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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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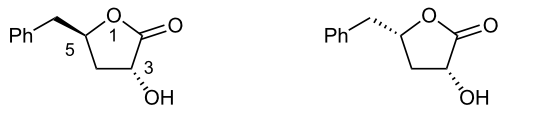
Abstract

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}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.



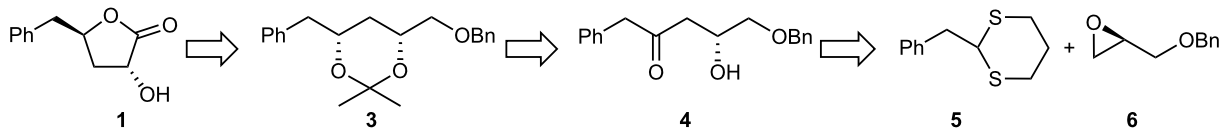
(3*R*,5*R*)-harzialactone A (**1**) (3*R*,5*S*)-harzialactone A (**2**)

Figure 1: Natural harzialactone A (**1**), and its (3*R*,5*S*)-isomer (**2**).

The retrosynthesis is depicted in Scheme 1. Harzialactone **1** could be made from **3** by successive protecting group transformations. **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 $BF_3{\cdot}Et_2O$ in CH_2Cl_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**).

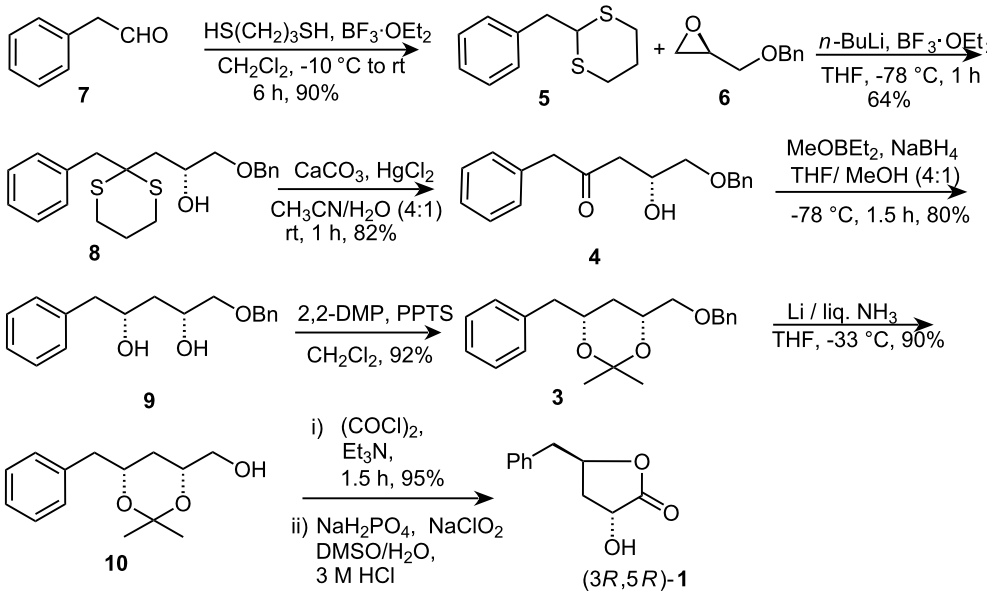
equivalent **5** (1.0 equiv), prepared by metallation at –78 °C with 1.0 equiv of *n*-butyllithium in the presence of $BF_3{\cdot}Et_2O$ to obtain **8** in 64% yield. Removal of the dithioketal using $HgCl_2$/$CaCO_3$ in CH_3CN/H_2O (4:1)[12] provided the corresponding hydroxyketone **4** in 82% yield. Treatment of **5** with $NaBH_4$ and $MeOBEt_2$ [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 CH_2Cl_2.

In the ^{13}C 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. NH_3 gave alcohol **10**. Oxidation of alcohol **10** under Swern conditions and further oxidation of the resulting aldehyde using NaH_2PO_4, $NaClO_2$ in $DMSO/H_2O$ 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.

