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Total synthesis of (+)-varitriol via a symmetrical furanose diol as the key intermediate

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ABSTRACT

Alternative, simple and efficient route for (+)-varitriol (**1**), a marine-derived natural product with potent biological activity, has been synthesized from D-ribose. In this synthetic strategy symmetrical diol (**6**) with mono alcohol protection, the key intermediate, was produced in eight steps with 35% overall yield and the significance of **6** as the key furanoside building block for the synthesis of novel analogues of **1** for SAR studies was explained.

Cancer is commonly viewed as, at best, minimally controlled by modern medicine[1] especially when compared to other diseases. The new era in cancer research calls for stronger working relationships between chemistry and biology for the discovery of more selective drugs. This situation emphasized the discovery of natural products with potential anticancer activity, establishing synthetic methodologies for their synthesis and the synthesis of their analogues for SAR studies.

(+)Varitriol (**1**) is a marine derived[2] natural product, which shows significant activity against a variety of tumor cell lines. In particular it shows more than 100-fold increased potency (over the mean toxicity) toward the RXF 393, T-47D, and SNB-75 cell lines and lower potency against DU-145, HL-60, CCRF-CEM, SNB-19, and COLO 205 cell lines, through an unknown mode of action. Hence, in our on-going research program to discover new anticancer agents[3] we aimed to develop a furanoside building block from which we can synthesize **1** and simultaneously its analogues. After a comprehensive literature search, we came to the conclusion that symmetrical diol[4] with selective protection could be the best furanoside building block (**6**) (Fig. 1) for the synthesis of **1** and also its novel analogues of **1** for SAR studies.

The combination of potent biological activity and a relatively straight forward molecular structure of **1** has fascinated many researchers to articulate its synthesis. Initial research efforts by Jenning[5] and Taylor[6] groups, have foreseen the total synthesis of (−)varitriol (**2**). In 2008, Shaw and co-worker[7] described the first total synthesis of **1** starting from methyl D-mannopyranoside. Later, a few more synthetic strategies[8] from methyl D-mannopyranoside, D-mannitol, D-ribose, vinyl oxirane, D-glucose, dimethyl tartarate, ribonolactone and ethyl (S)-lactate, have been demonstrated. The key furanoside building blocks in these methods are depicted in Figure 2. We have reported[9] novel analogues of **1** for

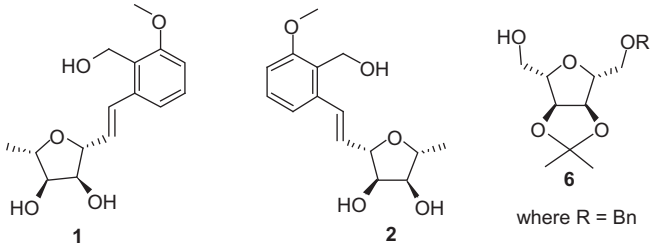

Figure 1. (+)-Varitriol (**1**), (−)-varitriol (**2**) and symmetric diol (**6**).

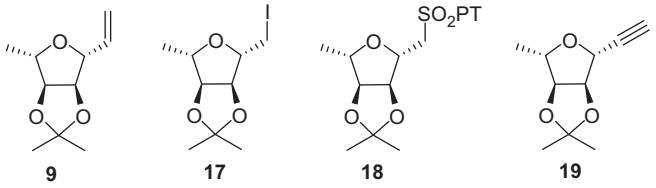

Figure 2. Furanoside building blocks used in the synthesis of (+)-varitriol (**1**).

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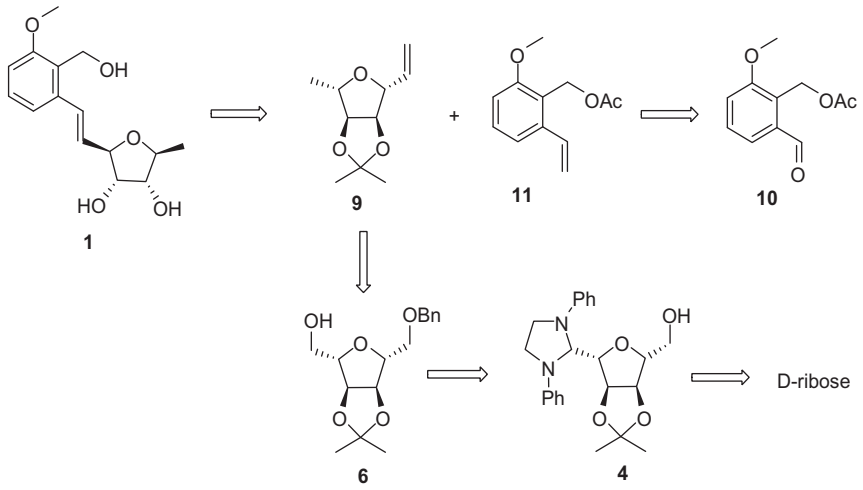


Scheme 1. Retrosynthetic analysis of (+)-varitriol (**1**).

