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The strategic marriage of method and motif. Total synthesis of varitriol

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ABSTRACT

Detailed in this report are several new efficient synthetic approaches toward the natural product *anti* cancer agent varitriol, culminating in a concise total synthesis. A common theme for these routes is that they employ a new catalytic stereoselective vinyl oxirane ring expansion reaction, which provides rapid access to the common *cis*-2,5-tetrahydrofuran core. The combination of careful synthetic design and proper selection of starting materials results in an excellent marriage between this new method (vinyl oxirane ring expansion) and the motif (varitriol).

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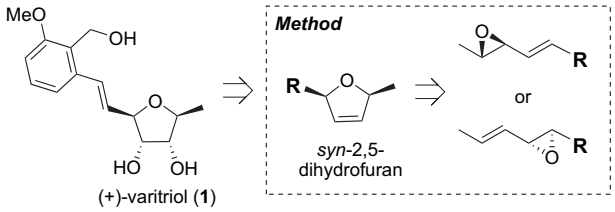
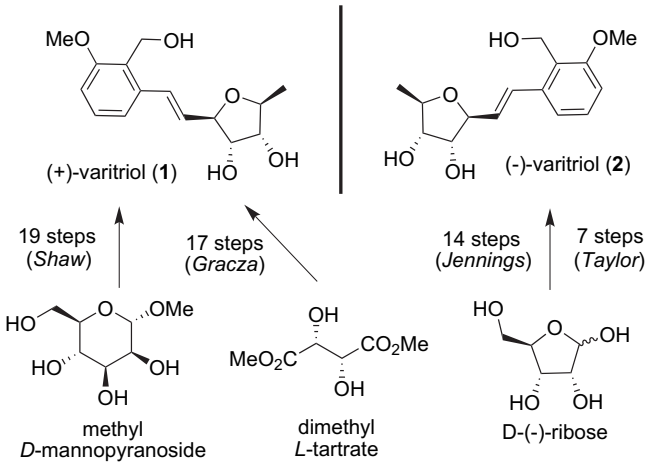
1. Introduction

The marine natural product varitriol (**1**, Scheme 1) was recently isolated and characterized.[1] Screening efforts of varitriol against the National Cancer Institute 60-cell line in vitro panel revealed promising activity against a number of important types of cancer. This encouraging *anti*-cancer activity, coupled with varitriol's heavily substituted tetrahydrofuran core, constitutes an ideal opportunity to showcase the strengths of our new copper-catalyzed vinyl oxirane ring expansion reaction (the 'method'),[2] which we have recently demonstrated can proceed in a stereoselective fashion.[3] In other words, we propose that our method is especially well suited for expediently assembling varitriol (the 'motif'). Of course, this success depends on the judicious choice of substituents (R=?), source material and well matched accompanying reactions. The studies presented herein are aimed at identifying the most suitable vinyl oxirane substrates for accessing varitriol.



Scheme 1. Motif (varitriol) and method (vinyl oxirane ring expansion).

Not surprisingly, given varitriol's attractive biological profile it has attracted the attention of synthetic chemists. Four syntheses of varitriol (**1**)[4] and its enantiomer (**2**)[5] have been completed to date (Scheme 2).[6,7] Interestingly, all these approaches have utilized chiral pool source materials. With the exception of Taylor's synthesis of **2**, the longest linear sequences seem rather long for a molecule like varitriol.[8] Our approach focuses on the rapid synthesis of the dihydrofuran core from non-chiral pool starting



Scheme 2. Chiral pool total syntheses of (+)- and (−)-varitriol.

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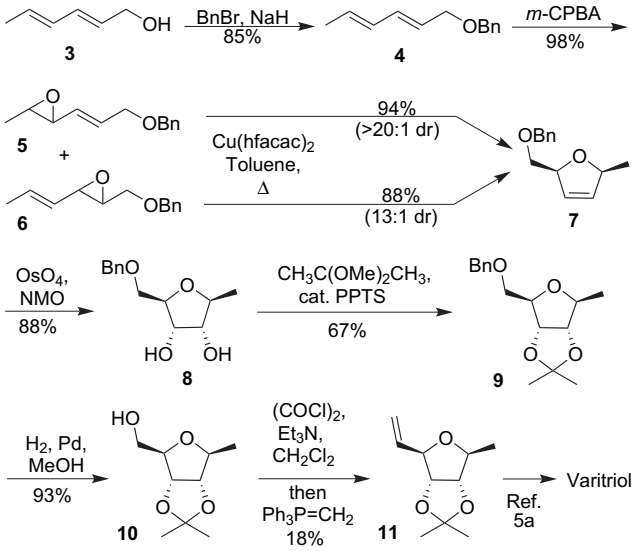
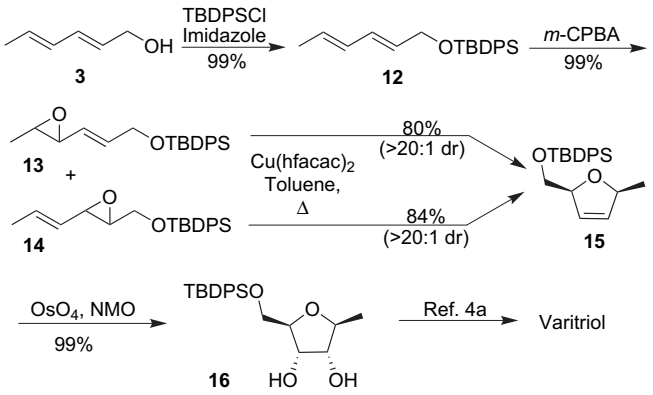
materials[9] with minimal use of protecting groups[10] and redox adjustments.[11]

