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Synthesis of the tetrahydrofuran unit of varitriol and γ-butyrolactones from 5-oxabicyclo[2.1.1]hexane derivative via oxidative cleavage reactions

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ABSTRACT

A formal synthesis of marine-derived antitumor natural product varitriol from a 5-oxabicyclo[2.1.1]hexane derivative is described. A tetrahydrofuran unit of varitriol embedded with four contiguous stereocenters was synthesized with an overall yield of 10.2% in 11 steps from an oxa-bicyclic system. An unprecedented oxidative cleavage reaction involving scissoring of two C—C bonds at oxa-quaternary carbon of THFs leading to γ-butyrolactones was reported and a plausible mechanism has been proposed.

Varitriol is a marine origin low molecular weight antitumor natural product, it was isolated by Barrero and co-workers in 2002.[1] The biological activity profile of varitriol was tested against cancer lines within the 60 cell line panel of NCI and found to be a potent cytotoxic toward renal ($GI_{50} = 1.63 \times 10^{-7}$ M), breast ($GI_{50} = 2.10 \times 10^{-7}$ M) and CNS ($GI_{50} = 2.44 \times 10^{-7}$ M) cancer cells.[1,2] The interesting structure due to contiguously substituted tetrahydrofuran connected with aromatic moiety and the potent anticancer activity toward human cancer cell lines attracted the attention of various synthetic groups. The total synthesis of (−)-varitriol and absolute configuration assignment were reported by Jennings and co-worker[3] in 2006 and then absolute configuration of (+)-varitriol (**1**) was established (Fig. 1).

The first total synthesis of **1** was reported by Shaw and coworker in 2008 starting from D-mannopyranoside and 2,6-dihydroxybenzoic acid.[4a] Furthermore, other reports have appeared in the literature for the total synthesis of (+)-varitriol by utilizing various sugar based chiral pool starting materials.[4b–g] Recently, a total synthesis involving Corey Chaykovsky reaction and triethylamine mediated epimerization as the key steps to construct the stereochemically pure furanoside unit of natural product has been reported.[4h] Additionally, carbohydrate based chiral pool synthetic routes employing transition metal catalyst in the bicyclization of

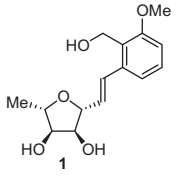

Figure 1. Structure of (+)-varitriol (**1**).

unsaturated polyol,[4i] vinyl oxirane ring expansion,[4j] α-hydroxyallene cycloisomerization[4k] reactions were also reported to achieve the synthesis of natural product. Likewise, in just appeared report, another total synthesis of **1** was disclosed using CSA induced intramolecular epoxide opening reaction to synthesize THF moiety of the natural product.[4l] The promising cytotoxicity of **1** also inspired some research groups toward synthesis of its analogues.[4g,k,m] Although, several reports are known for the synthesis of varitriol (**1**), we consider **1** as a target molecule in order to explore the in-house oxa-bridged derivatives[5] by using our recently reported methodology.[6]

As a part of our research program on exploration of the chemistry of oxa-bridged derivatives,[7] very recently we reported an efficient Lewis acid mediated Grob-type fragmentation reaction of 5-oxabicyclo[2.1.1]hexane system to access 2,2,5-trisubstituted tetrahydrofuran building blocks.[6] Ready availability of these diastereomerically pure oxa-bridged compounds in gram-scale

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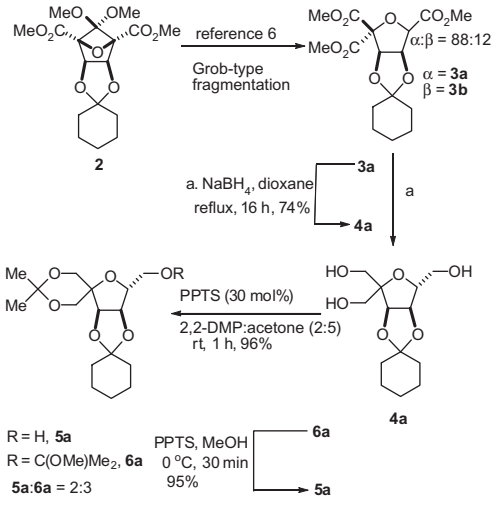
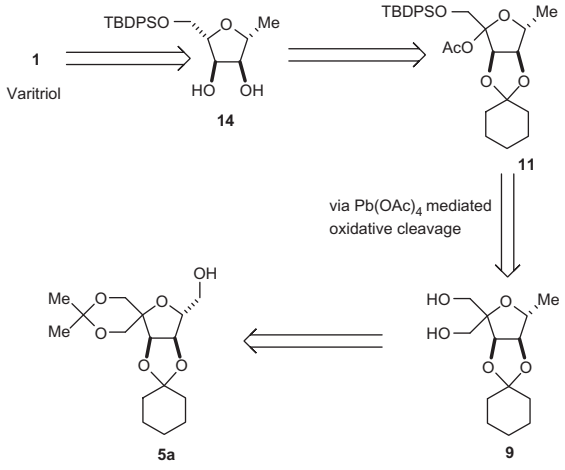


Scheme 1. Synthesis of THF alcohol **5a** from 5-oxabicyclo[2.1.1]hexane **2**.



