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Accessing columbianetin-containing natural products via a domino on-water, in-water process

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ABSTRACT

A domino on-water, in-water process has been developed for the rapid and efficient synthesis of (±)-columbianetin. This highlights the operational simplicity of on-water chemistry. The domino process forms the key step in the synthesis of the columbianetin-containing natural products (±)-columbianetin acetate, (±)-zosimin, (±)-libanorin and (±)-angelmarin.

An increased awareness of environmental sustainability, step-economy and atom-economy has led to the development of many innovative synthetic processes. Of these, perhaps none offers more promise than on-water chemistry. Popularised by Sharpless and co-workers, 'on-water' catalysis is an operationally simple methodology that has been enthusiastically adopted in many areas,[1–7] but has only rarely been employed in total synthesis.[8,9] The term 'on-water catalysis' describes the rate enhancements observed when certain reactions are performed as aqueous emulsions. The advantages are often touted: water is cheap, readily available, non-flammable, has a high heat capacity and allows for simplified product isolation. We recently extended the utility of the process by engineering a domino in-water, on-water sequence in which the reaction of an aqueous soluble starting material gave an insoluble product that migrated into the oil droplets of the emulsion and subsequently participated in an on-water catalysed reaction (Fig. 1).[5] There is no inherent reason why this shuttling of molecules between the phases of the emulsion should be restricted to one direction, that is, in-water followed by on-water. We elected to explore the corresponding on-water, in-water domino process in the context of the synthesis of coumarin-containing natural products. Herein we describe a concise synthesis of osthenol, (±)-columbianetin,[10] (±)-zosimin,[11] (±)-libanorin[12] and (±)-angelmarin[13] using an on-water, in-water domino process.

Coumarin-containing natural products are widespread in nature. To date, more than 150 members have been isolated that contain a columbianetin (**1**) substructure (Scheme 1),[10] including molecules in which the columbianetin skeleton has been modified by oxidation, glycosylation and esterification.[14,15] Although the chemistry of columbianetin has a long history,[16] there has been a recent revival in synthetic approaches to this molecule due to the discovery of angelmarin (**6**), a columbianetin cinnamate that displays promising anti-cancer properties.[10,11,13,17–19] More than 40 years ago it was hypothesised that columbianetin was biosynthesised by prenylation of umbelliferone (**2**) followed by epoxidation and cyclisation (Scheme 1).[20] That sequence of reactions constitutes a straight-forward synthetic route to columbianetin. The enzymes responsible for the direct prenylation of **2** to give **3** have been characterised,[21] and whilst there is no evidence for its involvement in columbianetin biosynthesis, the aromatic Claisen

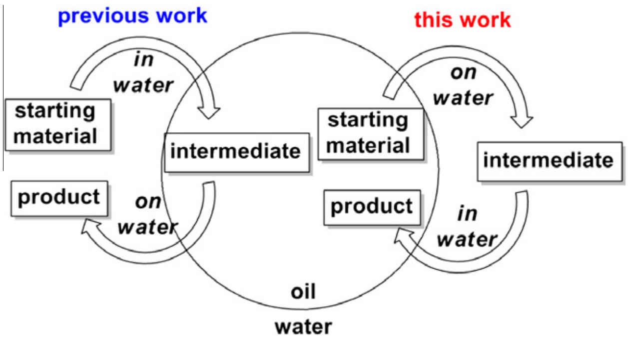

Figure 1. Domino processes with in-water and on-water components.

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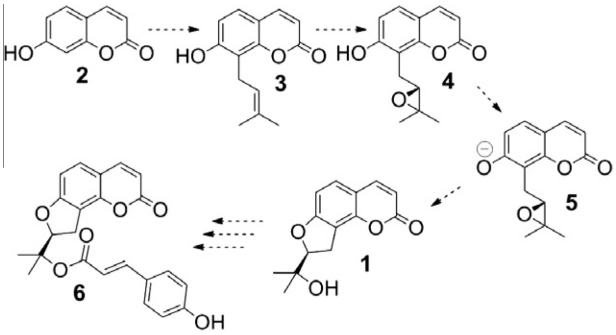


Scheme 1. Proposed biosynthesis of columbianetin.

