

Synthesis of (3*R*,5*R*)-harzialactone A and its (3*R*,5*S*)-isomer

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Full Research Paper

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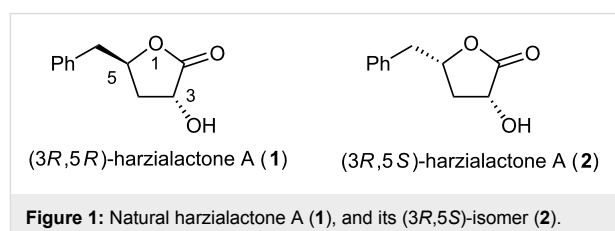
Abstract

The total synthesis of (3*R*,5*R*)-harzialactone A (**1**) and its (3*R*,5*S*)-isomer (**2**) is described. Epoxide opening with thioacetal and diastereoselective reductions are used as key reactions.

Introduction

Marine microorganisms such as bacteria, fungi, and microalgae have proved to be a rich source of structurally novel and biologically active secondary metabolites [1]. (+)-Harzialactone A (**1**), a marine metabolite isolated from the culture broth of a strain of *Trichoderma harzianum* OUPS-N115 by Numata and co-workers, exhibited antitumor and cytotoxic activities against cultured P388 cells [2]. The absolute configuration of (+)-**1** was established based on ¹H NMR studies and by its synthesis [3,4]. Harzialactone A (**1**) (Figure 1) is a synthetic target of considerable interest due to its potent biological activity and unique structure. A few methods for its synthesis have been documented in the literature [3-10] as well as a synthesis of nonnatural (–)-harzialactone A [11]. However, the anti-tumor activity of Harzialactone A coupled with its unique structural architecture prompted us to attempt its synthesis.

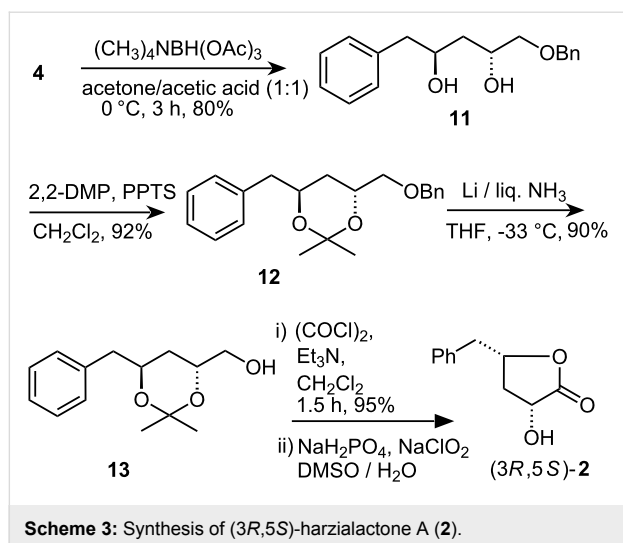
The retrosynthesis is depicted in Scheme 1. Harzialactone **1** could be made from **3** by successive protecting group trans-



formations. **3** can be made by hydroxyl directed reduction of **4** which in turn could be prepared by epoxide **6** opening with dithiane **5**.

Results and Discussion

The synthesis of natural (3*R*,5*R*)-**1** was initiated from the known epoxide **6**, which is commercially available. Treatment of 2-phenylacetaldehyde **7** with 1,3-propanedithiol in the presence of BF₃·Et₂O in CH₂Cl₂ afforded thioacetal **5** in 90% yield (Scheme 2). The epoxide **6** was coupled with the acyl anion



Supporting Information

Supporting Information File 1

Experimental section and analytical data.

[<http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-6-8-S1.doc>]

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