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MODEL STUDIES OF (+)-BERGENIN: A CONVENIENT FORMATION OF ARYL δ-LACTONES

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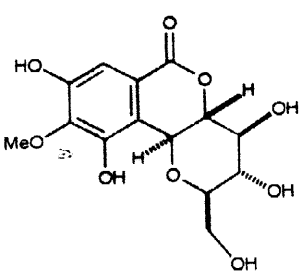
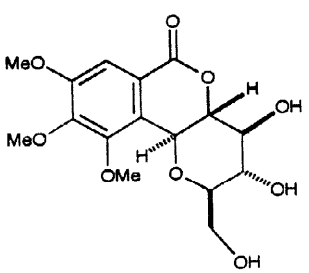
Summary. *The reaction of o-carboxyarylpropargyl bromides with aldehydes mediated by indium in aqueous medium conveniently generated aryl δ-lactones. The product formation was affected by the nature of the co-solvent.* © 1998 Elsevier Science Ltd. All rights reserved.

Bergenin (**1**) was first isolated from the root of *Saxifraga (Bergentia) crassifolia* L. and from *rhizome* of *S. sibirica L. Saxifragaceae.*[1] Subsequently, the compound was uncovered from a variety of sources and was reported to exhibit various biological activities.[2] The structure of **1** involves an aryl β-*C*-glucoside and an aryl δ-lactone ring[3] which was unequivocally confirmed by Schmidt and co-workers through X-ray analysis of its 3,4,8,10,11-penta-acetate derivative.[4] A second compound, 8,10-di-O-methyl bergenin (**2**), that was isolated along with bergenin has been synthesized by Schmidt and Frick through the use of a Lewis acid catalyzed carbon-carbon bond forming process.[5] The recent developments on Barbier-Grignard type carbon-carbon bond formations in aqueous medium offers opportunities in the syntheses of various heavily oxygenated biologically important agents.[6] Our continued interests in metal-mediated carbon-carbon bond formation in aqueous media[7] brought to our attention bergenin and other important biologically related compounds. Recently, we reported the synthesis of (+)-goniofufurone through a highly regio- and diastereoselective indium[8,9] mediated-allenylation of carbonyl compounds in aqueous medium.[10] Herein we report the formation of aryl δ-lactones, a key step toward the synthesis of bergenin (**1**) and its derivatives, by using the indium methods.



Bergenin

1



8,10-di-O-Methyl bergenin

2

The retrosynthetic analysis for bergenin is illustrated in Scheme 1. The styryl C-glycoside structure can be accessible from an aryl ketone **3**, which can be generated from the allene derivative **4** through standard ozonolysis. The allene, in turn, can be obtained through the reaction of the propargyl bromide, which has been readily prepared by standard reactions from trialkoxylbenzoate **6**, with arabinose (**7**) mediated by indium, possibly, in one step. In addition, we would be required to form the C-O bond of the newly

