An efficient total synthesis and absolute configuration determination of varitriol†‡

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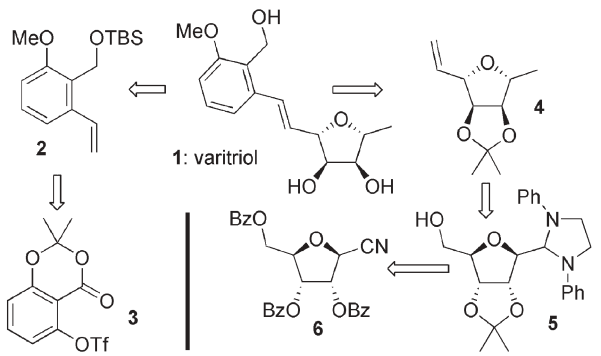
The first total synthesis and the absolute configuration determination of varitriol are described.

First isolated from the marine-derived strain of the fungus *Emericella variecolor* and disclosed in 2002 by Barrero and co-workers, varitriol (**1**) represented a novel, low-molecular weight, natural product that exhibited significant activity against a variety of tumor cell lines.[1] In particular, **1** showed a more than 100-fold increased potency over the mean toxicity toward the RXF 393, T-47D, and SNB-75 cell lines with GI_{50} values ranging from 1.63 to 2.44 $\times$ 10^{-7} M. In spite of the impressive levels of biological activity, the mechanism of action has not yet been established.[2] To date no synthetic approaches to **1** have been reported. Due to the relatively simple structure and coupled with its high level of cytotoxicity, we were interested in pursuing the total synthesis and determining the absolute configuration of **1**.

The retrosynthetic analysis of **1** is delineated in Scheme 1. We initially surmised that the natural antipode might be derived from D-ribose due to the similarities between the bottom portion of **1** and the natural carbohydrate. Given that compound **1** was tested by the National Cancer Institute (NCI) against the 60-cell line *in vitro* panel, we were interested in synthesizing both the natural and unnatural product for further physiological and biological testing. Consequently, our synthetic blueprint required swift access to either enantiomer of **4**, based on the limited availability of L-ribose. Furanoside **6** serves this purpose quite well with two orthogonal aldehyde surrogates present as a protected primary alcohol and a nitrile functional group. Selective manipulation of either moiety resident in **6** should allow for the synthesis of both enantiomers of **4**.

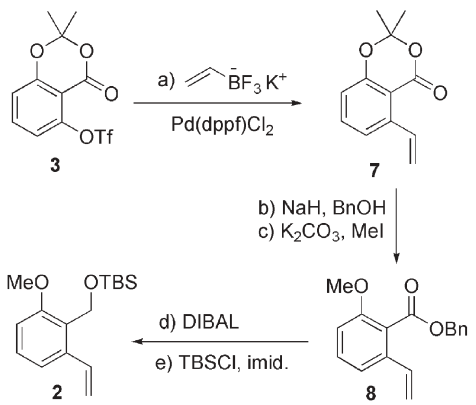


Scheme 1 Retrosynthetic analysis of **1**.

Thus, the β-*C*-furanoside subunit **4** could readily be derived from the aminal **5**, which in turn would originate from the "pseudo" C_2 symmetric compound **6**. We envisaged the final key convergence of the top styrene derivative **2** with the substituted furan **4** *via* an olefin cross-metathesis reaction.[3]

The completion of **1** commenced with the synthesis of the substituted styrene **2** as highlighted in Scheme 2. Hence, Suzuki–Miyaura[4] coupling of the previously reported aryl triflate **3**[5] with potassium vinyl trifluoroborate, utilizing Molander's procedure, readily provided substituted styrene **7** in 93% yield.[6] Subsequent manipulation of the 2,2-dimethyl-1,3-benzodioxan-4-one functional group to the methoxy benzyl ester **8** was accomplished by the treatment of **7** with the sodium anion of benzyl alcohol followed by an ensuing etherification of the free phenol with MeI and K_2CO_3 with a combined yield of 85% over two steps from **7**. Final reduction of the ester moiety resident in **8** with DIBAL-H and protection of the corresponding benzylic alcohol as a TBS ether provided the substituted styrene **2** in 82% yield over two steps.

