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Biomimetic approach to the stereoselective synthesis of acetogenins*

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Abstract: Acetogenins isolated from the *Annonaceae* family of tropical trees have drawn considerable attention owing to their broad spectrum of biological activities. They are structurally characterized by the presence of one to three tetrahydrofuran rings in the center of a long (partly hydroxylated) hydrocarbon chain that ends in a (functionalized) butenolide moiety. Here we describe some of our results toward the first asymmetric total synthesis of *cis*-gigantrionenin, a principal acetogenin. In this approach, an enzyme-catalyzed epoxide hydrolysis and an enzyme-triggered double cyclization are crucial and give stereoselective access to essential chiral building blocks.

INTRODUCTION

The custard-apple family (*Annonaceae*) is a large family of tropical plants including over 130 genera and over 2000 species have been described [1]. However, only relatively little is known about their biochemistry. In the early 1980s, it was discovered that these plants contain a class of natural products with a wide variety of biological activities. Since then, phytochemical and pharmacological studies on *Annonaceae* species intensified considerably.

In 1982, Cole and Jolad were the first to isolate such an acetogenin from the dried roots of *Uvaria accuminata* [2]. The compound, named uvaricin (Chart 1), showed potent in vivo antileukemic activity, which caused wide interest in these natural products. Now, more than 350 different acetogenins from 37 *Annonaceae* species have been isolated. Their interesting biological activities have been appreciated for a long time by Indian tribes from the South American rain forest, who still use the extracts from these plants as pesticidal and antiparasitic agents. Many other activities, like anthelmic, antimalarial, antimicrobial, and antiprotozoal, have been reported [1]. Most important seems the antitumor and cytotoxic activity. Acetogenins specifically target the mitochondrial nicotinamide adenine dinucleotide (NADH)-ubiquinone oxidoreductase, which is a membrane-bound protein essential for electron transport. Furthermore, they inhibit the ubiquinone-linked NADH oxidase located in the plasma membranes of tumor cells [1a]. Both inhibitive activities lead to adenosine 5′-triphosphate (ATP) deprivation, and the high energy demanding tumor cells suffer aptosis (programmed cell-death). More recently, it was demonstrated that acetogenins can also overcome multidrug-resistant cancers [1a].

In general, acetogenins consist of a C35 or C37 carbon chain, which is presumably derived from C32 or C34 fatty acids combined with a 2-propanol unit [1a]. They are further characterized by a cen-

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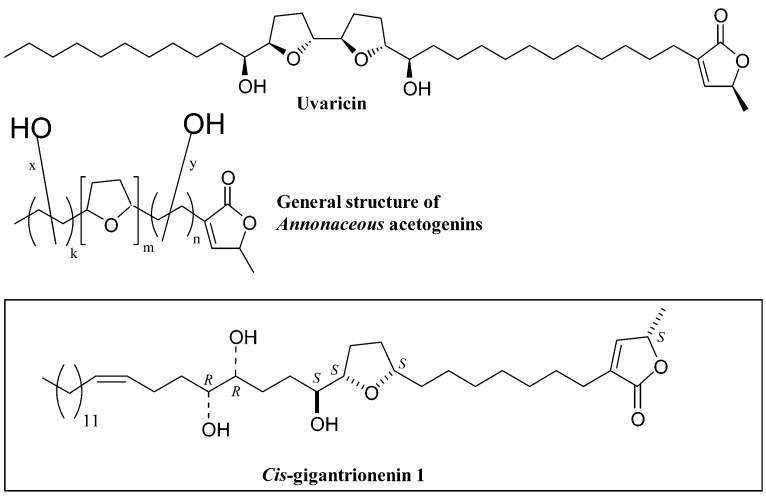


Chart 1 *Annonaceous* acetogenins.

