concentration of 10.0 μg mL^{-1}; alternatively pretreated leaves were infested with spider mites (*Tetranychus urticae*, approximately 50 mites per leaf; source: Neudorf, D-31860 Emmerthal, Germany) to induce volatile production. The vials with the leaves were placed into a closed system consisting of a desiccator (750 mL) equipped with a miniature circulation pump, fitted to a trap with activated charcoal (1.5 mg) for collection of the volatiles from the circulating air stream.[24] The collection of volatiles was maintained for 24 h and then the compounds were desorbed from the carbon traps with CH_2Cl_2 (2 × 20 μL) and immediately analyzed by GLC-MS. Inhibitor experiments with Mevastatin or Cerivastatin were conducted by sequential treatment of the plants with the inhibitor for 24 h (Mevastatin: 0.2 – 0.5 mg mL^{-1}; Cerivastatin: 0.2 mg mL^{-1}) followed by incubation with $[D_5]$MVA or $[D_2]$DOX and an elicitor as described above. All experiments were repeated at least twice ($n = 3$) to secure reproducibility. The GC-MS analyses were performed on a Fisons MD 800 equipped with a fused silica column, coated with SE 30 (15 m × 0.31 mm). The temperature was programmed from 50 °C (2 min isothermal) to 200 °C at 10 °C min^{-1}; GC-interface: 270 °C; scan area 35 – 350 Da s^{-1}.

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Catalytic Enantioselective Retro-Aldol Reactions: Kinetic Resolution of β-Hydroxyketones with Aldolase Antibodies**

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James Anderson, Subhash C. Sinha,
Richard A. Lerner,* and Carlos F. Barbas III*

The development of methodologies for the stereoselective synthesis of β-hydroxyketones (aldols) has long been the subject of intensive studies in organic chemistry. This challenge was initially met through the use of stoichiometric amounts of chiral auxiliaries[1] and most recently by the design of transition metal based catalysts.[2] An alternative to direct enantioselective synthesis is the application of the strategy of kinetic resolution.[3, 4] Surprisingly, the application of this strategy to the aldol problem has received little, if any, attention.[3b, 5, 6] Recently we have described the generation, broad scope, structure, high stereoselectivity, and mechanism of two aldolase antibodies 38C2 (Aldrich: Aldolase antibody 38C2, cat. no. 47,995-0 and 48,157-2) and 33F12.[7] Since these antibodies are able to catalyze both the aldol addition and the retro-aldol reaction we envisioned that they may be useful in the kinetic resolution of aldols. A single antibody catalyst could then be used for the preparation of both aldol enantiomers (Scheme 1).

In order to address the potential of antibody-catalyzed kinetic resolution of aldols, we studied the kinetics of the retro-aldolization of (*S*)- and (*R*)-**1**. Antibody 38C2 catalyzed the retro-aldolization of (*S*)-**1** following Michaelis – Menten kinetics (k_{cat} = 1.4 min^{-1}, K_m = 270 μM). The relative rate

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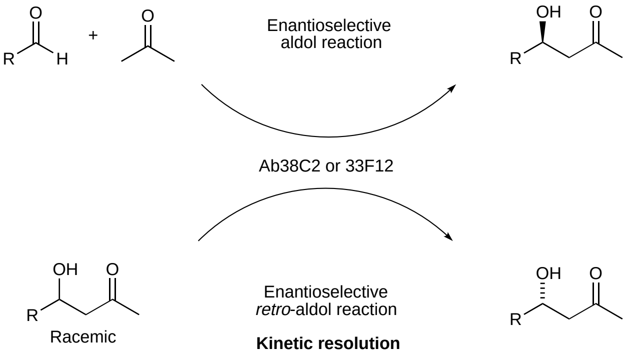
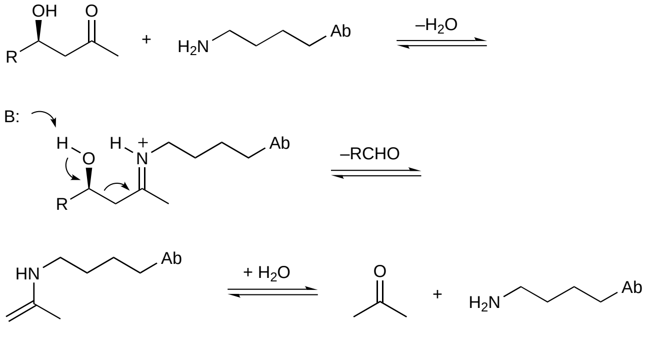


Scheme 1. Preparation of both enantiomers of β-hydroxyketones by the same antibody catalysts.



