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The total synthesis of (*S*)-2,4-dihydroxy-1-butyl (4-hydroxyl) benzoate

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ABSTRACT

This study is the first synthesis of (*S*)-2,4-dihydroxy-1-butyl (4-hydroxy) benzoate, a newly discovered natural product with anti-tumor properties from the fungus, *Penicillium auratiogriseum*. The key steps are a 1,3 diol protection followed by the coupling of *p*-anisic acid to the protected alcohol and subsequent de-protection steps.

(*S*)-2,4-Dihydroxy-1-butyl (4-hydroxy) benzoate (**1**) was isolated from the fungus, *Penicillium auratiogriseum* from the sponge, *Mycale plumose* from Quingdao, China.[1] The pure compound showed cytotoxic inhibition against the mouse cdc2 mutant cell line (tsFT210) in the micromolar range (8 μg/mL or 35 μM). The first total synthesis of this molecule is presented here. This synthesis would help in further evaluating the medicinal properties of the compound and its analogs (Fig. 1).

The synthesis of **1** (Fig. 2) started with (*S*)-(−)-1,2,4-butanetriol. 1,2,4-butanetriol is a versatile synthetic building block used in a diverse array of synthetic targets. For example, the 1,2 protected diol portion of 1,2,4-butanetriol was replaced by a highly activated cyclopropane ring en route to substituted pyrrolidines which are common in natural products.[2] Lewis acid ($BF_3{\cdot}Et_2O$) catalyzed 1,2 protection of 1,2,4-butanetriol was used to form the oxepane core of Zoapatanol,[3] a diterpenoid exhibiting contragestational activity. Commercial 1,2,4-butanetriol was used to make chiral derivatives of glyceraldehyde, a C_3 synthon that has widespread synthetic use: a bi(dihydropyran) derivative[6] was used for 1,2 diol protection which proceeded as a dispiroketal, which is sterically hindered and hence serves as a chiral auxiliary.

Most syntheses require either a 1,2 diol protection or a 1,3 diol protection of 1,2,4-butanetriol. Exclusive 1,2 protection methods generally use ketones or dimethyl acetals thereof[2,3] with catalytic amounts of organic acids[2] or Lewis acids.[3,4] Other reagents include phenanthrenedione[5] and the above-mentioned bi(dihydropyran) derivative.[6]

For exclusive 1,3 diol protection, simple aldehydes or their corresponding acetals have been used. One such commonly seen example is the exclusive protection of 1,3 diols in sugars bearing multiple hydroxyl groups.[7] Other examples involving chemistries very different from the aldehyde-based reagents include a silicon-ester reagent[8] and a Lewis acid-based route.[9]

Of note is a recent publication where serendipitous use was made of both 1,2-and 1,3-protected 1,2,4-butanetriol to make isoprostanes, prostaglandin-like compounds that were recently discovered in humans.[10]

The first step in the synthesis of **1** was the 1,3 protection[7] of commercial (*S*)-(−) 1,2,4-butanetriol as an acetal (**2**, 90% yield). For both 1,2 and 1,3 diol protections in butanetriol, it should be noted that the diol protecting group tends to be unstable with inter-conversion occurring between the five-membered ketal and six-membered acetal rings, the products of which are not easy to separate. Therefore all reactions subsequent to the diol protection were carried out under nitrogen and aqueous work-up was either avoided where possible or was carried out at 4 °C in the shortest possible time.

The 1,3 diol protection step was followed by an attempt to couple this protected alcohol with *p*-hydroxybenzoic acid using thionyl chloride and excess triethylamine. The reaction proceeded with very poor yield and hence was abandoned. Another attempt at coupling was made with *N*,*N*′-dicyclohexylcarbodiimide (DCC). Despite an earlier report of a similar reaction,[11] attempts to directly couple *p*-hydroxybenzoic acid with the protected alcohol **2** using DCC were unsuccessful, presumably due to interference by the phenol.

Coupling was then tried after acetylating *p*-hydroxybenzoic acid using acetic anhydride.[12] Coupling the acetylated *p*-hydroxybenzo-

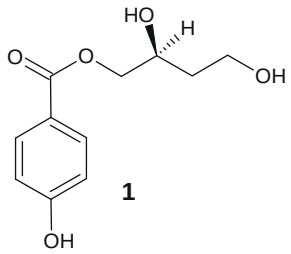

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Figure 1. (*S*)-2,4-Dihydroxy-1-butyl (4-hydroxyl) benzoate.

