



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.

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Cancer is commonly viewed as, at best, minimally controlled by modern medicine¹ 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 derived² 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 agents³ 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 diol⁴ 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 Jenning⁵ and Taylor⁶ groups, have foreseen the total synthesis of (–)varitriol (**2**). In 2008, Shaw and co-worker⁷ described the first

total synthesis of **1** starting from methyl D-mannopyranoside. Later, a few more synthetic strategies⁸ 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 reported⁹ novel analogues of **1** for

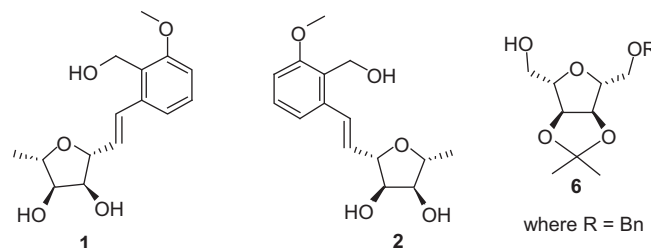


Figure 1. (+)-Varitriol (**1**), (–)-varitriol (**2**) and symmetric diol (**6**).

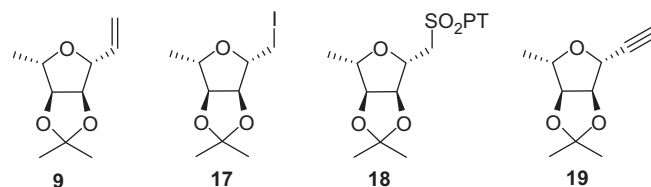
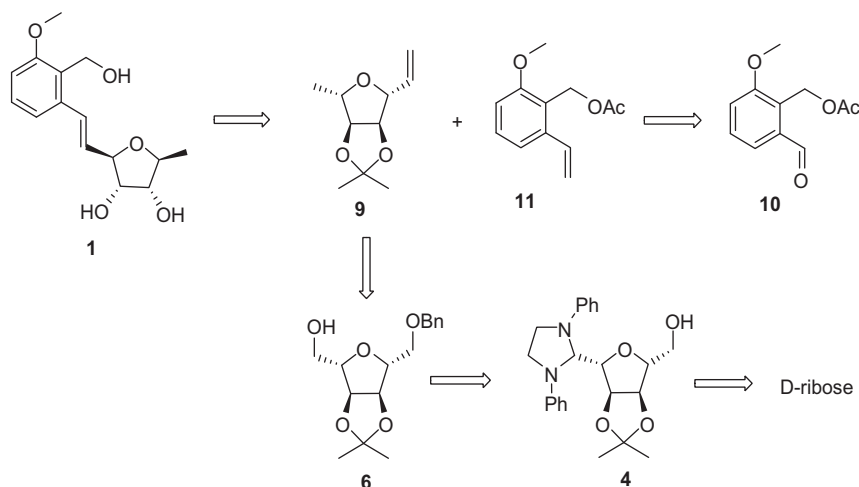


Figure 2. Furanoside building blocks used in the synthesis of (+)-varitriol (**1**).

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

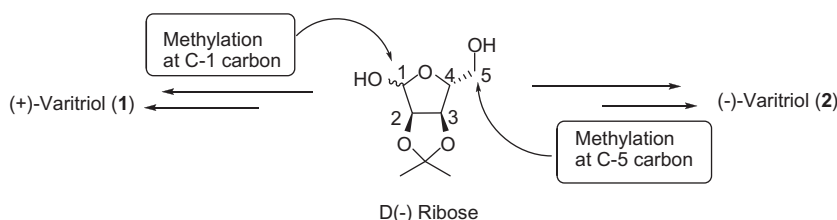
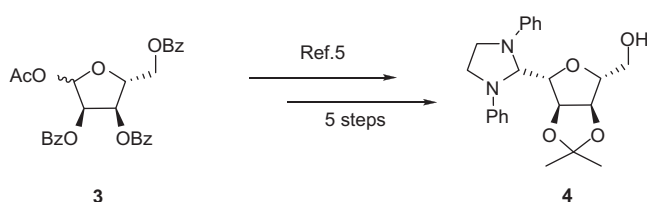
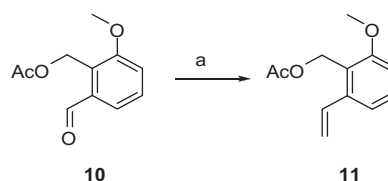


Figure 3. The concept of methylation at C-1 and C-5 carbon for the synthesis of (+)-varitriol (1) and (–)-varitriol (2) from D-ribose.



