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Synthesis of Optically Pure Pityol - a Pheromone of the Bark Beetle *Pityophthorus pityographus* - using a Chemoenzymatic Route.

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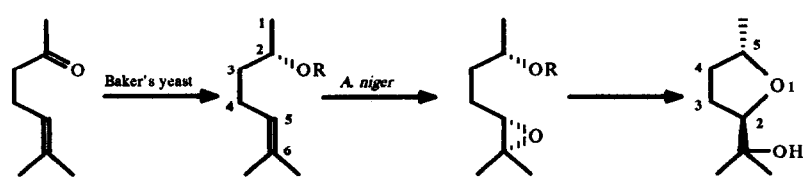
Abstract : A four step synthesis of (2R,5S)-pityol, the pheromone of *Pityophthorus pityographus*, is described using in particular two highly stereoselective microbiologically mediated reactions.

In the course of our work related to microbiogically mediated biooxygenation reactions, we have described recently the stereoselective oxidation of the remote double bond of geraniol (and some other similar compounds) by the fungus *Aspergillus niger*[1] . It is well known in catabolic processes that numerous other strains are able to perform biooxygenation of double bonds but only a few examples of preparative applications have been described[2] . Furthermore, these normally lead to the vicinal diols, probably resulting from *in situ* hydrolysis of an intermediate epoxide formed in a first step. Examples describing accumulation of such an epoxide in the medium are very scarce[3]. We have been interested in applying such a stereoselective biooxygenation to the synthesis of a pheromone of high enantiomeric purity. The target chosen was (2R,5S)-pityol **5**, a male-specific attractant of the bark beetle *Pityophthorus pityographus*[4]. The seven-step asymmetric synthesis of this pheromone has been previously described by Mori and coll.[5] (total yield < 6%), the two key steps of their synthesis being, first, the stereoselective reduction of ethyl acetoacetate with baker's yeast and, second, the thallium (III) induced cyclization of (S)-sulcatol.

Scheme 1



We describe here a four-step synthesis of optically pure **5** starting from prochiral ketone **1** as shown on Scheme 1. This synthetic way includes two reactions mediated by microorganisms, which allow successively the stereoselective reduction of the carbonyl group of **1**, followed by a stereoselective epoxidation of

urethane **3**. Recently, Veschambre and coll.[6] have described the preparation of the (S) enantiomer of sulcatol **2** by asymmetric reduction of prochiral 6-methyl-hept-5-en-2-one **1** with baker's yeast [yield 80 %, ee 94 %, $[\alpha]_{578}^{25}$ + 14 (c 0.03; EtOH)] or, respectively, of the (R) enantiomer using the fungus *Aspergillus niger* (yield 80%, ee 96%). In our hands, Baker's yeast reduction of 5g of **1** led to 3g of (S)-sulcatol **2** [(yield 60%, ee 98.5 %, $[\alpha]_{578}^{25}$ + 15 (c 2; EtOH)]. The enantiomeric excess of **2** has been determined using a chiral g.c. column [40°C, 25m, Lipodex E Octakis (3-O-butyryl-2,6-di-O-pentyl)-γ-cyclodextrin in OV 1701 (1 : 1)]. Since we have shown previously[7] that the presence of a carbamate moiety is necessary for such a biooxygenation to proceed, the (S)-urethane **3** [$[\alpha]_D^{24}$ + 21 (c 2; $CHCl_3$)] was prepared by condensation of (S)-sulcatol **2** with phenylisocyanate in dry hexane at room temperature (yield 71%). This urethane **3** (1g) was then submitted to bioconversion by the fungus *Aspergillus niger*, following the previously described procedure[1a] at neutral pH. Surprisingly, in this case, the product obtained was not the vicinal diol as expected, but we observed instead accumulation of the epoxide (5S)-**4** (50% yield) , [$[\alpha]_D^{24}$ 4 (c 1.7 ; $CHCl_3$)]. In a final step, treatment of the epoxycarbamate **4** with an alcoholic solution of sodium hydroxide (4N) at 80°C during 12 hours led to (2R,5S)-Pityol **5** [$[\alpha]_D^{24}$ + 16 (c 1.4; $CHCl_3$), lit.[5] $[\alpha]_D^{24}$ + 18 (c 1.57; $CHCl_3$)]. This was obtained in a good analytical yield (90%) but, because of its high solubility in water and of its high volatility, the preparative yield was only 35%. The relative trans configuration of this product has been established by comparison with published ^1H NMR literature data, and its 2(R) absolute configuration has been deduced from the sign of its optical rotation[5]. The four stereoisomers of pityol are well separated on the chiral g.c. column described above, showing excellent enantiomeric and diastereomeric excesses (ee = 100%, e.d. = 98%).

This synthesis is interesting for at least three reasons. First (2R,5S)-pityol can be obtained univocally in a high state of optical purity (total yield : 7.5% based on recovered material) by using this four step route. Moreover, each one of the three other stereoisomers of **5** is similarly accessible separately at will, using a different microorganism and/or methodology[1a, 6]. Second, since an inversion of configuration must occur during the intramolecular cyclization of (2S,5S)-**4** to (2S,5R)-**5**, we can conclude that the bioepoxidation of **3** proceeds *via* a perfect stereoselective oxygenation of the *si* face of the double bond, leading to the (2S,5S)-**4** epoxide . Finally, direct obtention of (2S,5S)-**4** instead of (2S,5R)-diol was unexpected with regard to our previous results[1a] and it would be interesting to know why, in this case, enzymatic hydrolysis of the epoxide did not occur. Work is in progress in our laboratory in order to answer this question.

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