

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

Gowravaram Sabitha^{*}, Rangavajjula Srinivas, Sukant K. Das and Jhillu S. Yadav

Full Research Paper		Open Access
Address: Organic Division I, Indian Institute of Chemical Technology, Hyderabad 500 007, India, Fax: +91-40-27160512	Beilstein Journal of Organic Chemistry 2010, 6, No. 8. doi:10.3762/bjoc.6.8	
	Received: 31 August 2009	
Email:	Accepted: 20 January 2010	
Gowravaram Sabitha [*] - gowravaramsr@yahoo.com	Published: 29 January 2010	
* Corresponding author	Associate Editor: J. N. Johnston	
Keywords: dithiane; harzialactone A; hydroxyl directed reduction; stereoisomer	© 2010 Sabitha et al; licensee Beilstein-Institut. License and terms: see end of document.	

Abstract

The total synthesis of (3R,5R)-harzialactone A (1) and its (3R,5S)-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 (3R,5R)-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



equivalent 5 (1.0 equiv), prepared by metallation at -78 °C with 1.0 equiv of *n*-butyllithium in the presence of BF₃·Et₂O to obtain **8** in 64% yield. Removal of the dithioketal using HgCl₂/CaCO₃ in CH₃CN/H₂O (4:1)[12] provided the corresponding hydroxyketone **4** in 82% yield. Treatment of **5** with NaBH₄ and MeOBEt₂ [13,14] stereoselectively formed the *syn* diol **9** in good yield (80%). The diol **9** was subsequently transformed into the isopropylidene derivative **3** by treatment with 2,2-dimethoxypropane and a catalytic amount of PPTS in CH₂Cl₂.

In the ¹³C NMR spectrum of **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. NH₃ gave alcohol **10**. Oxidation of alcohol **10** under Swern conditions and further oxidation of the resulting aldehyde using NaH₂PO₄, NaClO₂ in DMSO/H₂O furnished the target hydroxylactone (3*R*,5*R*)-**1** as reported earlier. The IR absorption at 1774 cm⁻¹ indicates the presence of δ -lactone system. The synthesis of (3R,5S)-2 was also accomplished in an identical manner from 4 (Scheme 3). The substrate hydroxyl directed asymmetric reduction with Me₄NBH(OAc)₃ [15,16] was performed at 0 °C to afford the *anti* diol 11 as the major product, which was converted into stereoisomer (3R,5S)-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 10 into 1. The IR absorption at 1775 cm⁻¹ confirms the presence of δ -lactone in (3R,5S)-2.

The *anti* relationship of two hydroxyl groups was studied in compound **12**. In the ¹³C NMR of **12**, the acetonide methyl groups resonated at 24.9 and 34.2 ppm indicating a 1,3-*anti*-relationship 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 (+)-(3R,5R)-harzialactone A and its nonnatural stereoisomer (3R,5S) has been accomplished.





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]

Acknowledgements

R. S. thanks CSIR, S. K. D thanks UGC, New Delhi for the award of fellowships.

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