Scheme 2. Retrosynthetic plan for synthesis of varitriol (**1**) via $Pb(OAc)_4$ mediated oxidative cleavage of β-hydroxy ether.

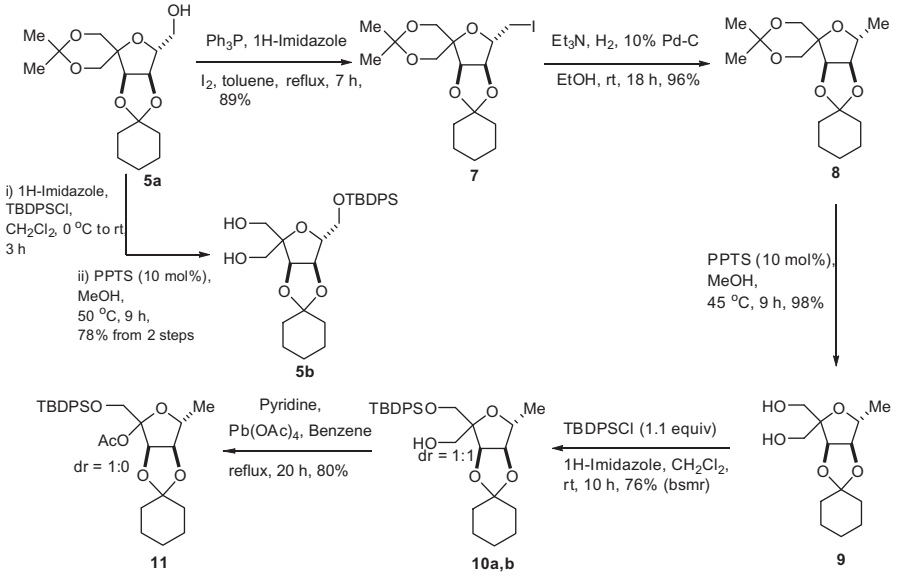
quantities prompted us to utilize them for the synthesis of biologically active natural products.

The oxygenated tetrahydrofuran tricarboxylates **3a**,**b** (dr = 88:12) could be prepared from oxa-bicycle **2** via $BF_3{\cdot}OEt_2$ mediated chemoselective Grob-type fragmentation reaction in excellent yield (97%). The chromatographically separable tetrahydrofuran derivative **3a** was converted into corresponding triol **4a** by reduction with $NaBH_4$ in refluxing 1,4-dioxane. When triol **4a** was subjected to acetonide protection with 2,2-DMP/acetone (2:5) using pyridinium *p*-toluenesulfonate (30 mol %), the desired monoalcohol **5a** and mixed acetal **6a** were obtained in 2:3 ratio with 96% yield. The mixed acetal was selectively deprotected by treating with PPTS (1.5 equiv) in MeOH at 0 °C to afford alcohol **5a** in 95% yield (Scheme 1).

In 2010, Bourgeois and co-worker reported a diastereoselective synthesis of (±)-1′,4′-dimethyluridine by utilizing $Pb(OAc)_4$ mediated decarboxylation/O-glycosylation reaction to generate anomeric acetate of a tetrahydrofuran.[8a] Moreover, Alvarez-Manzaneda group reported lead(IV) acetate mediated cleavage of β-hydroxy ethers leading to α-acetoxy ethers.[8b] In our approach, we planned to synthesize furanoside portion of varitriol without oxidizing the hydroxymethyl group to carboxylic acid and employing $Pb(OAc)_4$ mediated oxidative cleavage. The schematic plan for the construction of the THF unit of varitriol via $Pb(OAc)_4$ mediated oxidative cleavage of β-hydroxy ether is outlined in Scheme 2.

The synthesis of acetoxylated THF **11** from diastereomerically pure alcohol (**5a**) is depicted in Scheme 3. The furanyl alcohol (**5a**) was converted into corresponding iodide **7** in 89% yield.[9] When furanyl iodide **7** was treated with Et_3N, 10% Pd–C in EtOH under hydrogen atmosphere, it delivered THF **8** in 96% yield. Chemoselective deprotection of acetonide **8** with PPTS (10 mol %) in MeOH afforded the diol **9** in 98% yield. Subsequently, the selective mono TBDPS ether protection was carried out on diastereotopic 1,3-diol to afford mono alcohols **10a**,**b** (dr = 1:1). The treatment of THF alcohols (**10a**,**b**) with lead(IV) acetate and 3.0 equivalents of pyridine in refluxing benzene elicited oxidative cleavage at oxa-quaternary center to afford acetoxy-tetrahydrofuran **11** (dr = 1:0) in 80% yield. Further, compound **5a** was transformed into 1,3-diol **5b** with an overall yield of 78% in 2 steps.

Having sufficient quantity of acetoxy-tetrahydrofuran **11** in hand, we focused our attention on the stereoselective reductive



Scheme 3. Synthesis of acetoxylated-tetrahydrofuran **11** from furanyl alcohol (**5a**).