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An efficient chiral-pool synthesis of botryolide-E

Sridhar Madabhushi *, Kondal Reddy Godala, China Ramanaiah Beeram, Narsaiah Chinthala

Fluoroorganics Division, Indian Institute of Chemical Technology, Hyderabad 500607, India

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ABSTRACT

An efficient stereoselective total synthesis of botryolide-E by a chiral-pool approach is described.

Chiral pool synthesis, which involves the application of readily available enantiopure natural products such as monosaccharides and amino acids as starting materials, has become an increasingly important approach in recent years for the synthesis of complex organic molecules,[1] Recently, Gloer co-workers,[2] isolated a metabolite botryolide-E from the cultures of the fungicolous *Botryotrichum* sp. (NRRL 38180) and it exhibits an anti-bacterial activity against *Bacillus subtilis* (MTCC 441), *Staphylococcus aureus* (MTCC 96), and *Escherichia coli* (MTCC 443), and an antifungal activity against *Aspergillus niger* (MTCC 1344) and *Saccharomyces cerevisiae* (MTCC 171). Botryolide-E is a γ-butenolide derivative and it contains three chiral carbon centers. In the literature only one report exists on stereoselective total synthesis of botryolide-E and it was reported by a non-chiral pool approach in 14-steps with 8% overall yield, starting from racemic propylene oxide.[3] Herein we report the first chiral-pool approach to the total synthesis of botryolide-E in enantiopure form with 40% overall yield in 12-steps starting from (+)-diethyl (L)-tartrate as shown in Scheme 1.

The sequence of reaction steps in stereoselective total synthesis of botryolide-E starting from (+)-diethyl-L-tartrate is shown in Scheme 2. In the first step, (+)-diethyl-L-tartrate **2** was reacted with 2,2-dimethoxypropane using *p*-toluenesulfonic acid as the catalyst to obtain (4*R*,5*R*)-diethyl-2,2-dimethyl-1, 3-dioxolane-4,5-dicarboxylate **3** in 90% yield.[4] Next, the acetonide **3** was reduced with lithium aluminum hydride to obtain ((4*S*, 5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)dimethanol **4** in 95% yield. In the next step, compound **4** was converted into a mono *O*-benzyl ether using sodium hydride and benzyl bromide to obtain ((4*S*, 5*S*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl) methanol **5** in 82% yield.[5] Oxidation of **5** with *o*-iodoxybenzoic acid (IBX) and subsequent Wittig olefination of the resulting aldehyde with ethylene triphenylphosphonium bromide furnished (4*S*,5*S*,*Z*)-4-(benzyloxymethyl)-2,2-dimethyl-5-(prop-1-enyl)-1,3-dioxolane **6** in 90% yield. Here, the *Z*-configuration of the double bond was confirmed from the homodecoupled ^{1}H NMR spectrum of **6**, which shows the coupling constant (*J*) between two olefinic protons as 10.847 Hz.[6] Next, **6** was subjected to Wacker oxidation[7] using $PdCl_2$ as the catalyst to obtain 1-((4*S*,5*S*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-one **7** in 91% yield, which upon stereoselective reduction[8] with triethyl lithium borohydride and K-Selectride® was converted into (*R*)-1-((4*S*,5*S*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-ol **8** in 90% yield. In the next step, the hydroxyl group present in **8** was protected as an acetyl ester[9] with acetic anhydride and pyridine to obtain (*R*)-1-((4*S*, 5*S*)-5-(benzyloxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-yl acetate **9** in 93% yield. Reductive debenzylation[10] of **9** with H_2-Pd/C gave (*R*)-1-((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)propan-2-yl acetate **10** in 97% yield. Oxidation of **10** with IBX and subsequent modified Horner–Wadsworth–Emmons olefination using an Ando's phosphonate[11] (ethyl (diphenyl-phosphono) acetate) gave (*Z*)-ethyl-3-((4*S*,5*S*)-5-((*R*)-2-acetoxypropyl)-2,2-dimethyl-1, 3-dioxolan-4-yl)acrylate **11** in 90% yield. In the final step, **11** was treated with 50% aqueous trifluoroacetic acid[12] at room temperature to obtain botryolide-E **1** ($[\alpha_D^{25}] = -37.737$ (*c* 0.05, $CHCl_3$); Lit.[2] ($[\alpha_D^{25}] = -38.0$ (*c* 0.05, $CHCl_3$)) in 95% yield. We obtained satisfactory spectral data (^{1}H NMR, Mass, and ^{13}C NMR) and optical rotation value for botryolide-E **1**, which were identical to the reported data of the isolated botryolide-E.

