Oxepane Synthesis Along a Disfavored Pathway: The Rerouting of a Chemical Reaction Using a Catalytic Antibody

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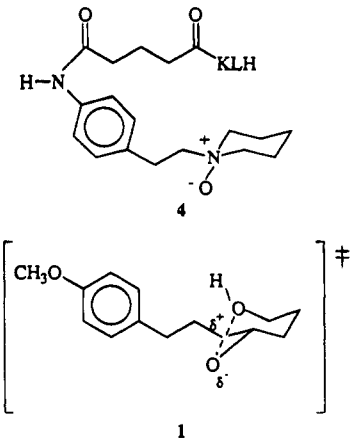
One of the many goals of antibody catalysis is to provide reagents which are useful in organic synthesis. Toward this end, an important recent advance has been the development of antibody catalysts that can steer a chemical transformation along a course that otherwise would be energetically disfavored.[1-3] Here, we describe how this approach can be utilized to develop a facile method for construction of 3-hydroxyoxepane rings from simple hydroxy epoxides.

Hydroxyoxepanes are a common structural motif found in many biologically active substances.[4] One can envisage the construction of such compounds from the corresponding hydroxy epoxide (Scheme 1).

At first this method seems particularly attractive when one considers that the olefin can be epoxidized enantiospecifically using the methodology pioneered by Sharpless,[5] thus allowing the experimenter to set the desired stereochemistry for subsequent transformations. However, this rather attractive approach suffers from the fact that the ring closure reaction greatly favors formation of a pyran ring instead of the desired oxepane. Such regioselectivity is well documented and has come to be known as "Baldwin's rules" for ring closure[6] (Scheme 2).

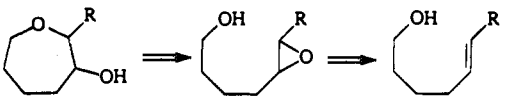
Previous attempts to synthesize oxepanes from the corresponding epoxy alcohols have met with varying success.[7,8] In fact, the use of epoxy alcohols for the synthesis of seven-membered cyclic ethers has largely been abandoned in favor of more difficult, albeit higher yielding routes.[4b,9]



4 1

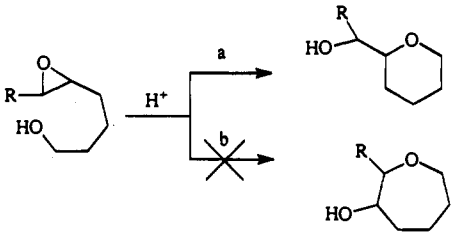
Figure 1. Comparison of hapten **4** with the possible transition state leading to the formation of **2**.

Scheme 1. Retrosynthetic Approach to the Synthesis of the Oxepane Ring System[a]

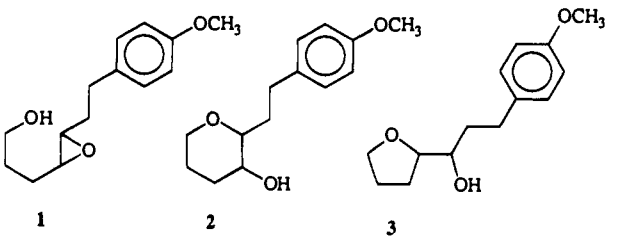


[a] Guidelines outlined by Baldwin obviate this methodology in most cases because 6-*exo*-tet are favored over 7-*endo*-tet ring closures.

Scheme 2. Closure along Path a (*exo*-ter) Predominates That of Path b (*endo*-tet), as Predicted by Baldwin's Rules



Recently, we developed an antibody (26D9) that catalyzes both regio- and stereoselective closure of epoxy alcohol **1** to form the tetrahydropyran **2**.[1] When the reaction is carried out without the antibody, **3** is formed in >95% yield. Thus, the antibody-catalyzed formation of **2** is in formal violation of Baldwin's rules.



1 2 3

The hapten **4**, used to elicit 26D9, was designed to induce an antibody that interacted with critical features of the rate-limiting transition state (Figure 1). The conformation of the piperidinium ring was expected to induce antibodies that stabilize the chairlike conformation to the substrate thought to exist during the ring closure. The *N*-oxide functionality was used to mimic the developing changes expected in the transition state so as to induce complementary charges that decrease the energy of the reaction. An additional feature of the design is that product inhibition should be minimized due to the charge difference between **2** and **4** (Figure 1).

