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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 communication⁶ 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



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.



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.



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).



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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