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A catalytic approach to the MH-031 lactone: application to the synthesis of geralcin analogs

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ABSTRACT

A concise, 5-step synthesis of the hepatoprotective lactone MH-031 was achieved. Our approach utilizes several catalytic processes, namely, a Rauhut–Currier reaction, a chemoselective Fisher esterification, and a ring closing metathesis. Further elaboration of this lactone yielded the hydrazide natural product geralcin A and dihydrogeralcin B, a saturated analog of geralcin B. Biological evaluation of the latter indicated that the presence of the enehydrazide moiety in geralcin B is critical for anticancer activity.

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Hydrazine derivatives have ubiquitous applications, varying from polymers and dyestuff to pharmaceuticals.[1] Valuable hydrazine therapeutics include antidepressants such as the MAO inhibitors iproniazid and isocarboxazid, and the antituberculosis agent isoniazid.[2] In contrast, natural products containing a hydrazine-derived motif are rarely found.[3] Recently, the study of *Streptomyces* sp. LMA-545 yielded the hydrazine derivatives geralcins A–E (Fig. 1).[4,5] Of these, geralcin B, containing an enehydrazide motif, showed activity against MDA231 breast cancer cell line (IC_{50} = 5 μM) and geralcin C, containing both hydrazide and azoxy moieties showed activity against KB and HCT116 cancer cell lines (IC_{50} = 0.8 μM).

The interesting biological properties along with the unusual structural motifs make the geralcin family of natural products attractive targets for total synthesis.

Using a bio-inspired approach, Ouazzani reported the first total synthesis of geralcin A, featuring the coupling of lactone MH-031 (**1**) with a protected hydrazine derivative.[6] Herein, we wish to report our work on a new synthesis of MH-031, the plausible biogenetic precursor of the geralcins, using catalytic transformations, and its use in the total synthesis of geralcin A and dihydrogeralcin B.

Lactone MH-031 (**1**) was first isolated from a strain of *Streptomyces rishiriensis* by Itoh et al.,[7] and was shown to possess hepatoprotective activity. MH-031 was also isolated from *Streptomyces* LMA-545, the same culture producing the geralcins.[4] For this reason, lactone **1** has been proposed as the plausible biogenetic precursor of both geralcin A and B. Martin and co-workers[8] prepared the benzyl and methyl derivatives of **1**, as an inseparable mixture of *endo* and *exo* olefins, using an ethylene oxide epoxide opening reaction. More recently, during the first total synthesis of geralcin A, Ouazzani accomplished the synthesis of **1** in six steps and 33% yield.[6]

We became interested in lactone MH-031 because of its potential use in the total syntheses of the geralcins, and aimed to develop a different approach to **1**, that would be practical and compare favorably with the previous synthesis.

Catalytic methods are preferred over stoichiometric alternatives because of the potential to reduce the amount of chemical waste and increase step, atom, and redox economies. Herein, we wish

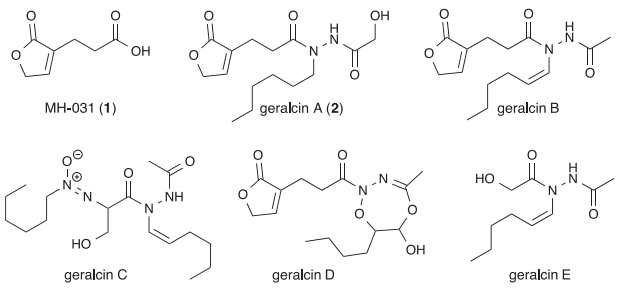

Figure 1. MH-031 and the geralcin natural products.

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to report a synthetic approach to MH-031 (**1**) relying on a catalytic Rauhut–Currier reaction, a chemoselective Fisher esterification, and a ring closing metathesis reaction.

