (**1**).

In summary, we achieved the first synthesis of the highly complex flavonoid trimers dragonbloodin A1 and A2 in racemic form and developed a formal asymmetric synthesis. A practical and scalable route to dracorhodin, nordracorhodin and the corresponding flavanol has also been developed. Our synthesis clarifies the biogenetic and stereochemical relationships between the more complex components of *Demonorops draco* "Dragon's Blood" and identifies dragonbloodin A2 (**11b**) as a *pseudo*-enantiomer of dragonbloodin A1 (**11a**). It also reveals how the "umpolung" of highly electron rich phenols can be achieved in the absence of oxidizing enzymes, i.e. by autoxidation. Finally, our work is another demonstration for the power of biomimetic reaction cascades, which can be highly efficient even when multiple intermolecular steps are involved.[20]

Acknowledgements

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Keywords: biomimetic synthesis • total synthesis • natural product • cascade reactions • autoxidation

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Layout 1:

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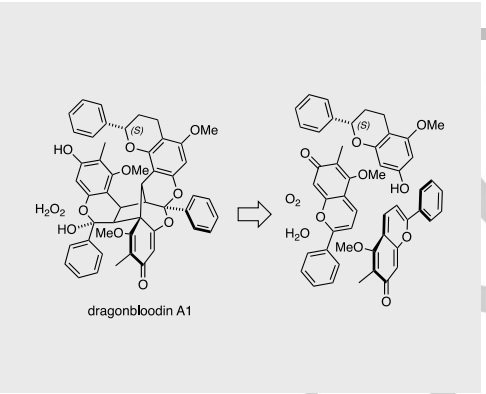
Dragonbloodin A1 and A2 are two flavonoid trimers isolated from the palm tree *Daemonorops draco*, one of the sources of “Dragon’s Blood”. We present an efficient synthesis that clarifies their relative configuration and suggest that the complex molecules form spontaneously from the red colorants of Dragon’s Blood in the presence of air.



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