Our synthetic efforts commenced with epoxidation of benzyl protected dienyl alcohol **4** (Scheme 3). The two vinyl oxirane constitutional isomers (**5** and **6**) were separated and subjected to the copper-catalyzed rearrangement conditions. Using $Cu(hfacac)_2$, both vinyl oxiranes rearranged to form the expected *cis*-2,5-dihydrofuran **7** in excellent yield and with high stereoselectivity.[3] Substrate controlled dihydroxylation (**8**) installed the natural product's other two stereocenters. At this point in the synthesis, the *cis*-diol was protected as an acetonide (**9**) and the benzyl protecting group of the primary alcohol removed by hydrogenolysis. Oxidation of the free alcohol (**10**) afforded an aldehyde, which was immediately subjected to a Wittig olefination reaction (**11**). Tetrahydrofuran product **11** is a known synthetic intermediate in a recently completed synthesis of varitriol by Jennings and co-workers.[5a] This new synthetic approach, allowed us to access **11** in eight steps from dienol **3**, which is four steps shorter than the earlier route from D-ribose. It is important to note, in comparing the two sequences, that our new route has not been executed using chiral starting materials. Literature examples support the notion that our new synthetic sequence lends itself well to established asymmetric epoxidation protocols. For example, Somfai[12] has demonstrated that **4** can be oxidized to (2*R*,3*R*)-**5** in good yield and 95% ee using one of Yian Shi's chiral diooxirane reagents. Advancing this product would provide access to (−)-varitriol (**2**). Interestingly, Shi has demonstrated that when TBS-protected **3** is oxidized, a mixture of (2*R*,3*R*)- and (4*R*,5*R*)- epoxides are produced, with the latter being a perfect match with our method to access (+)-varitriol (**1**).[13]



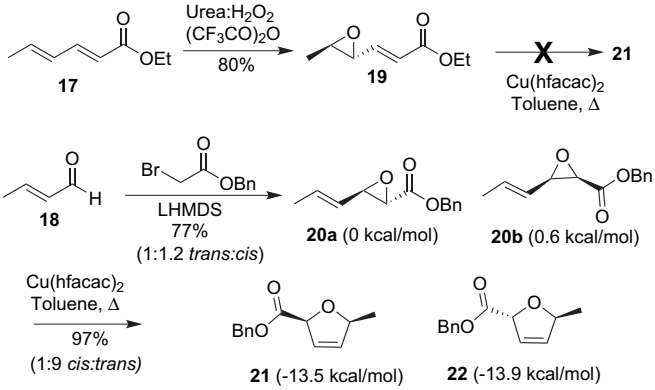
Scheme 3. Formal synthesis of varitriol (first approach).

In Shaw and co-workers total synthesis of natural (+)-varitriol (**1**),[4a] protected triol **16** (Scheme 4) served as a key intermediate. Our stereoselective vinyl oxirane ring expansion strategy seemed like a perfect fit for expediently accessing **16** and to further evaluate the functional group compatibility of our methodology. Furthermore, there seemed to be a need for a better diol protecting group as the aldehyde obtained from **10** performed very poorly in the Wittig reaction.[4a,5a] Shaw demonstrated in his synthesis that this issue could be addressed by using PMB-protecting groups instead of an acetonide to mask the diol. Our synthetic route commenced with silyl protection of dienol **3**. The resulting diene was epoxidized to furnish vinyl oxiranes **13** and **14**, which were readily separable. Both oxiranes ring expanded efficiently in the presence of $Cu(hfacac)_2$ to produce *cis*-2,5-dihydrofuran **15** in excellent yield and better than 20:1 stereoselectivity.[14] This result also establishes silyl group compatibility with our ring expansion conditions. Substrate controlled dihydroxylation using osmium tetroxide afforded **16** in only four steps from dienol **3**, which compares very favorably to Shaw's twelve step synthesis of **16** from methyl D-mannopyranoside.



Scheme 4. Formal synthesis of varitriol (second approach).

Although our new routes to these known synthetic intermediates are shorter than previous ones, they are not without room for improvements. In particular, there should be a way to bypass using a protecting group on the primary alcohol and thus truncate these routes by two more steps. Constitutional vinyl oxirane isomers **19** and **20** (Scheme 5), which can be accessed in a single step from **17**[15] and **18**,[16] respectively, seemed to fit this goal perfectly. Moreover, the significant steric and electronic differences between **19** and **20** might provide us with further mechanistic insights. Interestingly, vinyl oxirane **19** decomposed instead of ring expanding to the expected 2,5-dihydrofuran product **21**, while its constitutional isomers (**20**)[17] ring expanded nicely in high yield. From a mechanistic perspective, this result is interesting. If coordination of the copper catalyst is invoked for the mechanism of this reaction, then this result is not too surprising as the acrylate olefin moiety of **19** would be far poorer olefin donor than the olefin of **20**.[18] Upon further analysis, we learned that under the reaction conditions the *cis*-isomer (**21**) had epimerized to the thermodynamically more stable *trans*-isomer (**22**).[19] Although, the epimerization of **21** to **22** precluded advancement of this product,[20] this new route succeeded in avoiding the use of protecting groups to access a functionalized dihydrofuran product.



Scheme 5. Third synthetic approach toward varitriol.

Is there room for further improvements? Although this last route is potentially very short, the union of the furan moiety and

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