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Protecting group free syntheses of (±)-columbianetin and (±)-angelmarin

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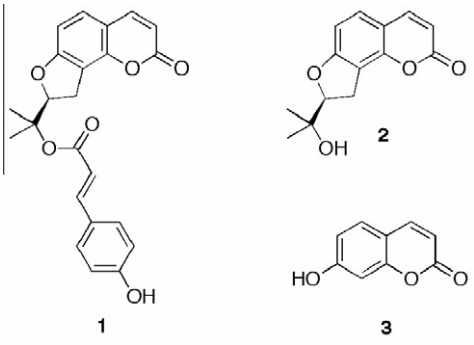
ABSTRACT

A five-step and protecting group free synthesis of (±)-columbianetin from cyclohexane-1,3-dione is reported. The former compound was converted into its *p*-hydroxycinnamate derivative, (±)-angelmarin, using Coster's esterification procedure. Efforts to modify the synthesis so as to prepare angelmarin and columbianetin in an enantioselective manner are described.

The coumarin-containing natural product (+)-angelmarin (**1**) was isolated in 2006 by Kadota and co-workers[1] from a CH_2Cl_2-soluble extract of *Angelica pubescens*, a plant used in Japanese Kampo medicine.[2] The compound was characterized by NMR techniques and shown to display completely selective cytotoxicity against PANC-1 cells at concentrations as low as 0.01 μg/mL.[1] Since PANC-1 cells are a pancreatic cancer cell line able to tolerate extreme conditions created by low nutrient and oxygen supplies, angelmarin represents a novel anti-cancer agent capable of eliminating the tolerance of cancer cells to nutrient starvation. Coumarin **1** can, therefore, be regarded as a lead compound for the development of a so-called anti-austerity cancer chemotherapeutic regime for the treatment of certain highly refractory forms of the disease.[3] Indeed, the compound shows particular potential for treating pancreatic cancer, victims of which have especially low five-year survival rates.[4]

Two total syntheses of angelmarin (**1**) have been reported so far, one by Coster[5] and the other by Hamada.[6] Each of these involves esterification of the related natural product columbianetin (**2**)[7] with *p*-hydroxycinnamic acid or an equivalent thereof. Compound **2** was, in turn, prepared from the commercially available coumarin umbelliferone (**3**) using a regioselective Claisen rearrangement/Shi epoxidation/5-*exo*-tet cyclization sequence.[5,6] This represents an adaptation of a protocol reported by Bohlmann and Franke in 1971[8] for the synthesis of the racemic modification of columbianetin.



Herein we report a quite distinct synthesis of (±)-columbianetin [(±)-**2**] that employs cyclohexane-1,3-dione (**4**) as starting material and a late-stage Au(I)-catalyzed intramolecular hydroarylation (IMHA)[9] reaction to form the six-membered heterocyclic ring of the target. Furthermore, no protecting groups are required during the course of the five-step synthesis, details of which are presented in Scheme 1. Thus, diketone **4** was efficiently *C*-alkylated with prenyl bromide (**5**) under conditions defined by Marazano et al.[10] and so affording the previously reported[10] β-hydroxycyclohexenone **6** (75%). Subjection of compound **6** to reaction with *m*-chloroperbenzoic acid (*m*-CPBA) in the presence of potassium carbonate gave, presumably via the intermediate epoxide, dihydrofuran (±)-**7** (95%), the structure of which was confirmed by single-crystal X-ray analysis.[11] In an initial attempt to aromatize the carbocyclic ring within the latter compound it was treated with manganese

