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Synthesis of (±)-Aureol by Bioinspired Rearrangements

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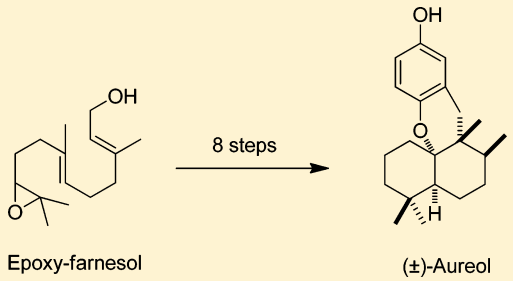
Supporting Information

ABSTRACT: A bioinspired and sustainable procedure for the straightforward synthesis of (±)-aureol has been achieved in eight steps (14% overall yield) from epoxyfarnesol. The key steps are the titanocene(III)-catalyzed radical cascade cyclization of an epoxyfarnesol derivative and a biosynthetically inspired sequence of 1,2-hydride and methyl shifts.



INTRODUCTION

Many biologically active compounds, some of them having a marine origin, are composed of a sesquiterpene unit linked to a phenolic moiety.[1] Prominent examples include (+)-aureol (**1**),[2,3] (+)-stachyflin (**2**),[4] and (+)-strongylin A (**3**)[5] (Figure 1). (+)-Aureol was originally isolated in 1980 by Faulker et al.[2]

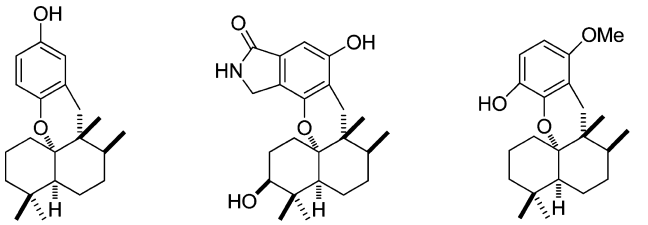


Figure 1. Representative members of the aureol family of sesquiterpenoid natural products.

from the caribbean sponge *Smeonspongia aurea*, and subsequently in 2000 by Fattorusso and his co-workers[3] from another species of caribbean sponge, *Verongula gigantea*. The aureol structure contains a compact tetracyclic ring system, with four contiguous stereocenters and a cis-relationship between the two cyclohexane rings of the decalin fragment. This marine natural product has been shown to exhibit selective cytotoxicity against A549 human nonsmall cell lung cancer cells (IC = 4.3 μg/mL)[6] and anti-influenza-A virus activity (IC = 4.3 μg/mL).[7]

Beside the unique structural features and interesting variety of biological activities of this group of compounds, there is still a need for efficient synthetic methods, as the already described approaches have too many steps or start from natural synthons which are not widely accessible.[8−14]

In recent years, titanocene(III)-catalyzed radical cyclization has become a powerful tool in organic synthesis.[15−18] In fact, this reaction has paved the way to the straightforward synthesis of several terpenes.[19]

RESULTS AND DISCUSSION

As part of our ongoing efforts in the synthesis of biologically active terpenoids of marine origin,[20−23] we were interested in the development of a new concise synthesis of aureol (**1**). It was our intention to use the already proposed biosynthesis of aureol (Scheme 1) as a guideline for our retrosynthetic analysis (Scheme 2).

The biosynthesis of aureol (**1**) presumably involves the stereoselective cyclization of polyene **4** to generate the tertiary carbocation **5** (Scheme 1). This carbocation could then undergo a sequence of stereospecific 1,2-hydride and methyl shifts to produce another tertiary carbocation **6**, which could be stabilized by cyclization with the adjacent hydroquinone to give aureol.

Inspired by this biosynthesis, we deemed that the synthesis of aureol (**1**) could be efficiently achieved through a key titanocene(III)-catalyzed cascade cyclization of the epoxyfarnesol derivate **7** and a new biogenetic-type rearrangement as the pivotal step (Scheme 2).

In this way, our synthesis of aureol (**1**) (Scheme 3) started with the epoxidation of farnesyl acetate following a previously described procedure[24] to form the epoxyfarnesol **7**. One-pot

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