With the completion of **2**, our attention was then focused on the synthesis of the β-*C*-furanoside subunit **4** as shown in Scheme 3. Following the general procedure of Utimoto, we utilized an



Scheme 2 Synthesis of intermediate **2**. Reagents and conditions: (a) potassium vinyl trifluoroborate (1.1 equiv.), Et_3N (1.3 equiv.), $Pd(dppf)Cl_2$ (5 mol%), 80 °C, 4.5 h, 93%; (b) benzyl alcohol (10 equiv.), NaH (2.1 equiv.), DMF, 0 °C to rt, 30 min, then **7**, 3 h, rt, 97%; (c) K_2CO_3 (2.5 equiv.) MeI (1.2 equiv.), THF, 0 °C to rt, 2 h, 88%; (d) DIBAL-H (2.5 equiv.), toluene, −78 °C to rt, 2 h, 85%; (e) TBSCl (1.2 equiv.), imidazole (3 equiv.), DMF, rt, 4 h, 97%. dppf = bis(diphenylphosphino)ferrocene; Bn = benzyl; DIBAL = diisobutylaluminum hydride; TBSCl = *tert*-butyldimethylsilyl chloride; imid = imidazole.

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† Electronic supplementary information (ESI) available: Full data for compounds **1**, **2**, **4**, **8**, and **12**. See DOI: 10.1039/b603931f

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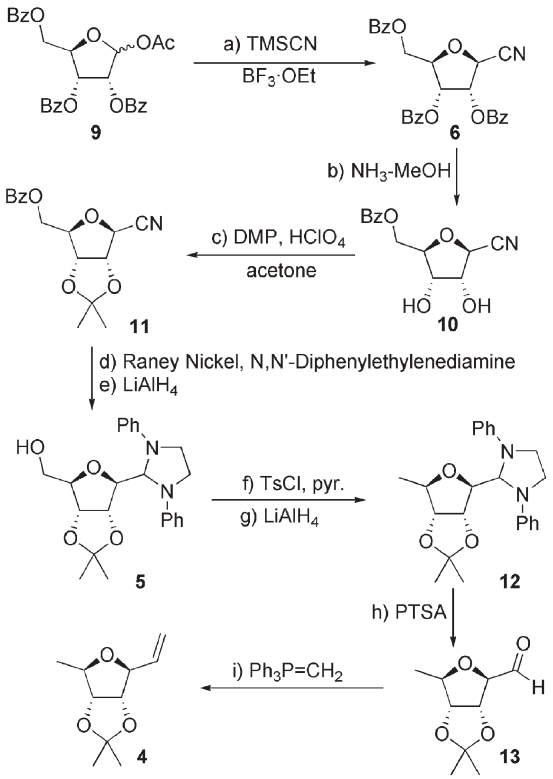
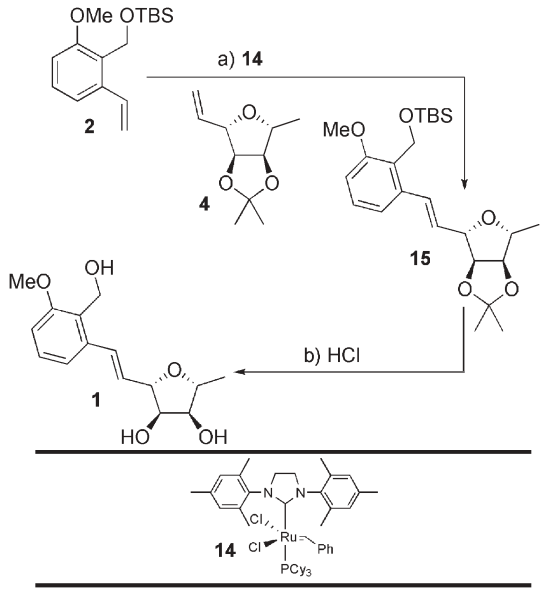


