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Asymmetric Synthesis of (*R*)-Sulcatol

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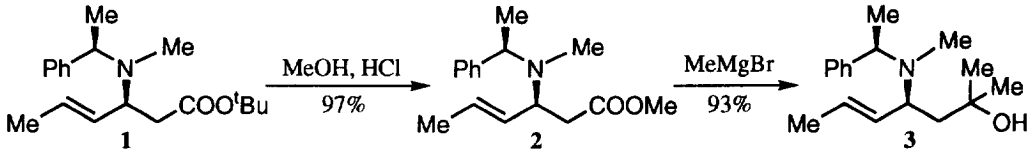
Abstract: The insect pheromone (*R*)-sulcatol, 2-hydroxy-6-methylhept-5-ene, is synthesised *via* a stereoselective conjugate addition of (*R*)-lithium *N*,α-dimethylbenzylamide to *tert*-butyl (*E,E*)-hexa-2,4-dienoate, Grignard addition, and stereospecific Meisenheimer rearrangement. Hydrogenation of the olefin, dehydration of the tertiary alcohol and N–O bond cleavage complete the synthesis. Copyright © 1996 Elsevier Science Ltd

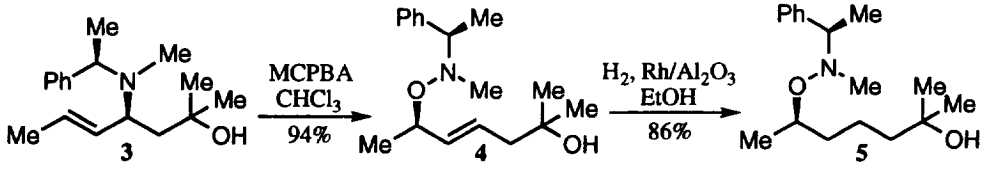
Sulcatol **8** is a male-produced aggregation pheromone of the ambrosia beetle, a pest of economic significance in coniferous forests in western North America. Interestingly, laboratory and field studies have revealed that different species respond to the compound in different enantiomeric excesses. *Gnathotricus sulcatus* produces the (*S*)-pheromone in 30% e.e.,[1] and exhibits a synergistic response to the two enantiomers.[2] Conversely, *Gnathotricus retusus* produces the homochiral (*S*)-enantiomer, and its response is inhibited by the (*R*)-isomer.[3] There has been much interest in the synthesis of sulcatol **8** in enantiomerically pure form,[4] initially for the biological studies above, and later as a potential agent for the trapping of the beetles in pest control programmes. Also, sulcatol has served as an intermediate in the synthesis of other natural products.[5] The asymmetric synthesis of secondary alcohols reported in the preceding communication[6] provides an attractive and concise route for the asymmetric synthesis of sulcatol from *tert*-butyl (*E,E*)-hexa-2,4-dienoate, which we now disclose.

The adduct **1**, prepared, as previously described,[6] by the conjugate addition of (*R*)-lithium *N*,α-dimethylbenzylamide to *tert*-butyl (*E,E*)-hexa-2,4-dienoate, formed the starting point for the synthesis. The *tert*-butyl ester proved resistant to methyl magnesium bromide, and so was transesterified to the corresponding methyl ester **2**, which readily underwent Grignard addition to give the tertiary alcohol **3** (Scheme 1).[7]



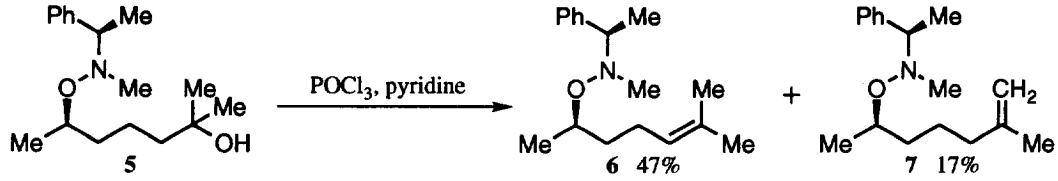
Scheme 1

Treatment of **3** with MCPBA, followed by passage of the reaction mixture through deactivated basic alumina, gave, on standing, the hydroxylamine **4** (Scheme 2). Only one diastereomer of product was detected, consistent with the rearrangement being completely stereospecific. The reaction was run with a deficiency of oxidant (*ca.* 0.9 equivalents), to avoid the possibility of by-products from further oxidation of the rearranged product, and resulted in recovery of 7% starting material. The yield quoted is based on consumed starting material. The hydroxylamine **4** was hydrogenated over a rhodium/alumina catalyst to afford **5**.



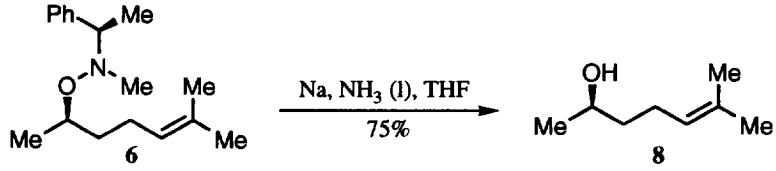
Scheme 2

Dehydration of **5** was examined using a number of reagents, and in all cases the regioselectivity obtained was low. Best results were obtained using phosphorus oxychloride in pyridine, which gave a mixture of **6** and **7** in a ratio of 2:1 (Scheme 3). The two regioisomers could be separated by column chromatography on silica gel doped with 10% silver nitrate.



Scheme 3

Finally the major isomer **6** was treated with sodium in liquid ammonia, affording (*R*)-sulcatol (*R*)-**8** (Scheme 4). The specific rotation obtained for this synthetic sulcatol, $[\alpha]_D^{23}$ = -16.3 (*c* 1.26 in EtOH), was in good agreement with the value reported in the literature,[5a] $[\alpha]_D^{24.5}$ = -16.0 (*c* 1.1 in EtOH).



Scheme 4

Thus a synthesis of (*R*)-sulcatol, employing an asymmetric conjugate addition coupled with a stereospecific Meisenheimer rearrangement strategy, has been achieved.

References and notes:

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7. All new compounds gave satisfactory spectroscopic and microanalytical data.

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