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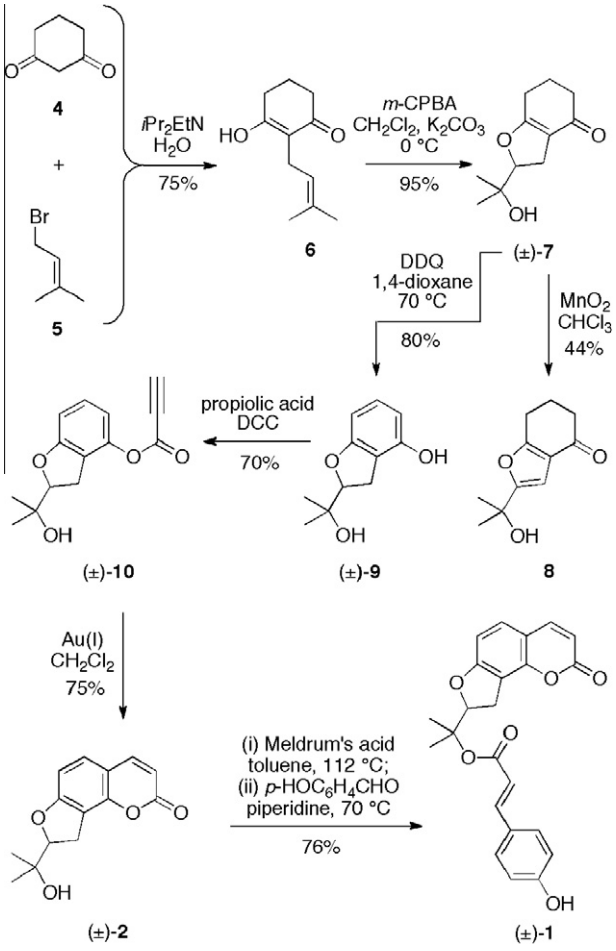


Scheme 1. Syntheses of (±)-columbianetin and (±)-angelmarin.

dioxide but this gave furan **8**[12] (44%) as the only isolable product. In contrast, reaction of compound (±)-**7** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in hot 1,4-dioxane effected the desired oxidation and thus afforded phenol (±)-**9**[13] in 80% yield. In anticipation of effecting an IMHA reaction[9] to generate the six-membered heterocyclic ring of target (±)-**2**, compound (±)-**9** was coupled with propiolic acid in the presence of dicyclohexylcarbodiimide (DCC) to afford ester (±)-**10** in 70% yield. Finally, exposure of compound (±)-**10** to Echavarren's Au(I) catalyst[14] in dichloromethane at room temperature resulted in the anticipated IMHA reaction[9,15] and formation of (±)-columbianetin [(±)-**2**] which was obtained as a crystalline solid in 75% yield.

All of the spectral data derived from coumarin (±)-**2** were in complete accord with the assigned structure and matched those reported previously[5,6,13] but final confirmation of this followed from a single-crystal X-ray analysis.[11] The ORTEP arising from this analysis is shown in Figure 1 and further details are presented in the Supplementary data.

While the acquisition of (±)-columbianetin constitutes a formal total synthesis of (±)-angelmarin,[5,6] in order to secure a sample of the latter for biological evaluation the procedure described by Coster[5] was employed to effect the desired conversion. Thus, treatment of compound (±)-**2** with Meldrum's acid followed by Knoevenagel condensation of the resulting malonate half-ester with *p*-hydroxybenzaldehyde gave a crystalline sample of (±)-angelmarin [(±)-**1**] in 76% yield. All the NMR, IR, and mass spectral data obtained on this material matched those reported[1,5,6] for both the naturally- and synthetically-derived samples of (+)-angelmarin.

