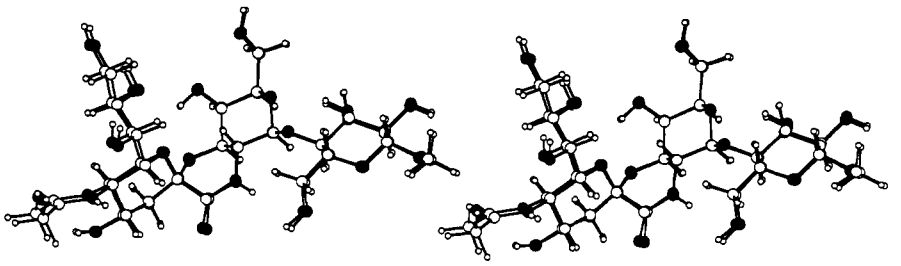
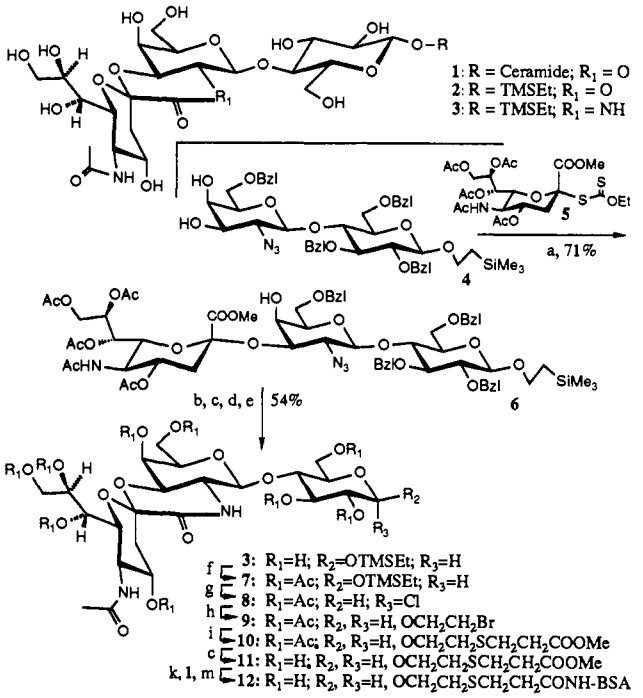


Figure 1. Stereoview of the superimposed low-energy [MM2(91)] boatlike conformers of the methyl glycosides that correspond to **2** and **3**.

Scheme I[a]



[a] (a) $CF_3SO_3Ag/MeSBr/CH_3CN/CH_2Cl_2$/molecular sieves (3-Å)/2 h, then iPr_2NH/−78 °C/1 h. (b) $NiCl_2{\cdot}6H_2O/H_3BO_3/NaBH_4$/EtOH/0 °C/20 min. (c) MeONa/MeOH/22 °C/12 h. (d) Pyridine/22 °C/12 h. (e) H_2/Pd–C, 10%/1 atm. (f) Ac_2O/pyridine-/22 °C/24 h. (g) $Cl_2CHOMe/ZnCl_2/CHCl_3$/22 °C/12 h. (h) $BrCH_2CH_2OH/CF_3SO_3Ag$/molecular sieves (4 Å)/CH_2Cl_2/N_2/−28 → 22 °C/16 h. (i) $HSCH_2CH_2COOMe/Cs_2CO_3/N_2$/DMF/22 °C/2.5 h. (k) H_2NNH_2/EtOH/22 °C/12 h/freeze drying. (l) *t*-BuO-NO/HCl–dioxane/$HOSO_2NH_2$/DMSO. (m) BSA/pH ~9 buffer/22 °C/16 h/dialysis and freeze drying.

DMSO-d_6/D_2O 98:2[11]; 4.28 for **2**, 4.32 for **3**, and 4.32 for **11**, all in D_2O). Such deshielding has been observed[13,14] for ring protons that are in van der Waals contact (≤2.7 Å) with a hydroxyl, carbonyl, or ether oxygen atom. According to MM2 calculations, it is only the boatlike conformations of GM_3 lactone and lactam that place H-4″ in van der Waals contact with the carbonyl oxygen atom. (ii) In the chairlike conformation (Dreiding models), H-3″eq and H-3′ are closely situated (~2.2 Å); however, no strong NOE effect was observed, thus supporting the boatlike conformation (a ROESY experiment suggested a H-3″eq/H-3′ distance of 3.7–4.2 Å). (iii) A molecular mechanics [MM2-(91)[15,16]] calculation, where both a chair and a boat were used as starting conformations, resulted in boatlike conformations in both cases, with lactones as well as lactams (H-3″eq/H-3′ distance ~4 Å).