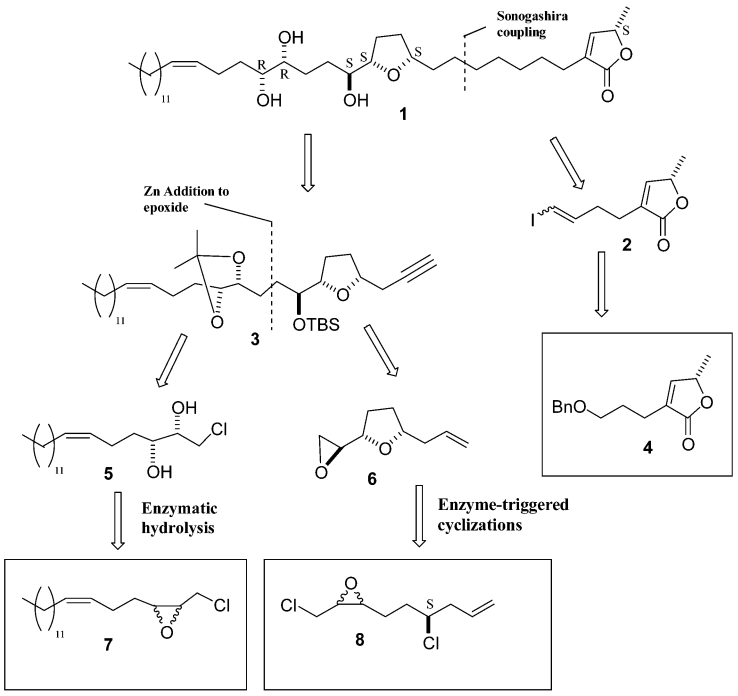
tral poly-oxygenated core comprising one, two, or three tetrahydrofuran (THF) rings along with a number of flanking hydroxyl groups. At one end of the carbon chain a mostly methyl-substituted α,β-unsaturated γ-lactone ring is situated (Chart 1). The largest site of variation in acetogenins is the central core, where the rings can be *cis*- or *trans*-substituted, adjacent or nonadjacent to each other, but also mono-THF acetogenins are known. Further acetogenins have been described with one or two flanking hydroxyl groups per THF ring, and recently, tetrahydropyran-containing acetogenins have also been reported [1].

From structure–activity relationship (SAR) studies it became clear that bis-adjacent THF-containing acetogenins are pharmaceutically most potent followed by mono-THF acetogenins. The lactone moiety seems crucial for activity. Acetogenins with a C35 carbon chain are more active then those with a C37 chain and a 13-carbon spacer between the γ-lactone ring and the first THF moiety is most beneficial. Not surprisingly, the stereochemistry at the THF rings appears important, although conflicting data have been reported [1a].

Due to the interesting physiological profiles, the limited natural abundance, and challenging structural features, acetogenins have been targeted by numerous synthetic groups. This resulted in several elegant asymmetric total syntheses of acetogenins [3]. We have focused our synthetic efforts toward *cis*-gigantrionenin **1** (Chart 1) using a chemoenzymatic approach. *Cis*-gigantrionenin (**1**) was isolated by Fang et al. in 1992 from the leaves of *Goniothalamus giganteous*, a tropical fruit tree from the West Indies [4]. The structure was completely elucidated by Zeng et al. in 1996 [5]. However, the determination of the absolute configuration of **1**, and of acetogenins in general, is cumbersome, because X-ray structure analysis is often difficult due to the amorphous nature of these compounds [1a]. Ultimate structural proof by total asymmetric synthesis is desired.

RESULTS AND DISCUSSION

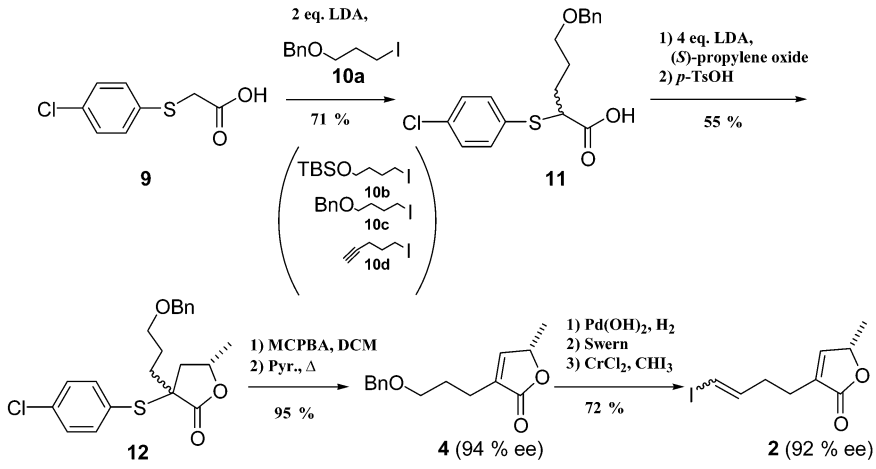
Based on well-established chemistry, which can be found in literature precedents in this area [3], we devised a highly convergent synthetic route toward **1** (Scheme 1). The final C–C bond in **1** could be formed using a Sonogashira coupling, which reduces the synthetic problem to the preparation of the vinylic iodide **2** and the THF fragment **3**. Synthesis of **2** from chiral building block **4** was planned via a hydrogenolysis, oxidation, one-carbon Takai homologation reaction sequence. Preparation of **4** should be straightforward because similar structures are reported in the literature [6]. For the synthesis of **3**, which contains five stereocenters, we envisaged a Zn-mediated addition of a (protected) dihydroxy



Scheme 1 Retrosynthetic analysis.

chloride **5** to an epoxy-THF derivative **6**. Similar Zn-mediated coupling reactions were reported to proceed under mild conditions [7]. This strategy requires synthesis of chiral building blocks **5** and **6**, with two and three stereocenters, respectively. Both building blocks should be accessible via enzyme-catalyzed transformations. The dihydroxy chloride **5** can be formed via stereoselective epoxide hydrolase (EH) catalyzed hydrolysis of the chloro epoxide **7** [8a]. The epoxy-THF building block **6** should result from an EH-triggered hydrolysis-double cyclization tandem reaction of dichloro epoxide **8** [8b,c]. Arguably, the latter approach is considered a biomimetic construction of a THF moiety [9].

