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CONCERNING THE ABSOLUTE STEREOCHEMISTRY OF HONGCONIN

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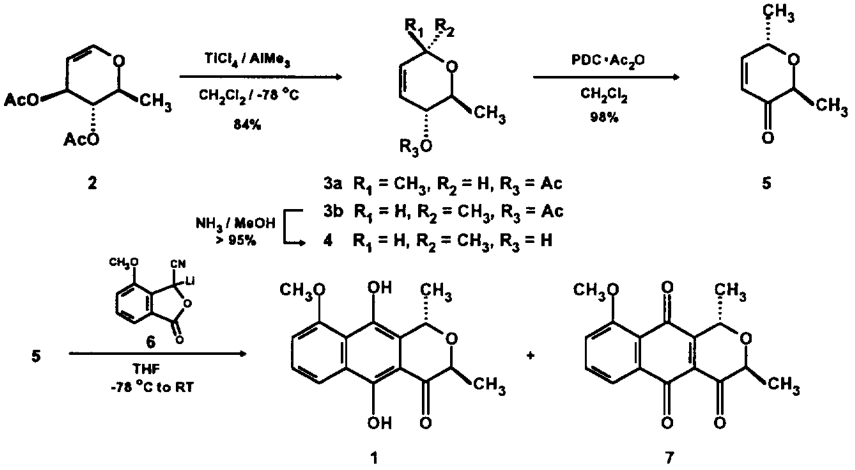
Abstract: The heretofore unknown absolute stereochemistry of hongconin has been established to be the 1*R*, 3*R* isomer via unambiguous chemical synthesis of its enantiomer. The synthetic scheme allows access to appreciable quantities of enantiopure (-)- or (+)-hongconin, analogues, and related diastereomers.

The rhizome of the South Chinese herbal plant *Eleutherine americana* Merr. et Heyne (Iridaceae), known as "Hong-Cong" in Chinese, has long been used as a folk remedy for coronary disorders.[1] Its therapeutic effects have been specifically attributed to four naphthalene derivatives isolated by Chen and co-workers,[2] namely previously known eleutherol, eleutherin, and isoeleutherin,[3] as well as a novel component, hongconin. A formulation of these four purified compounds was demonstrated to increase coronary blood flow in isolated guinea pig heart and to exhibit human anti-anginal efficacy roughly equal to that of Persantine (dipyridamol).[2a,4] To the best of our knowledge, the individual abilities of the four agents to confer cardioprotection have yet to be discerned. Studies necessary to clarify this phenomenon by perhaps pinpointing one superior component of the four, in addition to studies needed to investigate other medicinal applications of these compounds (warranted by their structural similarity to the kalafungin and nanaomycin antibiotics), will require amounts of material in excess of their low natural occurrence, making them synthetic targets of current interest.

In particular, our attention has focused on hongconin as an entry-point to studying the biological activity of these compounds. Although the chemical structure and relative stereochemistry of hongconin are known (based on chemical, spectral, and X-ray analyses by Chen and co-workers,[2] and confirmed in a racemic synthesis by Kraus and co-workers[5]), its absolute configuration has, until now, remained undetermined. However, since enantiopurity is increasingly regarded as a virtual necessity for chiral drugs, such stereochemical information is a clear prerequisite for a contemporary investigation into the therapeutic potential of hongconin and analogues. We report here a concise, enantioselective synthesis of (+)-hongconin (**1**) from 3,4-di-*O*-acetyl-6-deoxy-L-glucal (**2**), allowing the absolute configuration of the natural product to be assigned for the first time.

Lewis acid-catalyzed C-1 alkylation[6] of **2** led to a 5:4 mixture of epimers **3a** and **3b**, respectively, from which **3b** was easily isolated and distinguished from **3a** by NOE studies.[7] Routine conversions promptly converted **3b** to novel enone **5**. Reactions between 3-cyanophthalides and simple Michael acceptors, as developed by Swenton and co-workers, afford regiospecific 1,4-dihydroxynaphthalene derivatives.[8] This strategy proved to be effective in constructing hongconin's isochromanquinol system from **5**. Thus, addition of **5** to **6**[8a] in THF at -78°C, followed by warming to room temperature, afforded **1** directly in 56% yield, along with quinone **7** (26%). All physical data of synthetic **1** were identical to that of the natural product, except for the

Scheme



sign of optical rotation: $[\alpha]_D^{20}$ +25.8° (*c* 1.94, CHCl$_3$) {lit., natural product:[2b] $[\alpha]_D^{20}$ - 26° (*c* 1.94, CHCl$_3$)}. Naturally occurring (-)-hongconin is thus the enantiomer of structure **1**, and possesses the 1*R*, 3*R* configuration.

In summary, we have established the absolute stereochemistry of naturally occurring (-)-hongconin by unambiguous chemical synthesis of its enantiomer, and in so doing have developed a concise, enantioselective synthetic scheme whereby appreciable quantities of optically pure natural product and analogues may be prepared (for example, beginning with the D-isomer of **2**). These explorations are underway and will be reported elsewhere along with complete experimental details of the work described herein.

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