Table 1
Conditions for the aromatic Claisen rearrangement

Entry	Solvent	Temp (°C)	Time (h)	Yield[a] (%)	Ratio **3**:**8**[b]
1	Neat	130	1.5	88[c]	5.28:1
2	Neat	130	1.5	87[d]	4.64:1
3	$H_2O + CH_2Cl_2$	45	72	30	n.d.
4	Neat	45	72	—	—
5	Toluene	45	72	—	—
6	H_2O	75	1	60	6.50:1
7	H_2O	75	2	91	5.07:1
8	Neat	75	2	—	—
9	Toluene	75	2	—	—
10	Sat. aq $NaHCO_3$	75	2.5	85	5.07:1

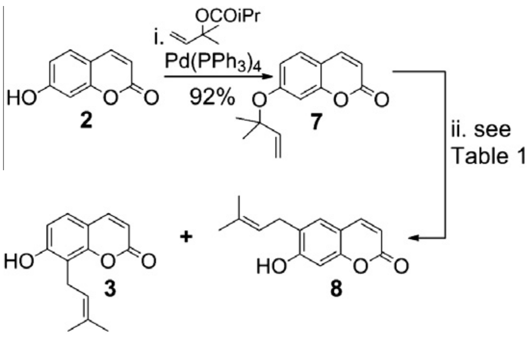
[a] Isolated yield after chromatography.
[b] Determined after isolation.
[c] Data from Ref. 23.
[d] Data from Ref. 11. n.d. = not determined.

rearrangement of **2** is known to give osthenol (**3**).[22] Sharpless reported a single example of an aromatic Claisen rearrangement that was subject to on-water catalysis.[1] We therefore anticipated that the transformation of **2** into **3** could be conducted on-water. Franke provided support for the biosynthetic proposal by showing that epoxy osthenol (**4**) could be cyclised to give the required five-membered heterocycle using a biphasic solvent system of dichloromethane and aqueous sodium bicarbonate.[23] We anticipated that the organic solvent in that reaction was superfluous, and that the phenolate **5** ought to have some water solubility, that is, the transformation of **4** into **1** could be conducted in-water. With a synthetic strategy that incorporated both on-water and in-water reactions, we pursued the development of a domino on-water, in-water process for the synthesis of (±)-columbianetin (**1**).

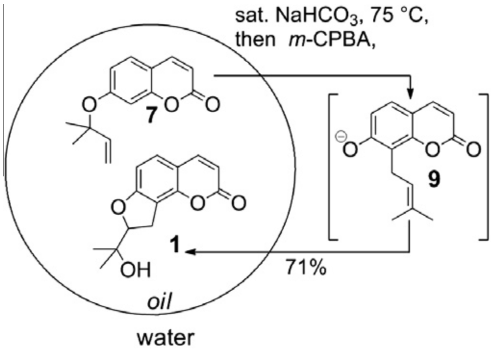
As shown in Scheme 2, umbelliferone (**2**) was converted into the prenyl ether **7** directly using a palladium-catalysed coupling in the manner described by Hamada.[11] This compound has previously been employed in thermal aromatic Claisen rearrangements at temperatures in excess of 130 °C (Table 1, entries 1 and 2). Our first priority was to ascertain that this substrate did indeed undergo an on-water accelerated Claisen rearrangement. Initial attempts to carry out the desired on-water rearrangement at ambient temperature were frustrated by an inability to generate an emulsion using the solid compound **7**. The formation of an emulsion is an absolute requirement for on-water catalysis and there is only a single report of solid compounds participating in an on-water catalysed reaction.[24] We therefore added a few drops of an organic solvent to generate a liquid oil phase. When the reaction was conducted at 45 °C the Claisen rearrangement proceeded to a small extent (entry 3). Whilst an extended reaction time rendered the process synthetically impractical, we were encouraged by the observation that no rearrangement occurred either neat, or in an organic solvent at the same temperature (entries 4 and 5). The prenyl ether **7** has a melting point of ca. 72 °C, so we next performed the reaction slightly in excess of that temperature. We were gratified to find that when compound **7** melted, an oil-in-water emulsion was readily generated and the on-water aromatic Claisen rearrangement progressed to 60% completion in just 1 h (entry 6). Extending the reaction time to 2 h gave the rearranged product in 91% yield and with the same regiochemical outcome as the thermal reaction (entry 7). To confirm that the rearrangement was not being thermally effected, but was indeed accelerated by the on-water effect, the reaction was attempted neat at 75 °C and in toluene at 75 °C for the same period of time (entries 8 and 9). In neither instance was any rearranged product detected.

