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# A Short Enantioselective Synthesis of 1-Deoxy-L-xylulose by Antibody Catalysis

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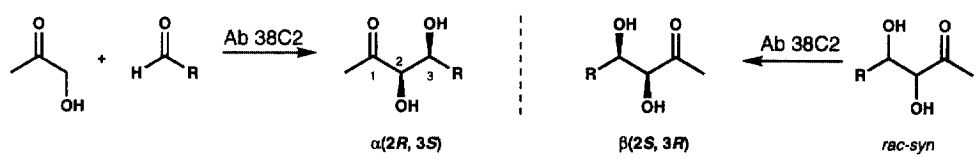
*Abstract: A new efficient synthesis of 1-deoxy-L-xylulose (1) is presented. The key step is achieved by a highly enantioselective aldol addition of hydroxyacetone to benzyloxyacetaldehyde via antibody catalysis. The synthesis described here should provide a convenient route to isotopically labeled derivatives.* 

The increased attention in the literature recently given to 1-deoxyxylulose has prompted us to report our results concerning the synthesis of this important carbohydrate. This carbohydrate was first isolated from *Streptomyces hygroscopicuus* in 1976.[1] 1-Deoxy-D-xylulose has been found to be an intermediate in the biosynthesis of thiamin (vitamin $B_1$)[2] and pyridoxal (vitamin $B_6$)[3]. Both L- and D- enantiomers are synthesized by a wide range of microorganisms from pyruvic acid and L- or D- glyceraldehyde, respectively.[4] Recently this sugar has been found to be an alternate non-mevalonate biosynthetic precursor to terpenoid building blocks.[5]

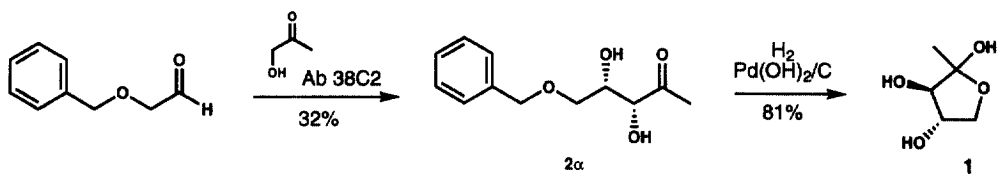
Several syntheses of both enantiomers of 1-deoxyxylulose have been reported to date, including one involving isotopic labeling.[4,6-8] Some of these are multi-step syntheses with low overall yields. Here we report a new highly efficient enantioselective synthesis of 1-deoxy-L-xylulose utilizing the commercially available aldolase antibody 38C2. This antibody catalyzes over 200 different aldol and *retro*-aldol reactions, usually with excellent enantioselectivities.[10] Hydroxyacetone is one of the best aldol donors for antibody 38C2. This is remarkable in the context that no other catalyst, chemical or biological, is capable of using hydroxyacetone as a donor substrate for the aldol reaction. As a general rule we found that hydroxyacetone reacts with different aldehydes, highly regio-, diastereo-, and enantioselectively, to give the corresponding α-(*2R,3S*)-dihydroxy ketones. The corresponding β-(*2S,3R*)- isomer can be obtained from the racemic mixture *via* 38C2 catalyzed enantioselective *retro*-aldol reaction (Scheme 1). This strategy has been successfully demonstrated with the kinetic resolution of many aldols and in the total synthesis of ten different brevicomins.[10d,e]




**Scheme 1**

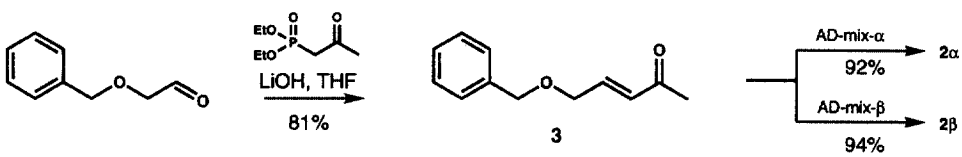
0040-4039/99/$ - see front matter 
*PII:* S0040-4039(98)02699-9

Antibody 38C2 catalyzed aldol addition of hydroxyacetone to commercially available benzyloxyacetaldehyde afforded α,β-dihydroxyketone **2α** in 32% isolated yield. This reaction used very low catalyst loading, 0.04 mol%, and was worked up after conversion of 56% of the aldehyde. The reaction rate had slowed at this point, probably because of minor oxidation of **2α** to the corresponding 1,3-diketone. β-Diketones bind to the active site lysine of the antibody and react to form enaminones, potently inhibiting the catalyst. As observed in earlier cases, some amount of the *anti* diastereomer was formed. In this case only 7% of the undesired *anti* product was observed, however silica gel chromatography furnished the pure product. Ketone **2α** was easily transformed to 1-deoxy-L-xylulose (**1**) by hydrogenation (Scheme 2).[11]




**Scheme 2**

In order to determine the enantiomeric purity of the aldol product, we synthesized reference compounds as shown in Scheme 3. Horner-Wadsworth-Emmons reaction of diethyl-2-oxopropyl-phosphonate with benzyloxyacetaldehyde gave the known olefin **3** which was dihydroxylated according to the Sharpless procedure to give reference aldols **2α** and **2β** in high ee's.[12,13] Sharpless AD reactions were purposely performed under suboptimal conditions, the reaction was performed at room temperature, in order to use the small fraction of the undesired enantiomer formed under these conditions as a chromatographic standard.