Scheme 2. The mechanism of the antibody-catalyzed retro-aldol reaction.

enhancement over background provided by the antibody for this reaction (k_{cat}/k_{uncat}) is 1.7×10^7 and the catalytic proficiency[8] with this substrate, (k_{cat}/K_m)/k_{uncat}, is $6.2 \times 10^{10}\,\text{M}^{-1}$ making it the most proficient catalytic antibody prepared to date.[9]

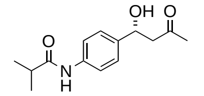
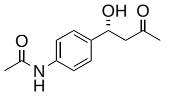
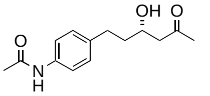
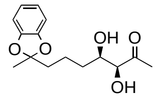
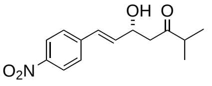
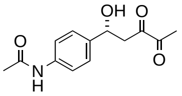
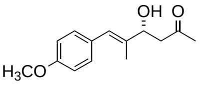
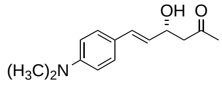
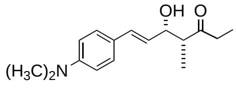
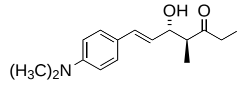
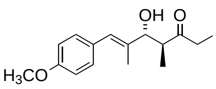
To confirm catalysis proceeded as designed, we studied the reaction in the presence of the mechanism-based inhibitor 2,4-pentanedione. This inhibitor forms a UV-active vinylogous amide with the ε-amino group of the active site lysine residue of these catalysts.[7a] Incubation of ab38C2 with a mole equivalent of 2,4-pentanedione prior to this retro-aldol reaction assay resulted in nearly complete inhibition of catalysis, indicating that the retro-aldol reaction takes place at the active site of the antibody with the essential participation of the ε-amino group of the active site lysine residue. In contrast, antibody catalysis of the retro-aldol reaction of *R*-**1** did not follow Michaelis–Menten kinetics and the reaction was not inhibited by 2,4-pentanedione, suggesting that catalysis occurred without the essential participation of the active site lysine residue. Treatment of the data obtained for (*R*)-**1** as a general base-catalyzed reaction allowed for the determination of a rate constant of $1.0 \times 10^{-5}\,\text{min}^{-1}\,\mu\text{M}^{-1}$, which is similar to the value of $1.7 \times 10^{-4}\,\text{min}^{-1}\,\mu\text{M}^{-1}$ determined for aminoacetonitrile catalyzed retro-aldolization of this substrate.[7e] In accord with our earlier structural and kinetic studies of these catalysts the mechanism of the antibody-catalyzed retro-aldol reaction of (*S*)-aldols is shown in Scheme 2.

Given this high degree of enantioselectivity, we studied ab38C2-catalyzed kinetic resolution of *rac*-**1**. Since the K_m value for acetone is approximately 1 M in the aldol reaction and the aldol is provided at 5.0 mM in the retro-aldol reaction, the equilibrium between the aldol and its components favors retro-aldolization. Determination of the *ee* of the unconverted aldol (*R*)-**1** as a function of reaction progress allowed for the stereoselectivity factor *s* to be determined to be 228.[10] At 52% completion of the retro-aldol reaction catalyzed by either antibody 38C2 or 33F12, the unconverted aldol (*R*)-**1** was obtained in essentially optically pure form (>99% *ee* as determined by chiral-phase high-performance liquid chromatography). We have previously reported antibodies 38C2 and 33F12 catalyzed syntheses of (*S*)-**1** with >99% *ee*. Thus, by applying antibody-catalyzed aldol and retro-aldol reactions both optical isomers of **1** were obtained in essentially enantiomerically pure form. This high degree of enantioselectivity has been observed previously in antibody-catalyzed ester hydrolysis reactions but is certainly not a feature common to all such catalysts.[9c, 11]

We studied the generality of antibody-catalyzed kinetic resolution of a variety of aldols (Table 1). Most reactions reached ~50% conversion after 4 h, the unconverted aldol was recovered and the *ee* value determined as described above. The antibody catalysts are very stable and could be recovered for reuse. Further, the aldehyde product could also be recovered and recycled. In most cases the unconverted aldols were recovered with very high *ee* values.