* Corresponding author. Tel.: +91 40 27191772; fax: +91 40 27160387.
E-mail address: smiict@gmail.com (S. Madabhushi).

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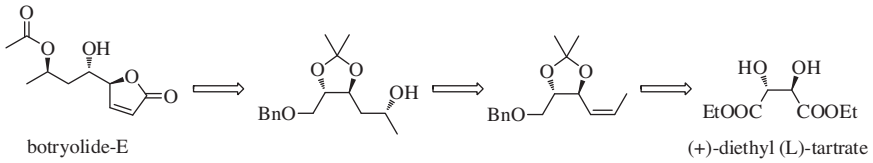
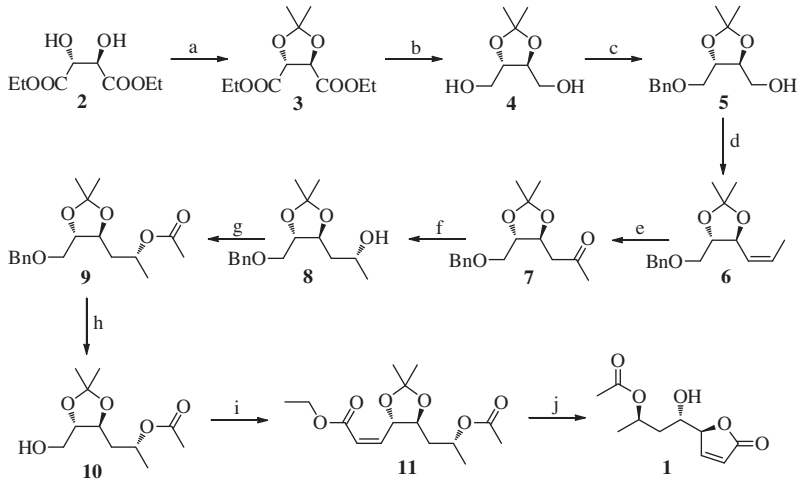


Scheme 1. Retrosynthetic route to botryolide-E starting from (+)-diethyl-L-tartrate.



Scheme 2. Total synthesis of botryolide-E. Reagents and conditions: (a) 2,2-DMP, *p*-TsOH, dry benzene, 60 °C, 8 h, 90%; (b) LAH, THF, 70 °C, 4 h, 95%; (c) BnBr, NaH, THF, rt, 5 h, 82%; (d) (i) IBX, dry DMSO, DCM, 5 h; (ii) $EtPh_3P^+.Br^-$, *n*-BuLi, THF, −78 °C, 2 h, (90% for two steps); (e) $PdCl_2$, CuCl, DMF/H_2O (7:1), O_2, 60 °C, 6 h, 91%; (f) (i). K-Selectride, THF, −78 °C, 2 h; (ii) $LiEt_3BH$, −78 °C, 1 h, 90%; (g) Ac_2O, pyridine, 5 h, 0 °C to rt, 93%; (h) 5% Pd/C, H_2, MeOH, 6 h, rt, 97%; (i) (i) IBX, dry DMSO, DCM, 5 h; (ii) $(PhO)_2P(O)CH_2COOEt$, NaH, THF, −78–0 °C, 3 h, (90% for two steps); (j) 50% aq. CF_3COOH, 0 °C to rt, 12 h, 95%.

In conclusion, this work describes the first chiral pool approach for an efficient and stereoselective total synthesis of botryolide-E in 12-steps and 40% overall yield starting from (+)-diethyl-L-tartrate.

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Supplementary data

Supplementary data (experimental procedures, characterization data, and ^1H & ^{13}C NMR spectra of the compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.08.019.

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