Superimposition and RMS fitting[16] of the low-energy boat conformations of the methyl glycosides corresponding to **2** and **3** (using all ring atoms) showed them to have very similar overall shapes (RMS = 0.097 Å), as depicted in Figure 1.

Acknowledgment. This work was supported by the Swedish Natural Science Research Council.

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Highly Enantioselective Protonation Catalyzed by an Antibody[1]

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One of the goals of antibody catalysis[2] is to facilitate unique chemical transformations. Herein we report an antibody which catalyzes the carbon protonation of a prochiral enol ether. This catalytic system allows highly enantioselective proton delivery, thereby accomplishing a reaction which to date has remained difficult for conventional organic chemistry.

The enantioface selective protonation of prochiral enol derivatives is a very simple and attractive route for the preparation of optically active carbonyl compounds. Examples have been reported where stoichiometric protonation of a metal enolate by a chiral proton source at low temperature leads to optical yields from 20 to 85% ee.[3] Enantioselectivities between 41 and 96% ee for enol protonation were reported for the yeast esterase catalyzed hydrolysis of 1-acetoxycycloalkenes.[4] Recently, an antibody from our laboratories was shown to catalyze a similar transformation with 42% ee.[5] All of these reactions involved enolates under basic conditions. The acid-promoted hydrolysis of enol ethers is an interesting alternative which has not been investigated for enantioselectivity.[6] Hydrolysis of enol ethers

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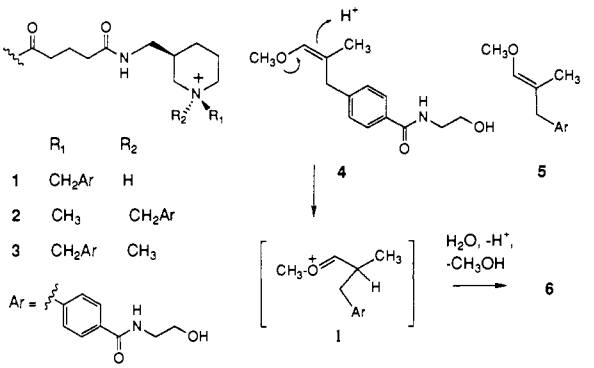


Figure 1. Structures of the racemic haptens **1**, **2**, and **3**,[8] prochiral enol ether substrates **4** and **5**, and their hydrolysis via oxocarbonium ion I.[7]

Table I. Kinetic Parameters of Antibody 14D9 for Substrates **4**, **5**, and **7**

substrate	K_m, 10^{-6} M	k_{cat}, s^{-1}	k_{cat}/k_{uncat}	ee, %[c]
4[a]	340	9.5×10^{-5}	2500	96
5[a]	130	8.3×10^{-6}	290	93
7[b]	100	7.8×10^{-5}	70	

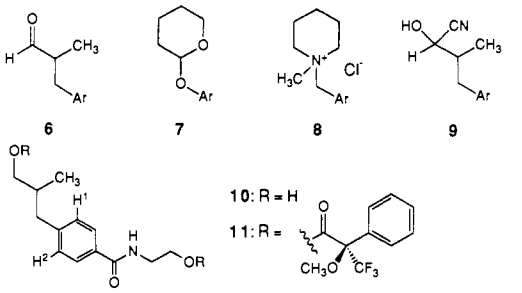
[a] Conditions: 100 mM MES (morpholinylethanesulfonic acid) buffer, pH 5.7, 100 mM NaCl, 37 °C.[10] [b] Assayed in the same buffer at 20 °C.[8] [c] Determined by ^1H NMR analysis of the Mosher ester **11**.[10,11] The absolute configuration of the product was not determined.

under acidic conditions proceeds by rate-determining carbon protonation and is catalyzed by carboxylic acids.[7] We reasoned that the carboxyl groups expected in the binding sites of antibodies raised against the cationic haptens **1**, **2**, and **3**[8] should be in an optimal position to assist carbon protonation of enol ethers **4** and **5** (Figure 1). Furthermore, binding interactions to the tetrahedral ammonium center should favor pyramidalization of the trigonal carbon atom undergoing protonation.