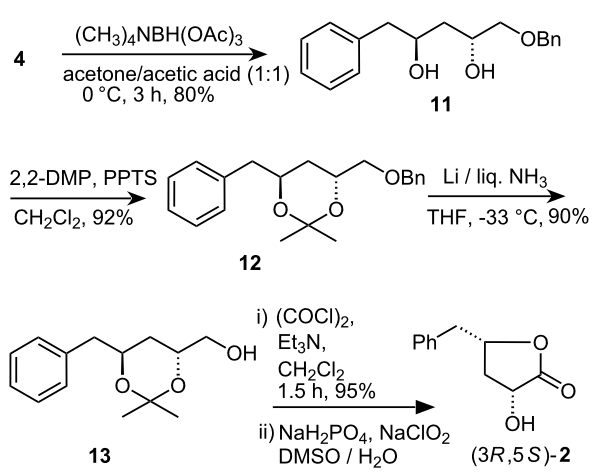
The synthesis of (3*R*,5*S*)-**2** was also accomplished in an identical manner from **4** (Scheme 3). The substrate hydroxyl directed asymmetric reduction with $Me_4NBH(OAc)_3$ [15,16] was performed at 0 °C to afford the *anti* diol **11** as the major product, which was converted into stereoisomer (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 **10** into **1**. The IR absorption at 1775 cm^{-1} confirms the presence of δ-lactone in (3*R*,5*S*)-**2**.

The *anti* relationship of two hydroxyl groups was studied in compound **12**. In the ^{13}C 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 (+)-(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 (3*R*,5*S*)-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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References

1. Blunt, J. W.; Copp, B. R.; Munro, M. H. G.; Northcote, P. T.; Prinsep, P. R. *Nat. Prod. Rep.* **2004,** *21,* 1–49. doi:10.1039/b305250h (and references cited therein).
2. Amagata, T.; Usami, Y.; Minoura, K.; Ito, T.; Numata, A. *J. Antibiot.* **1998,** *51,* 33–40.
3. Mereyala, H. B.; Gadikota, R. R. *Tetrahedron: Asymmetry* **1999,** *10,* 2305–2306. doi:10.1016/S0957-4166(99)00245-1
4. Mereyala, H. B.; Joe, M.; Gadikota, R. R. *Tetrahedron: Asymmetry* **2000,** *11,* 4071–4081. doi:10.1016/S0957-4166(00)00389-X
5. Ikota, N. *Heterocycles* **1991,** *32,* 521–528. doi:10.3987/COM-91-5669
6. Kumar, J. S. R.; Datta, A. *Tetrahedron Lett.* **1999,** *40,* 1381–1383. doi:10.1016/S0040-4039(98)02614-8
7. Kiyooka, S.; Goh, K.; Nakamura, Y.; Takesue, H.; Hena, M. A. *Tetrahedron Lett.* **2000,** *41,* 6599–6603. doi:10.1016/S0040-4039(00)01124-2
8. Moreau, X.; Campagne, J. *Tetrahedron Lett.* **2001,** *42,* 4467–4469. doi:10.1016/S0040-4039(01)00753-5
9. Kotkar, S. P.; Suryavanshi, G. S.; Sudalai, A. *Tetrahedron: Asymmetry* **2007,** *18,* 1795–1798. doi:10.1016/j.tetasy.2007.07.031
10. Kumar, A. N.; Bhatt, S.; Chattopadhyay, S. *Tetrahedron: Asymmetry* **2009,** *20,* 205–209. doi:10.1016/j.tetasy.2009.01.009
11. Jian, Y.-J.; Wu, Y.; Li, L.; Lu, J. *Tetrahedron: Asymmetry* **2005,** *16,* 2649–2651. doi:10.1016/j.tetasy.2005.07.003
12. Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975,** *16,* 2643–2646. doi:10.1016/S0040-4039(00)75203-8
13. Hanamoto, T.; Hiyama, T. *Tetrahedron Lett.* **1988,** *29,* 6467–6470. doi:10.1016/S0040-4039(00)82375-8
14. Chen, K. M.; Hardtmanna, G. E.; Prasad, K.; Pepc, O.; Shapinro, M. J. *Tetrahedron Lett.* **1987,** *28,* 155–158. doi:10.1016/S0040-4039(00)95673-9
15. Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988,** *110,* 3560–3578. doi:10.1021/ja00219a035
16. Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986,** *27,* 5939–5942. doi:10.1016/S0040-4039(00)85367-8

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