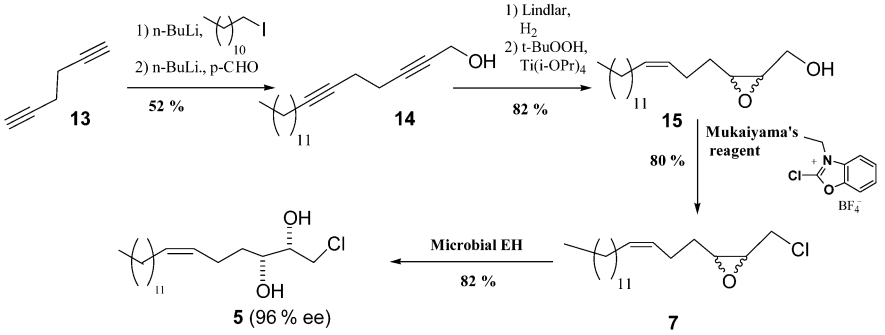
Synthesis of the γ-lactone **4** was achieved by following the procedure described by Iwai et al. [6], which was modified to improve the yields (Scheme 2). Exactly 2 equiv of lithium diisopropylamide



Scheme 2 Synthesis of vinylic iodide **2**.

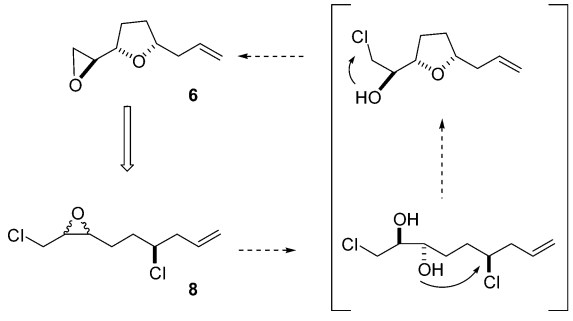
(LDA) were used to generate the dianion of sulfanyl acetic acid **9**, which was immediately alkylated using the protected iodide **10a** to afford exclusively the *C*-alkylated **11** in 71 % yield. Also, other readily available iodides (**10b–d**) can be used as alkylating agent, which makes this method more flexible than the literature procedure. Further alkylation of **11**, using (*S*)-propylene oxide and 4 equiv of LDA, followed by acidic work-up (pH < 3) gave the desired substituted lactone **12** in fair yield. Sulfoxidation and subsequent thermal elimination provided the (*S*)-α,β-unsaturated γ-lactone **4**, in 37 % overall yield and 94 % ee from **9**. Selective transformation of **4** into the desired vinylic iodide **2**, required for the final Sonogashira coupling, went smoothly following a recently described reaction sequence that makes use of a Takai homologation [3].

Synthesis of chiral building block **7** (Scheme 3) is straightforward and starts with 1,5-hexanediyne **13**. Subsequent alkylation and hydroxy methylation of **13** with 1-undecanyl iodide and *p*-formaldehyde, respectively, results in the propargylic alcohol **14**, which was isolated in 52 % yield. Reduction of both triple bonds in **14** using Lindlar's catalyst followed by regioselective epoxidation gave the hydroxy-epoxide **15** in good yield. Chlorination to afford **7** (34 % overall from **13**) was achieved under mild conditions using Mukaiyama's reagent [10]. Treatment of **7** with microbial EH [11] afforded the 2*R*,3*R*-diol **5** in 96 % ee and 82 % yield. The absolute configuration was derived by using the NMR method of Latypov et al. [12], in which changes of the δ's in the ^{1}H NMR spectra of the corresponding *R*-methoxyphenylacetate recorded at two different temperatures reveal the absolute stereochemistry.



Scheme 3 Synthesis of dihydroxy chloride **5**.