Franke demonstrated that epoxide **4** could be opened under basic conditions to generate the desired dihydrobenzofuran ring rather than the dihydrobenzopyran ring (see Scheme 1).[23] In order for the proposed on-water, in-water domino process to be viable, the on-water step of the sequence would have to be effected 'on' saturated aqueous sodium bicarbonate. We have previously demonstrated acid catalysis 'on' sodium hydroxide solutions,[4] so we were confident that the transformation was feasible. Pleasingly, the aromatic Claisen rearrangement 'on' saturated aqueous sodium bicarbonate gave the rearranged product in high yield and with the same regioselectivity as the on-water reaction (Table 1, entry 10). This confirmed that the on-water step of the proposed domino process was viable.

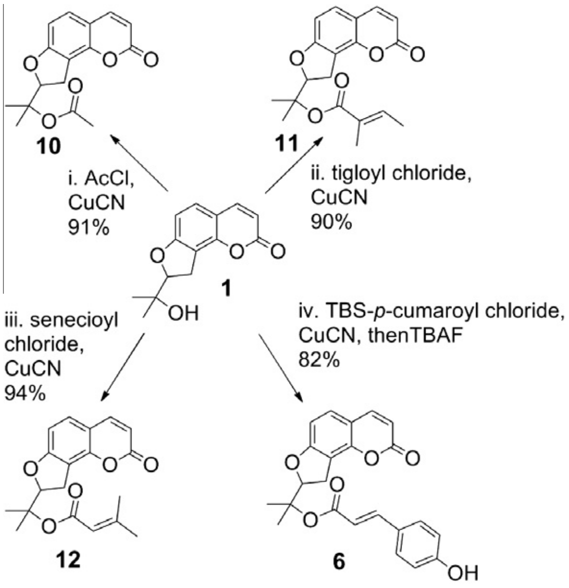
The 'on-water' emulsion containing the desired compound **3** was milky-white, whereas the 'on' saturated aqueous sodium bicarbonate reaction mixture containing compound **3** changed from milky-white to purple. We took this as evidence for the formation of the phenolate **9** (see Scheme 3). Given that *m*-CPBA is appreciably water soluble and assuming that the phenolate **9** is also water soluble, we felt confident that the in-water step of the domino process was also viable, and that the biphasic reaction system utilised by Franke was not required. Safety considerations



Scheme 2. On-water synthesis of osthenol (**3**).



Scheme 3. Domino on-water, in-water synthesis of (±)-columbianetin (**1**).



Scheme 4. Synthesis of columbianetin-containing natural products.

prevented us from having *m*-CPBA present in the on-water reaction mixture at temperatures above 50 °C. However, the domino on-water, in-water domino process was realised by conducting the 'on' saturated sodium bicarbonate catalysed aromatic Claisen rearrangement followed by the addition of *m*-CPBA (Scheme 3) when the mixture had cooled to 50 °C. This operationally simply procedure delivered (±)-columbianetin (**1**) in 71% yield from **7**, and in 65% overall yield from umbelliferone (**2**) in just two synthetic operations.

With a straightforward domino on-water, in-water route to (±)-columbianetin secured, we then generated several coumarin-containing natural products. As shown in Scheme 4, acylation with acetyl chloride gave (±)-columbianetin acetate (**10**) in high yield.[10,25] Acylation with tigloyl chloride gave the reported structure of (±)-zosimin (**11**) in excellent yield.[10,11] Similarly, reaction with senecioyl chloride gave (±)-libanorin (**12**) in high yield.[12] To the best of our knowledge, this is the first synthesis of this natural product. Finally, reaction with *tert*-butyldimethylsilyl-*p*-coumaroyl chloride followed by desilylation gave (±)-angelmarin (**6**) in high yield.[13]

In summary, we have used a domino on-water, in-water process as the key step in the synthesis of (±)-columbianetin (**1**) and several columbianetin-containing natural products. This work augments our previous work on the on-water, in-water domino process and shows that the concept of shuttling molecules between the phases of an emulsion is general. Additionally, this work provides an illustration of the advantages of using water in heterocyclic synthesis. Interfacial water functioned as a catalyst that allowed a significant reduction in the thermal requirements of the aromatic Claisen rearrangement, whilst having no effect on the regiochemical outcome. Although claims regarding the 'greenness' of on-water chemistry at temperatures above ambient may be dubious, the operational simplicity of these domino processes should see them adopted in other synthetic settings.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.11.150.

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