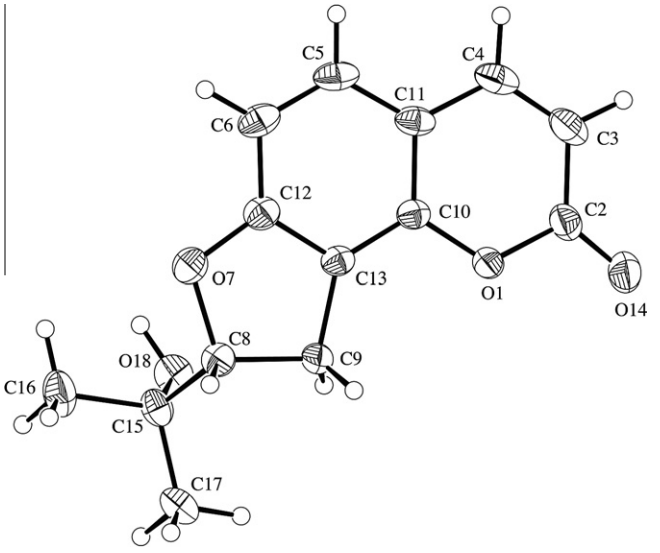
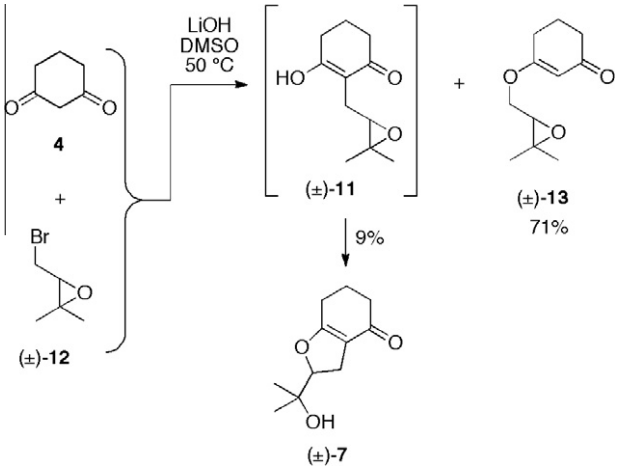
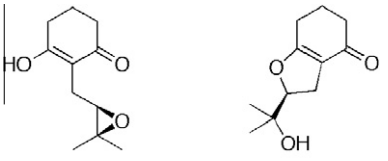


Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound (±)-**2** with labeling of non-hydrogen atoms. Anisotropic displacement ellipsoids display 30% probability levels. Hydrogen atoms are drawn as circles with small radii.



Scheme 2. Attempted enantioselective synthesis of (+)-angelmarin.

Various attempts have been made to adapt the chemistry shown in Scheme 1 to the enantioselective preparation of (+)-angelmarin. For example, reaction of compound **6** using the Shi reagent[16] was examined on the basis that epoxide **11** might be formed preferentially and that this would engage in a stereoselective 5-*exo*-tet cyclization process to form the dihydrofuran (+)-**7**. In the event, when substrate **6** was treated under the relevant conditions compound (+)-**7** was formed in just 13% ee as determined by chiral HPLC analysis.[17]



11 (+)-**7**

In another attempt to prepare (+)-angelmarin, the alkylation of cyclohexane-1,3-dione (**4**) with the epoxy bromide (±)-**12** was explored (Scheme 2). This study was carried out on the basis that the

enantiomerically pure iodo-analog of compound **12** would be available[18] as the replacement electrophile if needed. In the event, when the relevant experiment was carried out using equimolar quantities of substrates **4** and (±)-**12** a ca. 1:7 mixture of the chromatographically separable *C*- and *O*-alkylation products (±)-**7** (9%) and (±)-**13** (71%), respectively, was obtained. The structure of the latter product was confirmed by single-crystal X-ray analysis.[11] Presumably, the former product arises from intermediate (±)-**11**, the same species involved in the conversion **6** → (±)-**7** shown in Scheme 1. Various efforts to improve the *C*- to *O*-alkylation ratio associated with the reaction **4** + (±)-**12** → (±)-**7** + (±)-**13** proved fruitless.

Other methods for exploiting the synthetic sequence detailed in Scheme 1 so as to obtain (+)-angelmarin [(+)-**1**] in enantiomerically enriched form are now under investigation. Results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data ([experimental procedures and product characterization for compounds (±)-**7**, **8**, (±)-**9**, (±)-**10**, (±)-**2**, (±)-**1,** and (±)-**13** as well as the X-ray crystallographic data for compounds (±)-**2**, (±)-**7,** and (±)-**13**]) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.10.036.

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