Our synthetic approach commenced with a Rauhut–Currier reaction[9] of methyl acrylate to give diester **3** (Scheme 1). This nucleophile-catalyzed transformation has been reported in the literature for the synthesis of polymer products and building blocks. Of note, Verkade has reported yields of 85% for this reaction, using a proazaphosphatrane as catalyst,[10] and Yi has achieved yields of 91% using a ruthenium complex.[11] We chose to use the conditions reported by Coward using *n*-Bu_3P as catalyst[12] because of its commercial availability and the practical experimental setup and purification. Using 10 mol % of tributyl phosphine as the nucleophilic catalyst, we routinely obtain compound **3** in 65% yield in gram scale after distillation.

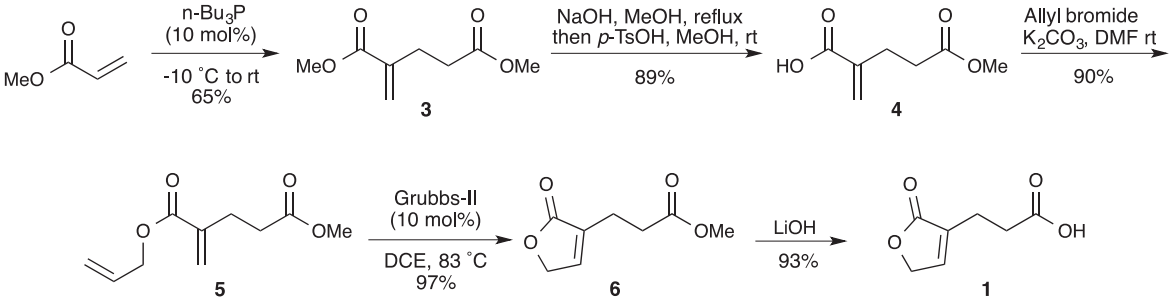
Hydrolysis of diester **3** under standard conditions afforded the corresponding diacid,[12] which was then subjected to a chemoselective Fisher esterification using *p*-TsOH as catalyst to produce mono-ester **4** in 89% yield. The basis for the observed selectivity might involve mesomeric resonance contribution in the case of the conjugated carboxylic acid.[13] The structure of mono-ester **4** was tentatively assigned by spectroscopic methods, and later confirmed by conversion to MH-031 as described below. Allylation of **4** under standard conditions gave diene **5** in 89% yield.

With diene **5** in hand, the formation of the required butenolide moiety by ring closing metathesis was examined. Although many examples of the use of olefin metathesis for the construction of butenolides are known, substrates bearing a 1,1-disusbstituted olefin conjugated to a carbonyl are less common.[14] Based on a survey of the literature, we chose to work with the Grubbs 2nd generation precatalyst.

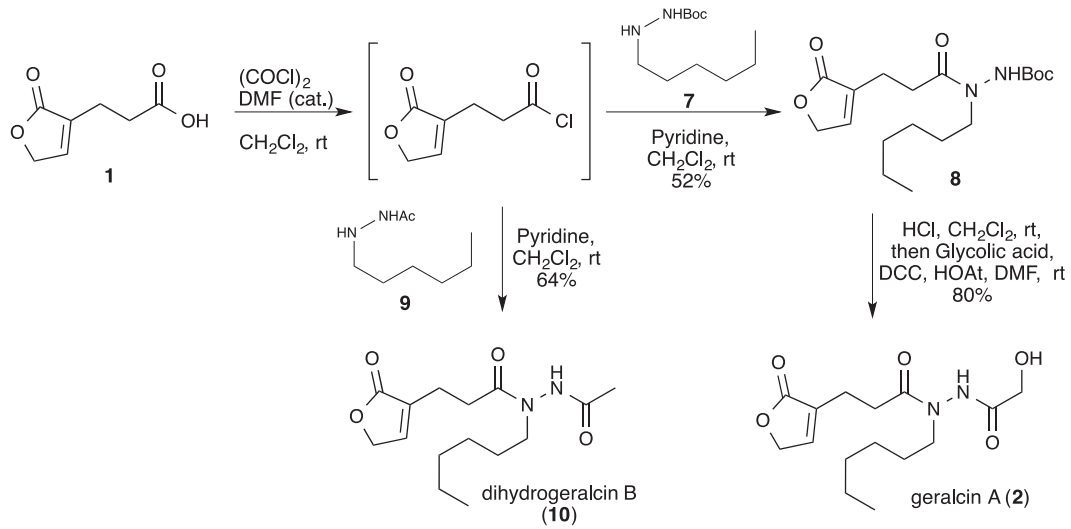
Initial attempts using 5–10 mol % of the 2nd generation Grubbs precatalyst in dichloromethane at 0.01 M substrate concentration met limited success, affording the desired lactone **6** in 40–50% yield, along with variable amounts of recovered starting material. Increasing the reaction temperature by changing the solvent to dichloroethane slightly increased the chemical yield to 55%. Increasing the temperature by performing the reaction in refluxing toluene did not provide any improvement in the isolated yield. For the experiments conducted in dichloroethane, unreacted starting material was accompanied by homodimerization at the allyl olefin as the major side-product. Both recovered starting material and homodimer could be re-subjected to the reaction conditions, slightly increasing conversion to about 60% after one cycle. Fortunately, the formation of the dimer byproduct was completely eliminated by decreasing the substrate concentration to 0.005 M and using 10 mol % of the Grubbs 2nd generation precatalyst, affording lactone **6** in an excellent 97% isolated yield.

