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ABSTRACT

A facile and stereoselective synthesis of vittarilide–A, having promising antioxidant property was accomplished in 12 linear synthetic steps with an overall yield of 6.34% using a chiral pool approach from naturally available diethyl tartarate. The key reactions employed were diastereoselective vinylation, Sharpless asymmetric dihydroxylation, (2,2,6,6-tetramethylpiperidin-1-yl)oxy radical (TEMPO), bis(acetoxy)iodo-benzene (BAIB) mediated tandem oxidation followed by lactonization and finally esterification under Yamaguchi conditions.

In the year 2005, Wu *et al*. reported[1] the isolation of 20 known and 12 new natural products from the crude methanol extract of whole plant *Vittaria anguste-elongata* Hayata. This plant belongs to Vittariaceae natural products family, is a unique linear grass-like fern which grows on moss covered rocks and trees of low altitude forests and it is aboriginal to Taiwan. This report also revealed that the crude plant extract displays moderate cytotoxicity against human lung cancer, gastric and nasopharynx carcinoma cell lines. One of the constituent from the newly isolated lot, vittarilide-A, a optically active colourless syrup (Figure 1) exhibited moderate antioxidant property with IC_{50} value of 91μM.[1] The unique structural features and bioactivity signifies its importance but poor natural abundance demands a concise and scalable synthetic approach, as true for many natural products. To date only one report is available by Yoda *et al*.[2] Wherein, absolute stereochemistry at C5 was establishment along with the total synthesis from D-gluconolactone in 17 steps. As part of our ongoing reserach on the synthesis of natural products in line with cytotoxic and anti-cancer activity recently[3], vittarilide-A attracted our attention and herein we disclose our successful 12 step linear synthetic approach utilizing diastereoselective vinylation, Sharpless asymmetric dihydroxylation, tandem oxidation followed by lactonization and esterification reactions.

Accordingly we have designed a retrosynthetic analysis (Scheme 1) utilising a chiral pool approach. We envisaged the esterification reaction between an acid **2** and an alcohol **3**, for the construction of desired compound **1**. The alcohol **3** can be easily accessed from *L*-(+)-diethyltartarate **4** by utilising standard synthetic transformations known in the literature.[4]

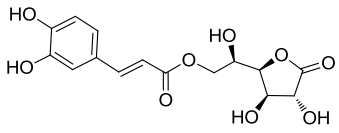

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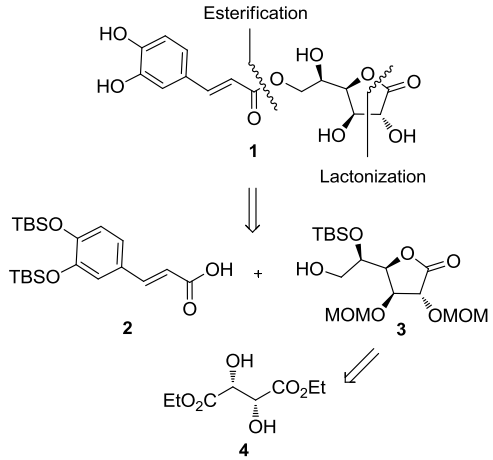
Figure 1. Structure of Vittarilide-A **(1)**

We commenced our synthesis towards intermediate **3** (Scheme 2) starting from inexpensive *L*-(+)-diethyl tartarate **4**, which was protected as its di-Methoxymethyl ether which inturn on reduction with Lithium aluminium hydride (LAH) in THF furnished the corresponding diol, which was further converted to mono benzyl ether **5**.