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

Scheme 3. Synthesis of aromatic olefin. Reagents and conditions: (a) $\text{Ph}_3\text{PCH}_2\text{Br}$, $t\text{-BuOK}$, 0°C to rt, 4 h, 72%.

the first time and evaluated their cytotoxicity. Recently, Annamalai and Indiana¹⁰ 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.

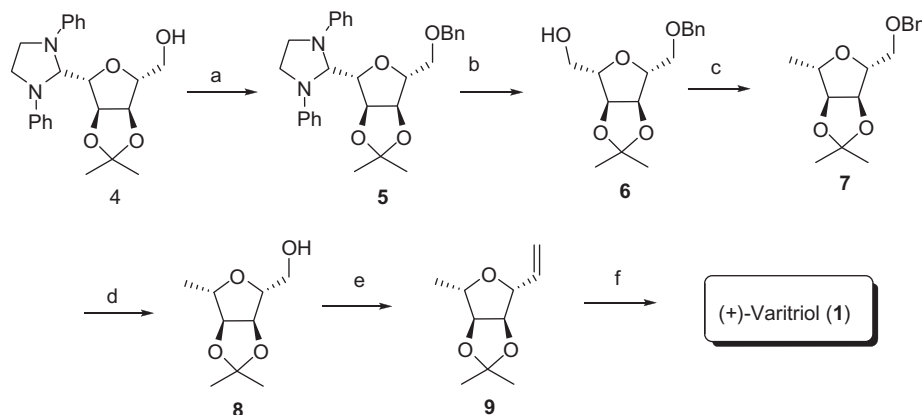
Our retro synthetic approach of 1 is shown in Scheme 1. We envisaged that the target molecule 1 can be accomplished through cross-metathesis reaction of furanoside unit 9 and aromatic unit 11 was crucial. Aromatic unit in turn could be clearly derived from suitably substituted benzaldehyde 10. Furanoside 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 Jennings 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.

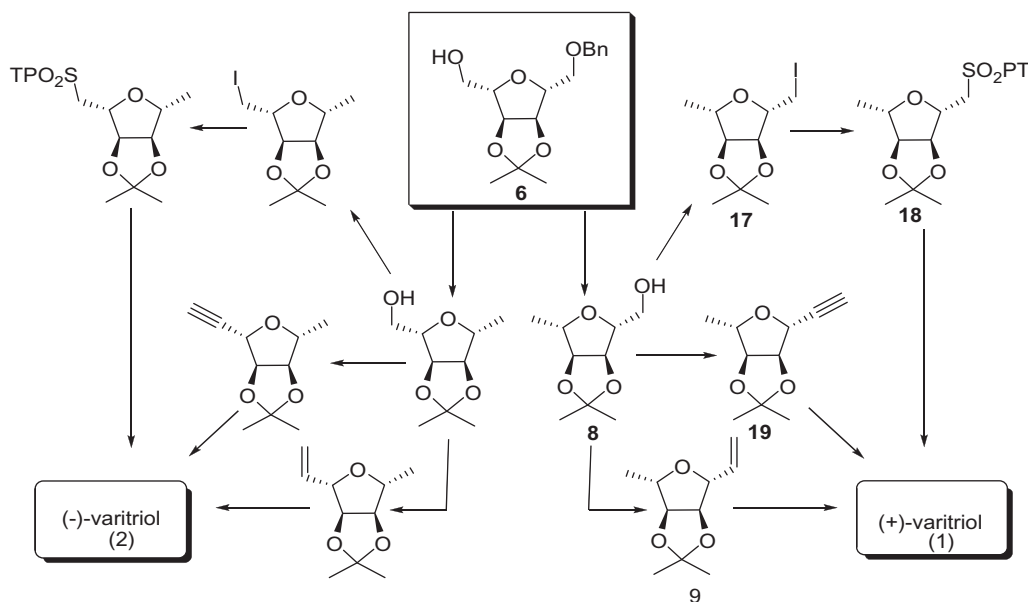
The synthesis was initiated with benzyl derivative (3) of D-ribose, followed by Jennings synthetic strategy⁹ to furnish alcohol 4 in five steps (Scheme 2). Compound 4 was the key intermediate for synthesizing both 1 and 2.

