# 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 ${ }^{1} \mathrm{H}$ 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 $\mathbf{3}$ by successive protecting group trans-


Figure 1: Natural harzialactone A (1), and its ( $3 R, 5 S$ )-isomer (2).
formations. $\mathbf{3}$ can be made by hydroxyl directed reduction of $\mathbf{4}$ 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 $\mathbf{6}$, which is commercially available. Treatment of 2-phenylacetaldehyde 7 with 1,3-propanedithiol in the presence of $\mathrm{BF}_{3} \cdot \mathrm{Et}_{2} \mathrm{O}$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ afforded thioacetal 5 in $90 \%$ yield (Scheme 2). The epoxide 6 was coupled with the acyl anion


Scheme 1: Retrosynthesis of harzialactone A (1).
equivalent 5 ( 1.0 equiv), prepared by metallation at $-78^{\circ} \mathrm{C}$ with 1.0 equiv of $n$-butyllithium in the presence of $\mathrm{BF}_{3} \cdot \mathrm{Et}_{2} \mathrm{O}$ to obtain $\mathbf{8}$ in $64 \%$ yield. Removal of the dithioketal using $\mathrm{HgCl}_{2} /$ $\mathrm{CaCO}_{3}$ in $\mathrm{CH}_{3} \mathrm{CN} / \mathrm{H}_{2} \mathrm{O}$ (4:1)[12] provided the corresponding hydroxyketone $\mathbf{4}$ in $82 \%$ yield. Treatment of $\mathbf{5}$ with $\mathrm{NaBH}_{4}$ and $\mathrm{MeOBEt}_{2}[13,14]$ stereoselectively formed the syn diol 9 in good yield ( $80 \%$ ). The diol 9 was subsequently transformed into the isopropylidene derivative $\mathbf{3}$ by treatment with 2,2-dimethoxypropane and a catalytic amount of PPTS in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$.

In the ${ }^{13} \mathrm{C}$ NMR spectrum of $\mathbf{3}$, the acetonide methyl groups resonated at 19.6 and 29.9 ppm indicating a 1,3 -syn-relationship that was further substantiated by the appearance of the quaternary carbon in the downfield region ( 98.7 ppm ). Deprotection of the benzyl group using Li/liq. $\mathrm{NH}_{3}$ gave alcohol $\mathbf{1 0}$. Oxidation of alcohol $\mathbf{1 0}$ under Swern conditions and further oxidation of the resulting aldehyde using $\mathrm{NaH}_{2} \mathrm{PO}_{4}, \mathrm{NaClO}_{2}$ in DMSO $/ \mathrm{H}_{2} \mathrm{O}$ furnished the target hydroxylactone $(3 R, 5 R)-\mathbf{1}$ as reported earlier. The IR absorption at $1774 \mathrm{~cm}^{-1}$ indicates the presence of $\delta$-lactone system.

The synthesis of $(3 R, 5 S)-2$ was also accomplished in an identical manner from 4 (Scheme 3). The substrate hydroxyl directed asymmetric reduction with $\mathrm{Me}_{4} \mathrm{NBH}(\mathrm{OAc})_{3}[15,16]$ was performed at $0{ }^{\circ} \mathrm{C}$ to afford the anti diol $\mathbf{1 1}$ as the major product, which was converted into stereoisomer ( $3 R, 5 S$ )-2 via acetonide 12, deprotection of benzyl group to give 13, and further functional group transformations by use of the same reagents and conditions as those described for the conversion of $\mathbf{1 0}$ into $\mathbf{1}$. The IR absorption at $1775 \mathrm{~cm}^{-1}$ confirms the presence of $\delta$-lactone in $(3 R, 5 S)$-2

The anti relationship of two hydroxyl groups was studied in compound 12. In the ${ }^{13} \mathrm{C}$ NMR of $\mathbf{1 2}$, the acetonide methyl groups resonated at 24.9 and 34.2 ppm indicating a 1,3-antirelationship that was further substantiated by the appearance of the quaternary carbon in the downfield region ( 100.5 ppm ) [7].

In conclusion, a stereoselective synthesis of natural (+)( $3 R, 5 R$ )-harzialactone A and its nonnatural stereoisomer $(3 R, 5 S)$ has been accomplished.



Scheme 2: Synthesis of natural harzialactone A (1).


Scheme 3: Synthesis of (3R,5S)-harzialactone A (2).

## 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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