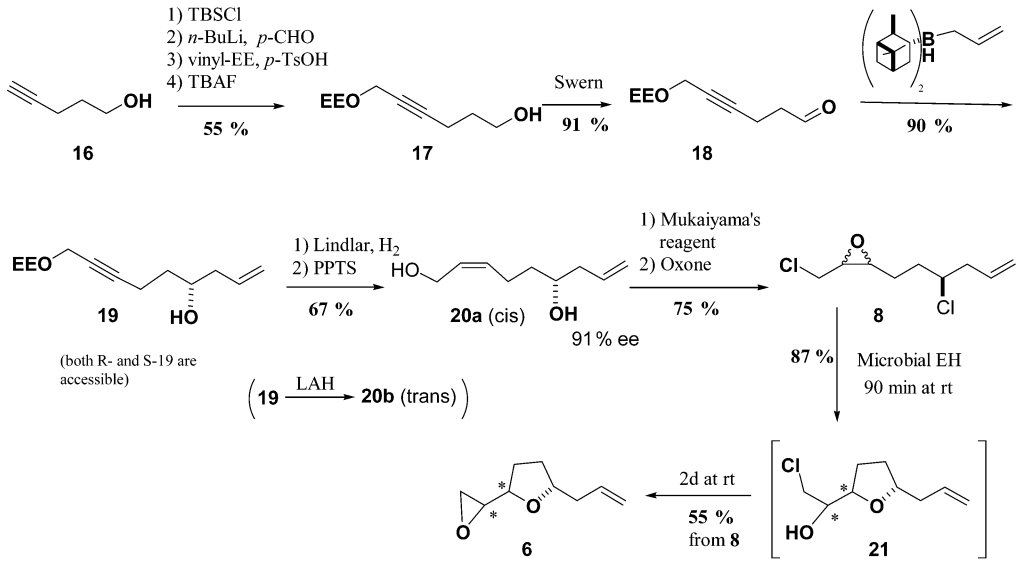
EH-catalyzed hydrolysis of internal 1-chloro *cis*-epoxides does not end at the diol stage, but is followed by cyclization [8b,c]. When only one carbon connects the epoxide moiety with the chloride functionality, the intermediate diol is easily isolated (cf. Scheme 3). Only prolonged reaction times result in hydroxy epoxides. On the other hand, with a two-carbon spacer between the epoxide and the chloride functions, an EH-triggered hydrolysis–cyclization tandem reaction is very fast and a THF



Scheme 4 EH-catalyzed hydrolysis followed by a double cyclization.

derivative is formed. Both enzymatic reactions proceed in an enantioconvergent fashion that results in only one stereoisomer, which can be obtained in good yield and ee [8b]. With these observations in mind, we envisaged formation of the chiral building block **6** through an EH-catalyzed hydrolysis of dichloro epoxide **8**, which is followed by an in situ double cyclization reaction (Scheme 4).

Synthesis of **6** commenced with pentynol **16**, which was transformed into the mono-protected alcohol **17** via a protection (*tert*-butyldimethylsilyl chloride, TBSCl), hydroxy methylation (*p*-CHO), protection (vinyl ethylether), and deprotection (tetrabutylammonium fluoride, TBAF) sequence in 55 % yield (Scheme 5). After Swern oxidation (91 %), the C(4)-stereocenter was introduced using an in situ generated optically pure allyl dicampheylborane reagent [13]. Both the *R*- and the *S*-enantiomers of **19** are accessible in this way. After reduction of the triple bond using Lindlar's catalyst and deprotection of the primary hydroxyl function, the *cis*-diol **20a** was obtained in 91 % ee and 67 % yield from **19**. A similar route, but now using $LiALH_4$ in refluxing THF instead of Lindlar's catalyst to reduce the triple bond in **19**, selectively afforded the *trans*-diol **20b**. Selective dichlorination of **20a** again using Mukaiyama's reagent resulted in complete inversion at C(4), and the dichloro epoxide **8** could be obtained in 22 % overall yield and >98 % de starting from **16**. Treatment of **8** with EH afforded the THF-chloride **21** in 87 % yield [14]. However, upon leaving the reaction mixture for two days at room temperature, it was possible to isolate a single isomer of the desired epoxy-THF compound **6** in 55 % yield. The structures of both **21** and **6** were confirmed by extensive (2D) NMR and mass spectrometry analyses.



Scheme 5 Synthesis of chiral building block **6**.

In conclusion, we have demonstrated that EH-catalyzed hydrolyses and EH-triggered tandem cyclization reactions can be useful synthetic tools for the construction of chiral building blocks **5** and **6**. The synthetic routes need to be further optimized, and the absolute stereochemistry of the enzymatic reactions have to be examined more closely. Future efforts will be directed toward the completion of the first asymmetric total synthesis of *cis*-gigantrionenin **1**.

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11. In general, hydrolysis of 1-chloro-2,3-oxiranes proceeds most effectively by using lyophilized cells of *Nocardia* sp. in 50 mM TRIS-buffer at pH = 8. (See also [8a,8b].)
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