Antibodies to haptens **1**, **2**, and **3**[8] were assayed against substrates **4** and **5** for production of aldehyde **6**.[9] Seven out of 15 antibodies against **1**, 13 out of 23 antibodies against **2**, and 12 out of 22 antibodies against **3** catalyzed the hydrolysis of both **4** and **5**. Antibody 14D9, an antibody against **2** which also catalyzed the hydrolysis of acetal **7**,[8] showed a remarkable activity for the cleavage of enol ethers **4** and **5** and was investigated further. The antibody-catalyzed formation of **6** followed Michaelis-Menten kinetics for both **4** and **5** (Table I). In both cases, potent inhibition by the achiral hapten analogue **8** allowed quantitative assignment of the catalytic activity to the antigen combining site[9] (Chart I).

The enantiomeric purity of aldehyde **6** was determined by reduction to alcohol **10** and derivatization to the Mosher ester **11**. The diastereomeric purity of **11** was measured by ^1H NMR integration of the aromatic protons H^1 and H^2 (500 MHz, $CDCl_3$, δ 7.10 (major) and 7.13 ppm (minor)). To prevent racemization of the product, the reaction was run in a cyanide buffer, which allowed reversible, quantitative protection of **6** as the cyanohydrin **9**.[10] Under these conditions, the measured diastereomeric ratio of the Mosher esters **11** was 50:1, corresponding to an enantiomeric excess of 96% ee. When **5** was used as a substrate, the same

Chart I



enantiomer was obtained with 93% ee.[11]

In conclusion, an antibody capable of nearly completely enantioselective enol ether protonation has been obtained from a hapten where a positively charged tetrahedral nitrogen atom is substituted for the trigonal β-carbon atom. The high proportion of catalytic antibody clones suggests that our hapten design should be quite general and thus applicable to other enol ether structures. Efforts are now being directed toward the understanding of the mechanism of action of this new catalyst.

Supplementary Material Available: Experimental procedures for the syntheses of **4**, **5**, **6**, and **11** (2 pages). Ordering information is given on any current masthead page.

(11) In both cases, the antibody reaction proceeds with very high enantiofacial selectivity of protonation, its efficiency being limited by the relatively modest efficiency of the catalyst. By applying the kinetic constants of 14D9 (Table I) to the preparative assay conditions, the level of racemic product from the background reaction can be estimated to be 1.5% with **4** and 5% with **5**. The effective selectivity for the antibody reaction with **4** and **5** is thus approximately 97.5% ee and 98% ee, respectively.

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(9) The binding of **8** to antibody 14D9 is illustrated by the following experiment:[8] A 4 μM solution of 14D9 was completely inhibited by 10 μM of **8**. After 5 days of extensive dialysis at 37 °C, the inhibited antibody sample recovered only 40% of the activity of a noninhibited control sample.

(10) Assay conditions: 20 μM antibody, 1 mM substrate, 50 mM Bis-tris pH 6.0, 100 mM NaCl, 37 °C. Formation of the aldehyde was followed by HPLC (Asahipac ODP-50 RP C-18, 77% H_2O, 33% CH_3CN, 0.8 mL min^{-1}, t_R = 6.1 min) against an internal standard (2-acetamidophenol, t_R = 8.5 min). Preparative assay: 50 mM MES, pH 5.6, 100 mM NaCl, 10 mM HCN, 20 μM 14D9, 5 mL. **4**: 300 μM (respectively, **5**: 200 μM). Incubation at 37 °C for 3 days (7 days) gave approximately 40% (20%) conversion of **4** (**5**) to cyanohydrin **9** (mixture of isomers).

Toward the Development of a General Chiral Auxiliary. 1. Preparation of a New Class of Camphor Lactam Imides and Their Application to the Construction of Quaternary Centers via Diels-Alder Cycloaddition

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Efforts to control absolute stereochemistry in both inter- and intramolecular variants of the Diels-Alder reaction via Lewis acid promoted cycloadditions employing chiral dienophiles or catalysts have recently enjoyed considerable success.[1-3] However, a significant limitation was apparent when we attempted to apply these methods to the construction of quaternary carbon centers.[4] Very few examples have been documented,[1c,2,3b] although concurrent efforts in other laboratories have also elegantly addressed this

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