Scheme 1. Retrosynthesis for Vittarilide-A **(1)**

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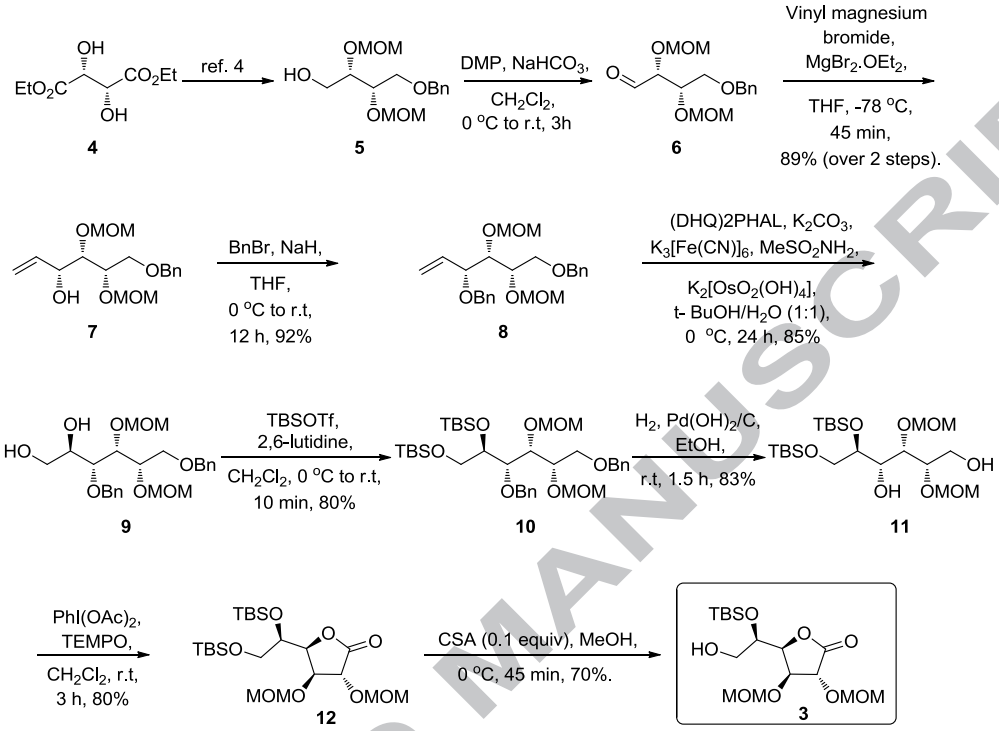
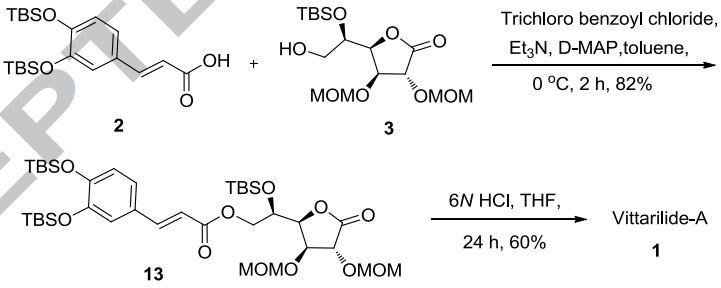
Then, the primary alcohol of **5** was oxidized by Dess–Martin periodinane (DMP) to obtain the corresponding aldehyde **6**. A chelation controlled diastereoselective vinyl Grignard reaction of **6** was performed in presence of $MgBr_2.Et_2O$ at –78 °C producing the desired *syn*-alcohol **7** in satisfactory 89% yield with high diastereomeric excess (de = >95%).[5] Subsequently, the allyl alcohol in **7** was protected as its benzyl ether and the terminal olefin **8** was subjected to Sharpless asymmetric dihydroxylation (SAD) conditions employing potassium osmate (5 mol%) and potassium ferricyanide as a co-oxidant in the presence of a $(DHQ)_2PHAL$ ligand (10 mol%) to furnish the corresponding diol allyltributyl **9** in 85% yield and 92% de.[6]



Scheme 2. Synthesis of lactone intermediate **(3)**



Scheme 3. Synthesis of Vittarilide-A **(1)**

The resulting diol **9** was then protected as its di-silyl ether **10** with TBSOTf[7] and subsequent deprotective hydrogenolysis of the benzyl groups in the presence of palladium hydroxide on carbon[2] afforded the desired diol **11** in 83% yield. It was further subjected to (2,2,6,6-tetramethylpiperidin-1-yl)oxy radical (TEMPO), bis(acetoxy)iodo-benzene (BAIB) mediated tandem oxidation/lactonization[8] producing the awaited gluconate **12**. A regio selective cleavage of the primary TBS ether with camphorsulfonic acid (CSA) in MeOH[9] furnished the required alcohol intermediate **3** in 70% yield.

The coupling of di-TBS protected *trans*-caffoeyl moiety **2**[2] onto the hydroxy group of gluconate **3** was successfully achieved under Yamaguchi conditions[10] (Scheme 3) obtained as protected ester-lactone moiety **13** in 82% yield. Finally the removal of all the MOM and TBS groups using 6 *N* HCl in THF[3d] furnished the targeted natural product vittarilide-A **(1)** in 60% yield. The spectroscopic data and optical rotation of our synthetic compound is in good agreement with the natural as well as the previously synthesized natural product.

In conclusion, we have accomplished the stereoselective synthesis of vittarilide-A **(1)** in a concise manner using diastereoselective vinylation, Sharpless asymmetric dihydroxylation, BAIB/TEMPO mediated tandem oxidation/lactonization and esterification under Yamaguchi conditions as key steps. The implementation of present strategy in synthesizing the other five and six membered polyhydroxy lactone natural products are underway and results will be communicated in details, in near future.

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Supplementary data

Experimental procedures, spectral data and Copies of ^{1}H NMR and ^{13}C NMR spectra are available under supporting information.

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