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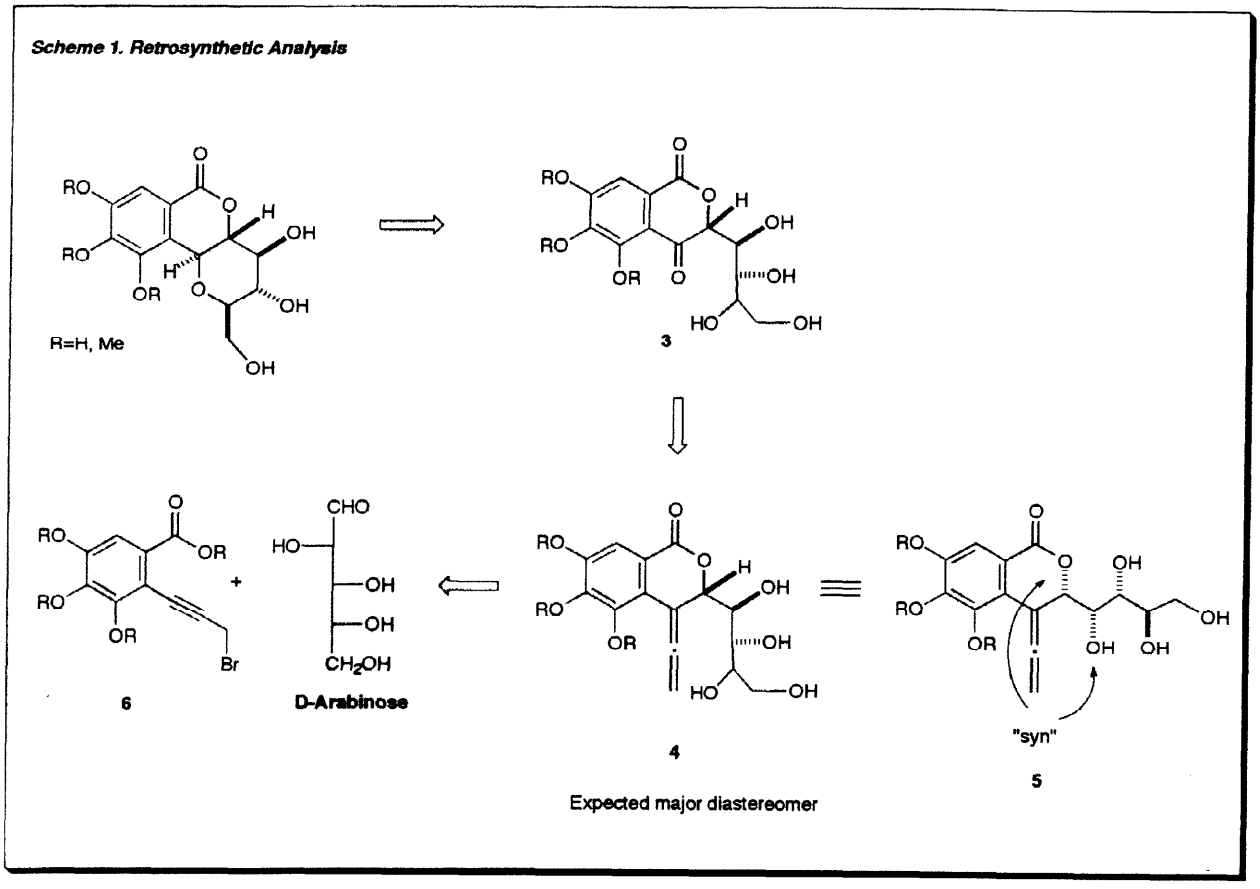
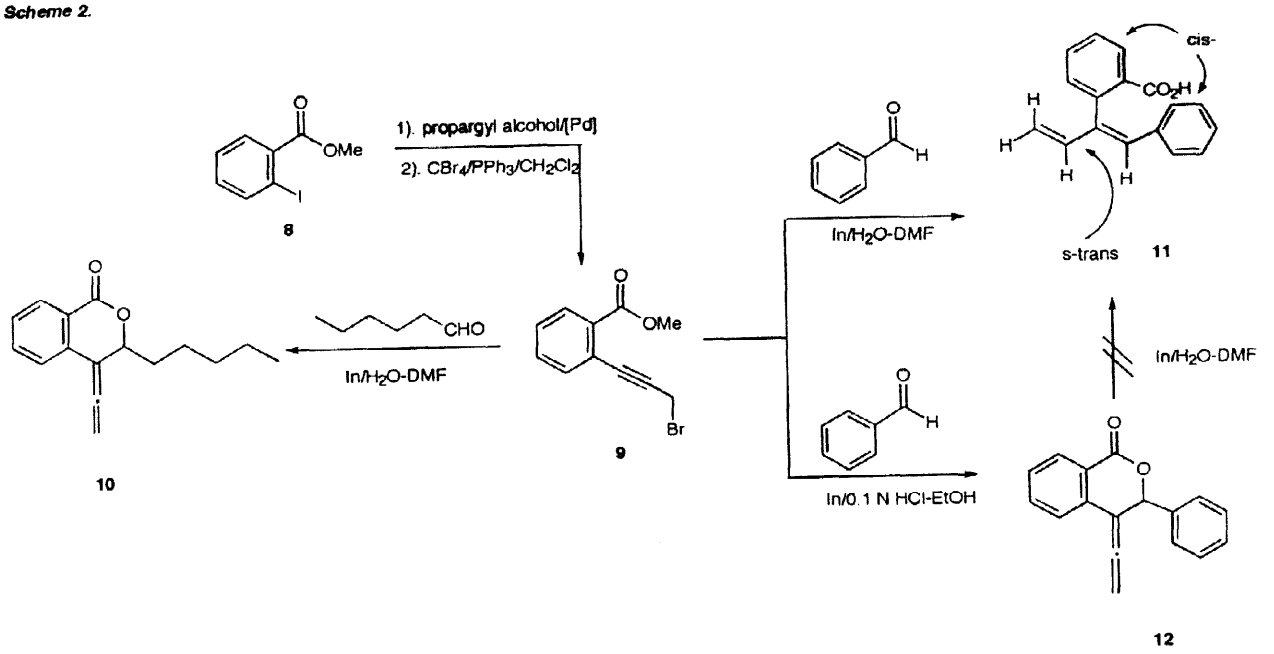
generated stereogenic center in a "syn" relationship, as shown in structure **5**, with the pre-existing neighboring hydroxy group. Previous studies on indium-mediated allylation[11] and allenylation assure the predominant formation of such a diastereomer.