Scheme 3 Synthesis of intermediate **4**. Reagents and conditions: (a) TMSCN (4.5 equiv.), $BF_3{\cdot}OEt_2$ (1.1 equiv.), CH_2Cl_2, rt, 2 h, 85%; (b) NH_3, MeOH, 0 °C, 4.5 h, 82%; (c) DMP (2.5 equiv.), $HClO_4$ (0.5 equiv.), acetone, rt, 2 h, 95%; (d) Raney nickel (20 equiv.), sodium hypophosphite (5.5 equiv.), *N*,*N*′-diphenylethylenediamine (1.4 equiv.), HOAc–pyridine–H_2O (1:2:1), rt, 1 h, 82%; (e) $LiAlH_4$ (3 equiv.), THF, −78 °C, 3 h, 92%; (f) TsCl (2.1 equiv.), pyridine, 0 °C to rt, 24 h, 95%; (g) $LiAlH_4$ (3 equiv.), THF, −78 °C, 3 h, 92%; (h) PTSA (2.5 equiv.), acetone, CH_2Cl_2, 5 min at 0 °C then rt, 1 h, 48%; (i) ^{t}BuOK (2.1 equiv.), methyltriphenylphosphonium bromide (2 equiv.), ether, 12 h, 56%. TMSCN = trimethylsilyl cyanide; DMP = 2,2-dimethoxypropane; TsCl = *p*-toluenesulfonyl chloride; PTSA = *p*-toluenesulfonic acid.

anchimeric assisted nucleophilic addition of a cyanide anion *via* TMSCN to the *in situ* generated oxocarbenium cation derived from **9**.[7] This procedure readily allowed for the stereoselective synthesis of the "pseudo" C_2 symmetric intermediate **6** in an isolated 85% yield which can serve as a divergent point toward both enantiomers of **4**. With **6** in hand, all of the required stereochemistry was in place for the completion of **4**. Selective removal of the secondary benzoate esters by means of dissolved NH_3 in MeOH at 0 °C provided the *syn* diol **10** in 82% yield.[8] Reprotection of the free hydroxyl groups as the acetonide was then readily accomplished upon the treatment of **10** with 2,2-dimethoxypropane and $HClO_4$ to afford the β-*C*-furanoside **11**.

Ensuing reduction of the nitrile functional group present in **11** with Raney nickel coupled with *N*,*N*′-diphenylethylenediamine furnished the corresponding aminal.[8] This was followed by removal of the benzoate ester *via* $LiAlH_4$ to afford intermediate **5** in a combined yield of 75% from **11**. Subsequent tosylation of the free primary hydroxyl moiety resident in **5** and reduction of the



Scheme 4 Synthesis of (−)-varitriol **1**. Reagents and conditions: (a) **14** (5 mol%), CH_2Cl_2, reflux, 18 h, 59%; (b) 1 M HCl, THF, rt, 2 h, 72%.

resultant leaving group with $LiAlH_4$ provided the protected aminal **12** in an 87% yield over two steps. Removal of the aminal in **12** by means of PTSA furnished **13** and resulting olefination of the aldehyde moiety *via* the methylene Wittig reagent allowed for the formation of the desired β-*C*-furanoside **4** with a collective modest yield of 27% from aminal **12**.

With the two key intermediates in hand, the stage was set for final convergence of **2** and **4** and ultimate completion of the target, product **1** (Scheme 4). Thus, treatment of **2** and **4** with Grubbs' second-generation carbene catalyst readily promoted the envisioned cross-metathesis to provide the protected natural product **15** in 59% yield.[9] Final global deprotection of **15** with aqueous HCl in THF furnished varitriol (**1**) in 72% yield. The spectral data (^{1}H NMR, 500 MHz;^{13}C NMR, 125 MHz) and HRMS data of synthetic varitriol were in agreement with the natural sample.[1] However, the optical rotation ($[\alpha]_D^{rt}$ −18.2°, *c* = 0.0033 g ml^{-1} MeOH) confirmed that **1** is the enantiomer of the natural product.

In conclusion, we have completed a highly convergent total synthesis of (−)-varitriol. The late stage convergence allows for the synthesis of a variety of analogues to examine the bioactivity of structurally diverse "varitriol-like" compounds against a collection of tumor cell lines.

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