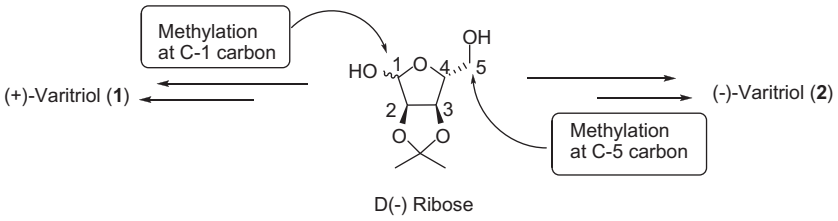
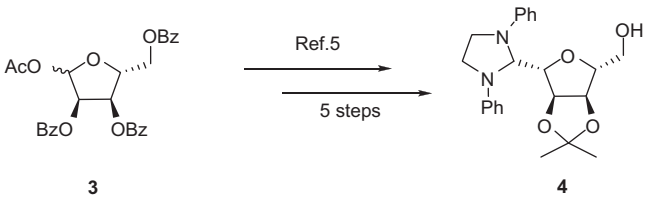
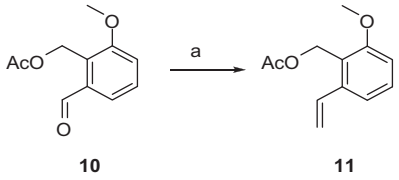


Figure 3. The concept of methylation at **C-1** and **C-5** carbon for the synthesis of (+)-varitriol (**1**) and (−)-varitriol (**2**) from D-ribose.



Scheme 2. Synthesis of alcohol (**4**) from benzyl derivative (**3**) of D-ribose.



Scheme 3. Synthesis of aromatic olefin. Reagents and conditions: (a) Ph_3PCH_3Br, *t*-BuOK, 0 °C to rt, 4 h, 72%.

the first time and evaluated their cytotoxicity. Recently, Annamalai and Indiana[10] have also reported some analogues.

In continuation of our earlier work, we have been successful in our attempt to synthesize the symmetrical furanoside diol (**6**) from D-ribose and furnished the total synthesis of **1** from it.

Our retro synthetic approach of **1** is shown in Scheme 1. We envisaged that the target molecule **1** can be accomplished through cross-metathesis reaction of furanoside unit **9** and aromatic unit **11** was crucial. Aromatic unit in turn could be clearly derived from suitably substituted benzaldehyde **10**. Furanoside moiety **9** can apparently be realized from the key subunit **6**, which in turn could easily be obtained from **4** by the process of reduction and finally **4** was derived from D-ribose.[5]

In the process of synthesizing **6**, we identified that Jenning has obtained the methyl group present in the furanoside unit of **2**, simply by deoxygenating at **C-5** carbon of D-ribose (Fig. 2) and laid an expectation that the synthesis of **1** might be possible from L-ribose whereas in our synthesis, the methylation was carried out at **C-1** carbon of D-ribose thus leading to the formation of furanoside fragment of **1**. The concept of methylation at **C-1** and **C-5** carbon is shown in Figure 3.

The synthesis was initiated with benzyl derivative (**3**) of D-ribose, followed by Jenning synthetic strategy[9] to furnish alcohol **4** in five steps (Scheme 2). Compound **4** was the key intermediate for synthesizing both **1** and **2**.

Alcohol **4** was protected as its Bn-ether by treatment with BnBr to afford compound **5** in a 91% yield. Hydrolysis of **5** with PTSA gave slightly unstable aldehyde[11] which was immediately reduced with sodium borohydride to furnish key intermediate **6**. Tosylation and deoxygenation of hydroxyl moiety of **6** in tandem produced **7** in high yield. Having obtained the required **7**, the next step called for debenzylation using liq.NH_3 and sodium to give alcohol **8** in a 70% yield. The formation of **8** was characterized by the appearance of methyl protons at δ 1.27 as doublet and specific rotation.[5] Oxidation of **8** (to aldehyde) and subsequent Wittig olefination using $Ph_3P{=}CH_2$ allowed the introduction of an additional one carbon fragment, thus affording olefin **9**, furanoside part of **1**, with a 27% yield[7] (Scheme 4).

The synthesis of aromatic part of **1** was initiated from substituted benzaldehyde **10**.[12] Single carbon Wittig olefination of **10** with $Ph_3P{=}CH_2$ in THF gave olefin **11**, aromatic part of **1**, in a 72% yield (Scheme 3).