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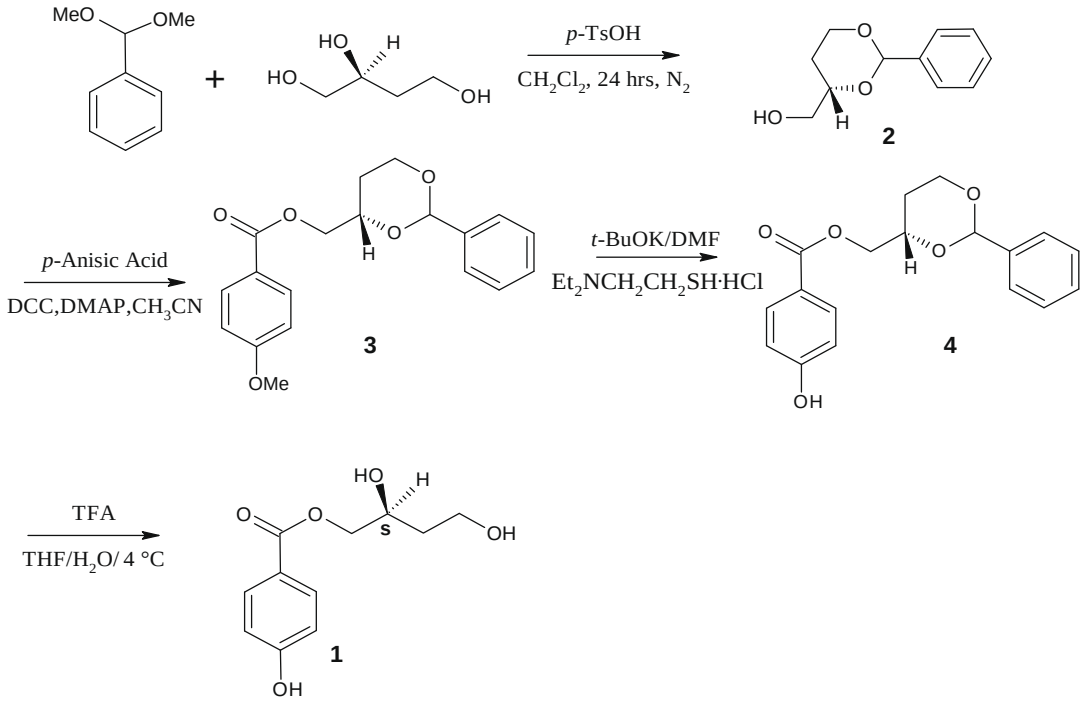

(*S*)-2,4-dihydroxy-1-butyl (4-hydroxy) benzoate

Figure 2. Synthetic scheme.

ic acid to **2** proceeded smoothly enough, with about 60–70% yield of the purified product. However, the subsequent phenolic de-protection with aniline or ammonium acetate[13] was problematic. Besides obtaining poor yields, neither reagent gave de-protected products that could be reasonably purified.

An ether protecting group for the phenol was used next, simply because *p*-anisic acid was cheaply available. The coupling of *p*-anisic acid to **2** with DCC proceeded very smoothly and yields were around 70% and very pure compound (**3**) was obtained.

What remained was the sequential de-protection of the phenol and the diol in **3**. An attempt to de-protect the acetal first using camphorsulfonic acid failed.[14] However, the next attempt with trifluoroacetic acid (TFA) was successful.[15] Next, the ether was de-protected to the phenol by refluxing with 2-(diethylamino) ethanethiol.[16] Unfortunately, the reaction conditions chosen did not yield the product. The work-up was very acidic (pH 1) and under these conditions the stability of the alcohol is suspect.

Therefore the de-protection sequenced was reversed and the ether in **3** was de-protected first to phenol **4** using the ethanethiol reagent (60% yield), followed by acetal de-protection with TFA to yield the final product (**1**, 50% yield). Characterization data were in complete agreement with the existing literature.[1]

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Supplementary data

Supplementary data (experimental details for the synthesis and the characterization data for intermediates are provided) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.04.016.

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