**Total Synthesis of (+)-Varitriol via Gold-catalyzed Cycloisomerization of Functionalized Allenes**

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**Introduction**

(+)‐Varitriol (+)+1 was isolated in 2002 from the marine‐derived fungus _Emericella variecolor_. It shows a more than 100‐fold increased potency (over the mean toxicity) towards renal cancer, breast cancer and CNS cancer.1 The total synthesis of (+)+1 had been reported in 2008 by Shaw et al.2 and in 2009 by Gracza et al.3 Here, we report a flexible synthetic route to (+)+1, in which we started from an achiral compound and applied a gold‐catalyzed cycloisomerization of α‐functionalized allene as the key step. Several analogues of (+)+1 were also synthesized.

**Retrosynthesis**

Catalytic Katsuki‐Sharpless epoxidation4 (Scheme 2) of enyne 4 provided 5 with 91% enantiomeric excess (ee). The enantiomer of 5, which can be used for the synthesis of (+)+1 and its derivates, was prepared with similar ee of 92%. Allene 7 was synthesized from 6 applying an anti‐stereoselective S$_2$2-reduction catalyzed by copper hydride complex LCuH,5 in which N‐heterocyclic carbene (NHC) is used as the ligand. The precursor of the NHC, imidazolium salt SIMes•HCl, is synthesized in three steps according to Arduengo et al.6 We have recently developed a stereoselective gold‐catalyzed cycloisomerization of α‐olefin, bearing a hydroxy, amino, or thiol group in the α- or β-position, to the corresponding five- or six-membered heterocycles.5 With this method, 7 was conveniently transformed to the 2,5‐dihydrofurane 8 which is accessible by gold‐catalyzed cycloisomerization9 of the α‐hydroxylallene 7. A reduction of the propargyl epoxide 6 catalyzed with NHC‐CuH will provide the key intermediate 9.

**Results**

Phosphonate 3 was synthesized from benzoate derivate 11 (Scheme 4). Reduction of 11 followed by protection and Arbuzov reaction gave the HWE reagent 3. The coupling of 2 and 3 to the disubstituted trans‐olefin 12 was realized by a HWE reaction11 (Scheme 3) at higher temperature. Running this reaction in a microwave oven gave a similar result.15 In both cases no cis‐diastereomer was detected.

Global deprotection of 12 by a standard procedure3 (Scheme 3) furnished the natural product (+)‐varitriol (+)+1. All chemical data are in agreement with those from isolated and synthesized products.1,2 With the same route seven derivates 13‐19 (Scheme 4) were also synthesized.

**Literature**