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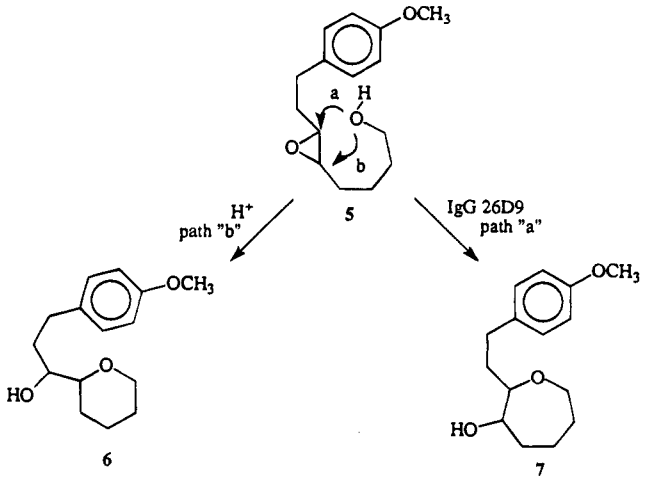
Scheme 3. Antibody-Catalyzed (Path A) and Acid-Catalyzed (Path b) Reaction of **5**



Calculations carried out by Houk et al.[10] predict that the placement of the charge distribution rather than the incorporation of a six-membered ring should be the important design features in **4**. The central idea stemming from these calculations is that antibody catalysis might be relatively indifferent to some structural components of the substrate so long as the mechanistic parameters remain constant. Thus, if most of the interactions between **1** and the antibody take place through the binding of the phenyl and epoxide moieties, the length of the methylene tether might not be important, and the more difficult synthesis of larger cyclic ethers should be allowed.

Consistent with the guidelines put forth by Baldwin[6] and others,[11-16] substrate **5** undergoes 6-*exo*-tet ring closure in preference to the 7-*endo*-tet process to yield almost exclusively **6** (ca. 98:2) when catalyzed by acid in both aqueous solution and organic solvents[1,3,17] (Scheme 3). However, when the reaction is carried out in the presence of antibody 26D9 (50 mM PIPES, pH 6.6), the epoxide opening occurs with almost complete regiocontrol to give a vastly different product distribution in that now instead of **6**, **7** is formed in >98% yield. In addition, the opening occurs stereoselectively, with an enantiomeric excess of 78%.

The initial rate of ring closure catalyzed by antibody 26D9, when measured as a function of substrate **5** concentration, followed Michaelis–Menton kinetics. The Michaelis constant K_m, the maximum rate V_{max}, and the catalytic rate constant k_{cat} values were 196 μM, 1.77 μM min^{-1}, and 0.89 min^{-1}, respectively. Comparison of k_{cat}/k_{uncat} was not possible because in the uncatalyzed reaction, formation of the oxepane **7** was undetectable under our assay conditions. The structural assignment for **7** was verified by co-injection of an independently synthesized sample into the HPLC, utilizing a chiral stationary phase analytical column. The structure was confirmed by direct comparison of the NMR spectra of the product of the antibody-catalyzed reaction to the spectrum of the material synthesized by an independent route.[18] The absolute stereochemistry for the antibody-catalyzed product was determined by converting the corresponding asymmetric dihydroxylation products of the starting olefin to their respective epoxides using both the α and β AD mix followed by double inversion dehydration as described by Sharpless and Kolb.[5] The antibody preferred the *R,R* epoxide over its *S,S*, antipode. The absolute configuration of the major oxepane formed was found by NMR to have the *S,R* configuration consistent with a process that proceeds by inversion at the reacting center.

The results presented here again illustrate how an interplay between libraries of binding molecules and the principles of chemical reactivity can be utilized to generated new catalysts that can reroute chemical reactions. An important point is that, since the catalyst is induced by the experimenter, one has a deeper appreciation for the probable distribution of binding energy than one would have for an enzyme evolved in nature. In the present case, knowledge of the probable mode of binding allowed an intelligent choice of alternative substrates. The ability to use a single enzyme for multiple substrates in a rational way is attractive chemically because it allows the enzyme and substrate to be paired on the basis of detailed binding interactions rather than chance.

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Supplementary Material Available: Experimental procedures and analytical data for the synthesis of **4–7** (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(18) Approximately 25 mg of enantiomerically pure sample was collected from the HPLC. However, it is possible to gather gram quantities using a device previously described by us (C.G.S. and K.D.J., ref 3).