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STEREOSPECIFIC C-C-BOND FORMATION WITH RABBIT MUSCLE ALDOLASE - A CHEMOENZYMATIC SYNTHESIS OF (+)-EXO-BREVICOMIN

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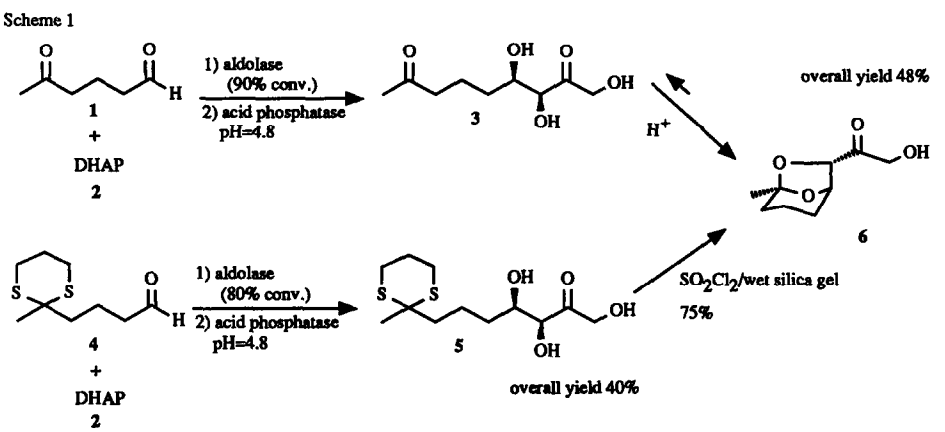
Abstract: (+)-(1*S*,5*R*,7*S*)-Exo-brevicomin **9**, a sex pheromone of the western pine bark beetle, is synthesized using an aldol reaction catalyzed by fructose-1,6-diphosphate aldolase (EC 4.1.2.13) from rabbit muscle as the key step by which the absolute configuration of the target is established.

During the last decades enzymes have been applied in numerous cases to solve prevailing problems in organic synthesis. In addition to the dehydrogenases and hydrolytic enzymes, biocatalysts which promote the stereoselective or even stereospecific formation of C-C-bonds hold a great potential for applications in organic syntheses. The most prominent and easily available representative of these catalytic biomacromolecules is fructose-1,6-diphosphate aldolase (EC 4.1.2.13) from rabbit muscle.[1] The enzyme catalyzes the stereospecific condensation of dihydroxyacetone phosphate (DHAP) **2** with aldehydes. Up to now rabbit muscle aldolase has been applied in the construction of various carbohydrates and carbohydrate-like compounds.[1] However, syntheses of non-carbohydrates using this enzyme have not been reported. We here describe its first application for this purpose, namely the construction of (+)-exo-brevicomin, a sex pheromone of the western pine bark beetle *Dendroctonus brevicomis*.

Several syntheses of brevicomin, which represents an inner ketal of (6R,7R)-6,7-dihydroxy-2-nonanone have been reported.[2] The absolute configuration of the diol unit corresponds to the stereochemistry which is built up stereospecifically in all known aldolase catalyzed reactions. The target thus should be available from the product of the aldolase- mediated reaction between 5-oxohexanal[3] **1** and DHAP **2**.

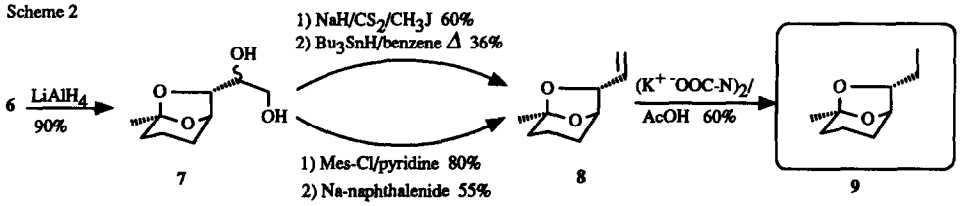
Scheme 1



Rabbit muscle aldolase accepts the ketoaldehyde **1** and its 5-dithioacetal **4** as substrates and catalyzes their condensation with DHAP (Scheme 1; **4** was prepared by alkylation of 2-methyl-1,3-dithiane with 4-chlorobutyraldehyde ethyleneacetal (80%) and subsequent treatment with 3N H_2SO_4 (60%)). In the enzymatic transformations the highest conversion rates are achieved at pH=6.3 with 10 mmolar DHAP solutions (prepared according to the method of Effenberger and Straub[4]). In addition, both aldehydes are used in a threefold excess and in the reaction with the selectively protected carbonyl compound **4** 10 vol% of DMSO serve to enhance the solubility of the aldehyde. Under these conditions after 12 h enzymatic assays indicate 90% conversion for **1** and 80% conversion for **4**. For a convenient separation of the aldol adducts they are precipitated as barium salts. The phosphate groups finally are removed with acid phosphatase at pH=4.8 giving **5** and a mixture of the triol **3** and the bicyclic compound **6**, respectively. The triol can be converted to the acetal by treatment with 1N $HClO_4/CH_2Cl_2$. From **5** the dithiane group can be removed by treatment with SO_2Cl_2 in the presence of wet silica gel[5] and the brevicomin precursor **6** is formed directly. The aldol adducts are characterized by elemental analysis and ^1H- and the ^{13}C-nmr spectra which prove that in the aldolase-catalyzed process only a single diastereomer is formed.

Thus, the enzymatic aldol reaction and the subsequent cyclization established the stereochemistry of the desired bicyclo[3.2.1]octene system and to complete the synthesis of brevicomin the side chain had to be deoxygenated. This could be achieved by a reduction of the keto group, elimination of the resulting diol to the olefin and reduction of the double bond (Scheme 2).

Scheme 2



The α-hydroxy ketone moiety in **6** was reduced to the vicinal diol **7** in high yield with $LiAlH_4$ in ether during which the two diastereomers were formed in a ratio of 2:1. For the desired conversion of the glycol to an ethyl group it was first transformed into an olefin. To effect this reaction we synthesized the bis-xanthate. However, the subsequent treatment with tributyltin hydride in refluxing benzene[6] gave the olefin **8** only with unsatisfactory results (Scheme 2). Significantly higher yields could be obtained by acylation of the diol with methylsulfonyl chloride (Mes-Cl) to give the bis-mesylate and treatment of this compound with sodium naphthalenide[7] in ether. Finally, reduction of the double bond with diimide[3] yielded (+)-exo-brevicomin **9**. A comparison of its specific rotation ($[\alpha]_D^{22}$= 72.3° (c=1.2, ether)) with literature data ($[\alpha]_D^{26}$= 84.1° (c=2.2, ether)[8]; $[\alpha]_D^{21}$= 67.7° (c=1.0, ether)[9]) proved its stereochemistry and the absolute configuration of the adducts formed in the aldolase-catalyzed process.

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