Comparison of the spectroscopic data for **6** with literature values[6,8] showed an excellent match, confirming the anticipated chemoselectivity of our Fisher esterification. Hydrolysis was carried out as described by Ouazzani[6] to afford MH-031 (**1**) in good yield. Our approach to lactone **1** proceeds in five steps and 47% overall yield.

Following Ouazzani's work,[6] treatment of **1** with oxalyl chloride led to the formation of the corresponding acid chloride (Scheme 2), which was then reacted with hexyl carbazate **7** to give hydrazide **8**. Cleavage of the Boc protecting group and acylation with glycolic acid afforded geralcin A as described previously.[6] Coupling of the acid chloride derived from **1** with acyl hydrazine derivative **9**[15] was also carried out to give dihydrogeralcin B (**10**), an analog of geralcin B containing a saturated side chain.



Scheme 1. Synthesis of MH-031.



Scheme 2. Synthesis of geralcin A and dihydrogeralcin B.

Ouazzani has previously shown that geralcin A is inactive against HCT116, MCF7, HT29 and MDA231 cancer cell lines, whereas geralcin B shows inhibition of MDA231 breast cancer (IC_{50} = 5 μM) and promoted 42% growth inhibition on MCF7 cells at 10^{-5} M concentration (no IC_{50} was reported for this cell line).[4] For this reason, we focused on the biological evaluation of dihydrogeralcin B (**10**), in order to gain insight into the role of the unsaturation on the side chain. Cytotoxicity assays were performed using a standard tetrazolium dye-based colorimetric test (MTT, details are provided in Supporting information). Dihydrogeralcin B (**10**) was tested against HeLa, U87 and MCF7 cell lines as models for cervical, brain, and breast cancer, respectively, resulting in no significant activity (IC_{50} - $\geqslant$ 100 μM) in all three cell lines tested. As the only structural difference between geralcin B and analog **10** is the absence of the alkene on the side chain, this result indicates that the enehydrazide moiety present in geralcin B is likely essential for anticancer activity.

In summary, we have presented here a catalytic approach for the synthesis of the lactone MH-031 (**1**) using a Rauhut–Currier reaction, a chemoselective Fisher esterification and ring closing metathesis as key steps. The synthesis of **1** proceeds in five steps and 47% overall yield, which compares favorably with previous syntheses. Lactone **1** was further elaborated to geralcin A and dihydrogeralcin B (**10**). Biological studies on **10** suggest that the enehydrazide moiety present in geralcin B is likely critical for activity. Our synthetic approach should prove applicable to the synthesis of other hydrazides containing the MH-031 fragment. These investigations are currently underway in our laboratory, and the results will be reported in due course.

Acknowledgments

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Supplementary data

Supplementary data (experimental details, characterization data and copies of ^{1}H and ^{13}C NMR spectra for new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.09.088.

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