**Scheme 3**

The enantiomeric excess of dihydroxyketone **2α** was determined by chiral HPLC analysis using a chiracell AD column and found to be 97% ee (Figure 1). Absolute configuration was assigned by comparison with authentic samples from Sharpless AD.

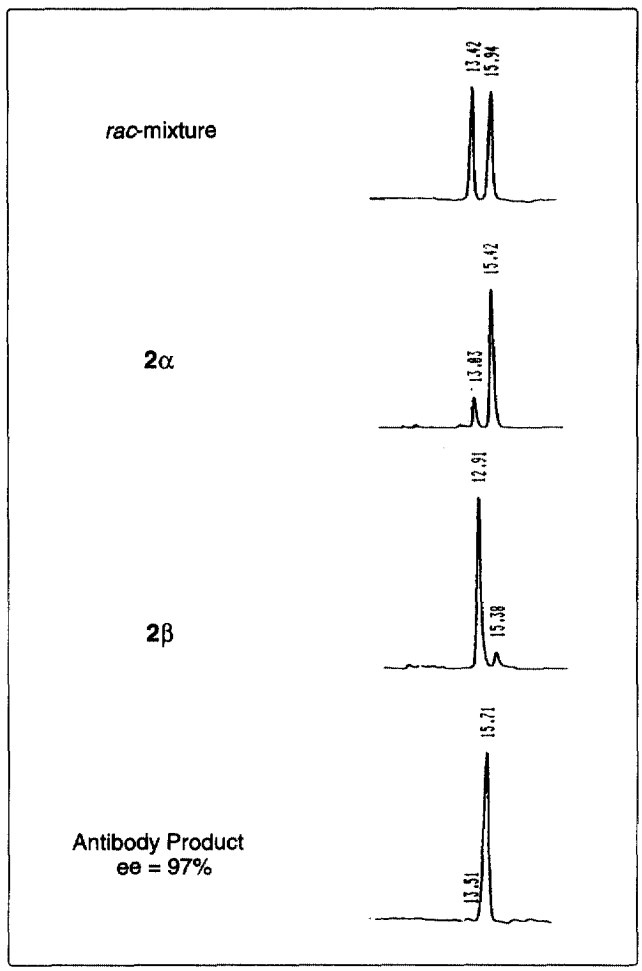



**Figure 1**. Determination of the absolute configuration and enantiomeric purity of aldol **2α** from the antibody catalyzed reaction. Chiracell AD column (12% *i*-PrOH/hexane, 1 ml/min, $\lambda = 254$ nm).

In conclusion we have shown here a new synthesis of 1-deoxy-L-xylulose. This two step synthesis is the shortest reported to date. The key step has been achieved through a highly diastereo- and enantioselective antibody catalyzed aldol reaction using hydroxyacetone as aldol donor. Antibody 38C2 (commercially available from Aldrich) is the only known catalyst that can catalyze the aldol addition of unprotected hydroxyacetone to an aldehyde. The preparation of isotopically labeled 1-deoxyxyluloses, required for further biological studies, can easily be envisioned by using our synthetic methodology and labeled benzyloxyacetaldehyde and/or hydroxyacetone.[9]

**Acknowledgement**

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11. Benzyloxyacetaldehyde (80 mg, 0.53 mmol) in ) in ) 0.5 mL of acetonitrile, was added to 9 mL of a solution of antibody 38C2 (35 mg, 0.23 μmol) in PBS (phosphate buffer saline, 100 mM), followed by the addition of of hydroxyacetone. (0.5 mL, 6.3 mmol). After 48 hr at room temperature the reaction reached 56% conversion and the mixture was freeze dried. The remaining residue was extracted with methylene chloride. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (silica gel, ethyl acetate/hexane, 1/1) to give pure **2α** (39 mg, 0.17 mmol, 32%) in 97% ee. Benzyl ether **2α** (39 mg, 0.17 mmol) was dissolved in 1 mL of methanol and hydrogenated with a catalytic amount of palladium hydroxide on carbon. After two hr, the mixture was filtered through celite and the solvent was removed under reduced pressure to give pure 1-deoxy-L-xylulose (19 mg, 0.14 mmol, 81%).
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