Toward the Total Synthesis of a Sesquiterpene

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Introduction
The sesquiterpene jungianol was isolated by Bohlmann and his group from Jungia malvaefolia.¹ The total synthesis of jungianol was investigated by Hashmi and his group, as an application of gold catalysts, yielding epi-jungianol as major isomer.² Recently, Dethe and Murhade attempted this synthesis, also obtaining epi-jungianol.³ This project aims the total synthesis of (±)-jungianol as main product from 5-methoxy-1-tetralone (1) using a ring contraction reaction promoted by iodine(III) as key step. Similar to this project are the racemic⁴ and asymmetric⁵ total synthesis of the isomer mutisianthol.

Results and Discussion
The initial plan for the synthesis was to transform 5-methoxy-1-tetralone (1) using classic reactions (Grignard, in situ dehydration and hydrogenation) to obtain tetralin 4. However, the hydrogenation step showed problems with reproducibility, and a new route was developed (Scheme 1).

Scheme 1. Preparation of tetralin 4

Iodination of 4 gave iodoarene 5. Stille coupling of 5 with SnMe₄ yielded tetralin 6 (Scheme 3). The next challenge of the synthesis was a benzylic oxidation. Several conditions were tested, however it was not possible to isolate the desired tetralone 7, as a major product (Scheme 2). Thus, we decided to continue the synthesis using 9.

Scheme 2. Benzyllic oxidation of tetralin 6

The dioxidated compound 9 was submitted to several hydrogenolysis conditions. Eventually, a freshly prepared complex of ethylenediamine (en) with Pd/C allowed the chemoselective hydrogenation of 10, yielding a mixture of alcohol 11 and tetralone 7, which was reduced to alcohol 11. After dehydrogenation, the dihydronaphthalene 12 was obtained (Scheme 3).

Scheme 3. Synthesis of jungianol

a. i) t-BuLi, TMEDA, rt., 6 h; ii) ICH₂CH₂I, 0 ºC – rt., 2 h; b. SnMe₄, Pd(PPh₃)₂Cl₂, PPh₃, LiCl, DMF, 160 ºC, 10 min.; c. DMAP, Ac₂O, AcOEt, 2 h; d. i) H₂ (balloon), Pd/C(en), MeOH, 18 h; ii) NaBH₄, MeOH, 0 ºC – rt., 2 h; e. H₃PO₄ (85%), THF, 95 ºC, 1 h.

Conclusions
Dihydronaphthalene 12 was synthesized from 5-methoxy-1-tetralone (1) in nine steps. After ring contraction, affording aldehyde 13, followed by a Wittig and a deprotection step, the target molecule will be obtained.

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