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TETRAHEDRON: *ASYMMETRY*

A concise synthesis of harzialactone A from D-glucose and revision of absolute stereochemistry

Hari Babu Mereyala * and Rajendrakumar Reddy Gadikota

Organic Chemistry Division-III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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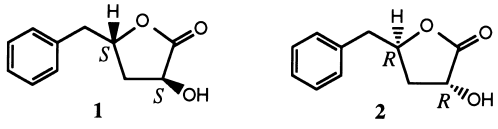
Abstract

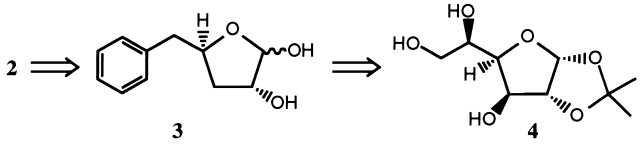
Synthesis of **2** by a chiron approach is described starting from monoacetone-D-glucose **4**. Absolute stereochemistry of natural harzialactone A **1** (2*S*,4*S*) is revised to **2** (2*R*,4*R*).

Marine organisms have been a useful source of bioactive metabolites with antitumor activity.[1] Thus, among the new antitumor metabolites inhabiting the marine environment harzialactone A **1** was isolated from a strain of *Trichoderma harzianium* OUPS-N 115 and characterized.[2] Compound **1** was shown to exhibit weak cytotoxic activity against P 388 lymphocytic leukemia test system in cell culture. In the course of our long-term program towards the design and synthesis of oxygenated lactones[3] with anticancer activity we targeted the synthesis of (2*R*,4*R*)-**2** which is an antipode of (2*S*,4*S*)-**1**. We intended to develop a general synthetic route to prepare **2** and its analogs for studying the structure–activity relationship starting from easily available homochiral sugars.



1 **2**

Retrosynthetic analysis of the hydroxy furanolactone **2** (Scheme 1) indicated that it could be derived from diol **3** by regioselective oxidation. Diol **3** in turn could be derived from commercially available monoacetone-D-glucose **4**.



3 **4**

Scheme 1.

Compound **4** was reacted with $NaIO_4$ in CH_2Cl_2/MeOH/saturated aqueous $NaHCO_3$ solution at room temperature for 2 h to obtain the aldehyde[4] that without purification was immediately reacted with

* Corresponding author. E-mail: haribabu@iict.ap.nic.in

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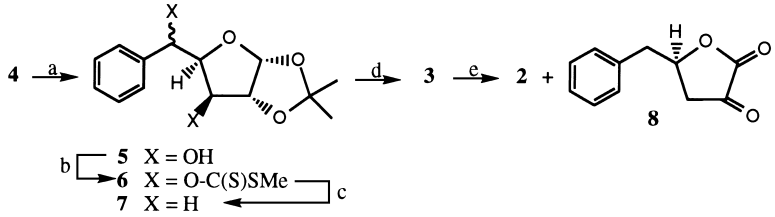
phenylmagnesium bromide at 0°C to obtain a diastereomeric mixture of diol (3:1) **5**[5] in 73% yield (Scheme 2). Compound **5** was reacted with NaH/CS_2/MeI to obtain the methyl xanthate derivative **6** that was characterized from the ^{1}H NMR spectrum from the appearance of methylthio protons at δ 2.5 (s, 3H) and δ 2.6 (s, 3H). Compound **6** was reacted with Bu_3SnH[6] at reflux temperature in toluene containing a catalytic amount of AIBN for 6 h to obtain dideoxy derivative **7** in 76% yield and was characterized from the appearance of H-3 at δ 1.6 (m, 1H), δ 2.0 (dd, 1H, J_{gem} 13.8, $J_{2,3}$ 3.5) and H-5 at δ 2.8 (dd, 1H, J_{gem} 14.4, $J_{4,5}$ 5.2) and 3.02 (dd, 1H, $J_{4,5'}$ 5.3). Compound **7** was treated with 60% aqueous HOAc/cat. H_2SO_4 at 45°C for 6 h to obtain diol **3** in 79% yield as a crystalline solid, mp 91–93°C.



Scheme 2. Reagents and conditions: (a) $NaIO_4$, CH_2Cl_2:MeOH:aq. satd. $NaHCO_3$, 0°C–rt, 2 h; PhMgBr, THF, 0°C–rt, 8 h; (b) NaH, CS_2, MeI, THF, 0°C–rt, 1 h; (c) Bu_3SnH, cat. AIBN, toluene, reflux, 6 h; (d) 60% aq. HOAc, cat. H_2SO_4, 45°C, 6 h; (e) Ag_2CO_3/Celite, benzene:DMF, reflux, 1 h

Oxidation of **3** with pyridinium dichromate (PDC) in CH_2Cl_2 at reflux for 1 h resulted in the formation of **2** (10%) along with the undesired diketo compound **8** (45%). However, regioselective oxidation of the C-1 hydroxyl group of **3** was achieved using Ag_2CO_3/Celite[7] to obtain the hydroxy lactone **2** as a crystalline solid, mp 78–79°C (lit. 82–84°C)[2] in 71% yield along with **8** in 11% yield. ^{1}H, ^{13}C NMR, IR (1769 cm^{-1}) spectroscopic[8] data of (2*R*,4*R*)-**2** were in complete agreement with the reported data of **1**, except that it exhibited a positive specific rotation of +38.0 (*c* 0.3, $CHCl_3$) instead of the expected negative rotation. We designed the synthesis for the optical antipode of (2*S*,4*S*)-**1**. Compound **1** has been reported to possess a specific rotation of +33.50 (*c* 0.3, $CHCl_3$).[2] Hence, the natural compound **1** should have the revised structure **2** based on the chiron approach followed to derive it.

In conclusion, synthesis of harzialactone **2** by a chiron approach has been achieved. The usefulness of the chiron approach is evident in the assignment of the correct absolute stereochemistry for natural harzialactone **1**. Thus, the stereochemistry of (2*S*,4*S*)-**1** has been revised to (2*R*,4*R*)-**2**.

Acknowledgements

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8. All new compounds gave satisfactory elemental analysis.