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 aldehyde¹¹ 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 debenzoylation 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 $\text{Ph}_3\text{P}=\text{CH}_2$ allowed the introduction of an additional one carbon fragment, thus affording olefin 9, furanoside part of 1, with a 27% yield⁷ (Scheme 4).

The synthesis of aromatic part of 1 was initiated from substituted benzaldehyde 10.¹² Single carbon Wittig olefination of 10 with $\text{Ph}_3\text{P}=\text{CH}_2$ in THF gave olefin 11, aromatic part of 1, in a 72% yield (Scheme 3).



Scheme 4. Synthesis of (+)-varitriol (**1**) from alcohol **4**. Reagents and conditions: (a) BnBr, NaH, DMF, 0 °C to rt, 4 h, 91%; (b) (i) $p\text{-CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}\cdot\text{H}_2\text{O}$, CH_3COCH_3 , rt, 15 min; (ii) NaBH_4 , MeOH, rt, 2 h, 75%; (c) (i) TsCl, Py, rt, overnight then LAH, dry THF, 75 °C, 5 h, 90.8%; (d) Liq. NH_3 , Na, –78 °C, 30 min, 72%; (e) Ref.^{6c} $(\text{COCl})_2$, Et_3N , CH_2Cl_2 , –78 °C then $\text{Ph}_3\text{PCH}_2\text{Br}$, $t\text{-BuOK}$, 0 °C to rt, 4 h, 18%; (f) (i) **11**, Grubbs second generation catalyst, CH_2Cl_2 , reflux, 18 h, 45%; (ii) 1 M HCl, THF, rt, 3 h, 81%; (iii) K_2CO_3 , MeOH, rt, 1 h, 81%.



Scheme 5. The possible way of synthetic sequence of conversions for the synthesis of (+)-varitriol (**1**), (–)-varitriol (**2**) and their analogues from alcohol **6**.

Finally, with the two olefins **9** and **11** in hand, cross metathesis has been performed using Grubbs IInd generation catalyst. Immediately after coupling, acetonide and acetate groups were deprotected and resulted in desired **1** in a 30% overall yield.

Coming to the significance of alcohol **6**, the alcohols present on either side can be converted into a number of other functional groups, thus making it a very useful building block for the synthesis of novel analogues of **1**. More importantly, the synthesis of **6** was established in eight steps, with 35% overall yield, without any chiral protocols, inversions, racemisations, diastereomers formation, and the usage of any metal-ligand catalysts. These advantages have encouraged us to synthesize **6** as a key furanoside building block for the synthesis of **1**. The possible way of synthetic sequence of conversions¹³ for the analogues of **1** from **6** was depicted in Scheme 5.

In conclusion, a new and alternative protocol for (+)-varitriol (**1**) from D-(–)-ribose has been disclosed through a symmetrical furanoside diol **6**, as the key intermediate. Furthermore, the utility of **6** as a versatile furanoside building block for the construction of novel analogues of **1** has been explained in detail. Efforts are being

made to develop novel analogues of **1** for SAR studies and will be reported in due course.

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Supplementary data

Supplementary data (experimental data) associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2011.10.076](https://doi.org/10.1016/j.tetlet.2011.10.076).

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