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 varicocolor. It shows a more than 100-fold increased potency (over the mean toxicity) towards renal cancer, breast cancer and CNS cancer. The total synthesis of (+)-1 had been reported in 2008 by Shaw et al. and in 2009 by Gracza et al.

Here, we report a flexible synthetic route to (+)-1, in which we started from an achiral compound and applied a gold-catalyzed cycloisomerization of functionalized allene as the key step. Several analogues of (+)-1 were also synthesized.

Retrosynthesis

Catalytic Katsuki-Sharpless epoxidation (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 derivatives, was prepared with similar ee of 92%.

The key precursor to the disubstituted trans-olefin 12 was realized by a standard procedure followed by debenzylation and oxidation afforded the chiral aldehyde 10.

Sharpless dihydroxylation transformed the cyclic dihydrofuran 7, which is accessible by gold-catalyzed cycloisomerization of the α-hydroxyallene 7. A reduction of the propargyl epoxide 6 catalyzed with NHC-CuH will provide the key intermediate 7.

Result

(+)-1 can be synthesized from aromatic phosphate 3 and chiral aldehyde 2 utilizing a Hörner-Wadsworth-Emmons (HWE) reaction (Scheme 1). 3 can be prepared by a modified Kamikawa procedure. 2 can be synthesized from 2,5-dihydrofuran 8, which is accessible by gold-catalyzed cycloisomerization of the α-hydroxyallene 7. A reduction of the propargyl epoxide 6 catalyzed with NHC-CuH will provide the key intermediate 7.

Literature