In order to assess the feasibility of the synthesis, a key connection is the formation of the δ-lactone. To begin the investigation, a simple o-carboxyarylpropargyl bromide **9** was prepared by the standard method from methyl o-iodobenzoate (**8**) and propargyl alcohol through a palladium catalyzed reaction in aqueous medium,[12] followed by bromination with carbon tetrabromide and triphenylphosphine. Subsequently, direct coupling between the bromide and hexaldehyde mediated by indium in aqueous DMF generated the desired δ-lactone **10** in 53% yield (unoptimized). On the other hand, indium-mediated coupling between the bromde and benzaldehyde under indentical conditions resulted, instead of the δ-lactone, in a 1,3-butadiene derivative **11** (55%) as the major isolated product. X-ray crystal analysis (Figure 1) [13] of compound **11** showed an interesting structure in which the two aromatic moieties located on the same side of the carbon-carbon double bond existed in a cis relationship. Detailed examination of the crystal structure revealed that neither aromatic rings are fully co-planar with the 1,3-diene moiety, in which the internal aromatic ring is perpendicular to the diene and the terminal benzene ring slightly twisted from the co-planar position with the diene. It is not clear at the moment why such a seemingly unfavorable structure is predominant in the present reaction. The intermolecular interaction during crystal packing or ring-edge aromatic interaction might play some role here. Interestingly, when the solvent was switched from aqueous DMF to aqueous ethanol, the desired lactone was formed in 71% yield. Initially, the lactone was suspected as the intermediate for the 1,3-diene. However, under the indentical reaction conditions, **11** was not formed from **12**. This implies that **12** might be formed through a separate reaction.

Scheme 2.



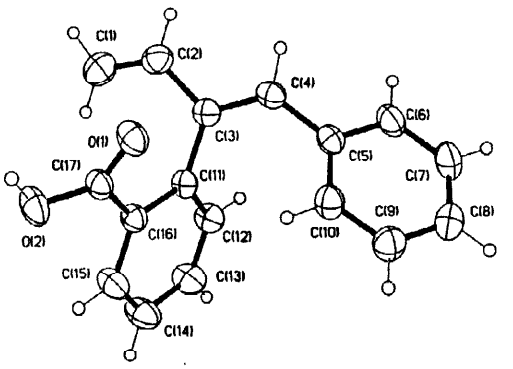


Fig.1. Crystal Structure of **11**

In a more advanced study, an o-carboxyarylpropargyl bromide **16** was prepared by the same method from gallic acid derivative **13**. Iodination of the benzoate **13** with periodic acid and iodine in acetic acid/sulfuric acid generated the desired iodobenzoate derivative **14** in 72% yield. Palladium catalyzed coupling between **14** and propargyl alcohol generated **15** which was readily converted to propargyl bromide **16** with carbon tetrabromide and triphenylphosphine. Reaction of bromide **16** with heptaldehyde mediated by indium generated the desired δ-lactone **17** in 59% yield. This convenient δ-aryl lactone formation provides the basis for the synthesis of bergenin (**1**) and related compounds.

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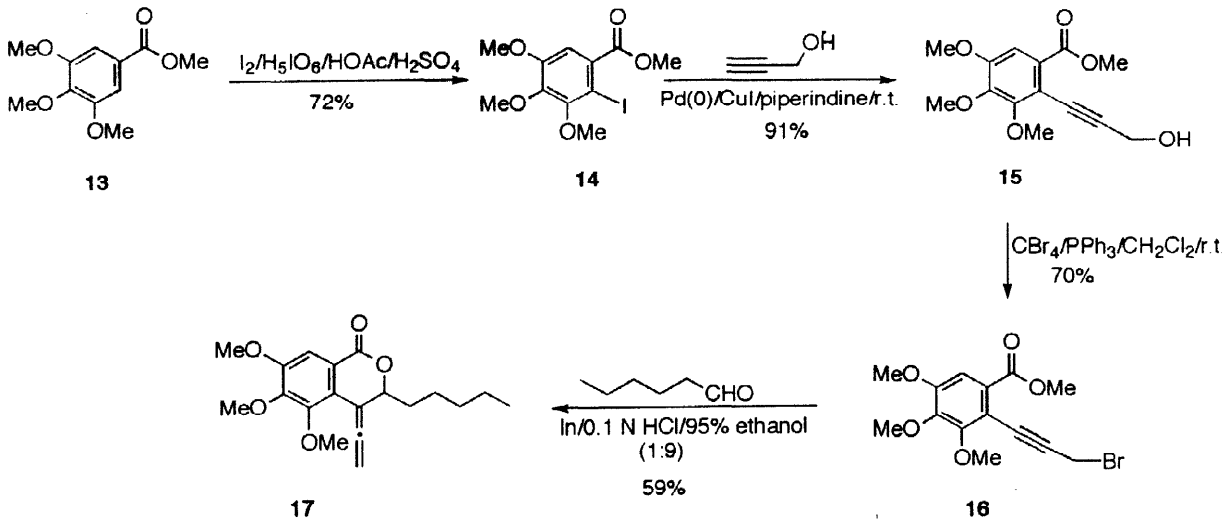
Scheme 3.



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