The isolation of (*S*)-**3** in >99% *ee* at 67% conversion demonstrates the power of kinetic resolution to provide high *ee* values in a case where the antibody-catalyzed synthesis of (*R*)-**3** provided only 58 or 69% *ee* for antibodies 38C2 and 33F12, respectively. Preparation of (3*S*,4*R*)-**4** in >99% *ee* demonstrates the utility of ab38C2 in the preparation of enantiomerically pure α,β-dihydroxyketones. We have subsequently used this compound and its optically pure enantiomer, (3*R*,4*S*)-**4**, prepared by antibody-catalyzed synthesis in >99% *ee* in the synthesis of members of the brevicomin family of beetle pheromones.[12] Resolution of compounds **5** and **6** demonstrate that the scope of these catalysts is greater in the retro-aldol direction than we previously observed in the synthetic aldol addition direction. Previously we failed to observe antibody catalysis of reactions involving either 2,3-butanedione or 3-methyl-2-pentanone as aldol donor substrates, yet aldols incorporating these fragments are substrates for kinetic resolution with these catalysts.[7e] The increased scope of the catalysts for these substrates may be explained by more favorable K_m values for these substrates in the retro-aldol reaction as compared to their constituents. Compounds **7**–**10** were designed to allow for a sensitive continuous UV assay to monitor retro-aldolization. Retro-aldolization of these substrates results in the production of either 4-methoxy-α-methylcinnamaldehyde ($\varepsilon_{315} = 21\,722\,\text{M}^{-1}\text{cm}^{-1}$) or 4-dimethylaminocinnamaldehyde ($\varepsilon_{400} = 23\,000\,\text{M}^{-1}\text{cm}^{-1}$), each exhibiting a new λ_{max} removed in the spectra from that of their parent aldols. These assays were applied in kinetic studies. As shown in Table 2 the efficiency with which these compounds are processed by ab38C2 is exceptional. The cinnamoyl functionality present in these aldols may be desirable for their subsequent transformation since the alkene may be oxidatively cleaved by ozonolysis to yield a ketone or aldehyde group.

Table 1. Antibody-catalyzed kinetic resolution of a variety of β-hydroxyketones (aldols).

Product		Conversion [%]	*ee* [%]
	(*R*)-**1**	52	> 99[a]
	(*R*)-**2**	52	> 99
	(*S*)-**3**	67	> 99
	(3*S*,4*R*)-**4**	55	> 99
	(*R*)-**5**[b]	51	> 99
	(*R*)-**6**[b]	81	80
	(*R*)-**7**	50	95
	(*R*)-**8**	50	90
	(4*R*,5*S*)-**9**	59	> 99
	(4*S*,5*S*)-**9**[b]	50	58
	(4*S*,5*R*)-**10**	54	98

[a] Both antibodies 38C2 and 33F12 were used. [b] Absolute configurations were assigned by analogy.

Table 2. Kinetic parameters for antibody-catalyzed retro-aldol reactions.

Substrate	k_{cat}[b] [min^{-1}]	K_m [mM]	k_{cat}/k_{un}	$(k_{cat}/K_m)/k_{un}$ [M^{-1}]
(*S*)-**1**	1.4	0.27	1.7×10^7	6.2×10^{10}
(±)-**7**	2.2	0.016	1.0×10^5	6.3×10^9
(±)-**8**[c]	4.7	0.041	2.6×10^4	6.4×10^8
(±)-*anti*-**9**	1.5	0.017	4.4×10^4	5.3×10^8
(±)-*anti*-**10**	1.4	0.093	1.9×10^4	2.1×10^8

[a] Conditions: pH 7.0 in the presence of 2.0 µM active sites of ab38C2. [b] Per antibody active site. k_{cat} obtained by fitting experimental data to nonlinear regression analysis using Grafit software. [c] Data was determined in phosphate-buffered saline (PBS) at pH 7.4.

Resolution of compounds **9** and **10** were studied since they represent key building blocks for the synthesis of more complex polypropionates.[13] For *syn*-**9**, 99% *ee* was obtained at 59% conversion. We had not previously addressed in detail the stereochemistry at the α-position in reactions with an aliphatic branch at this position. The resolution of *anti*-isomers of **9** and **10** provided 58 and 98% *ee* at 50 and 54% conversion, respectively. Thus, both *syn* and *anti* stereoisomers can be obtained with high *ee* values, making this an attractive strategy for polypropionate synthesis. While all entries in Table 1 are aromatic aldols, the scope of antibodies 38C2 and 33F12 is not limited to aromatic molecules as demonstrated in earlier studies.[7d,e] Thus, we expect that simple aliphatic aldols should also be good substrates for kinetic resolution with these catalysts.

The special ontogeny of these aldolase antibodies[7d] has resulted in biocatalysts of unusually broad scope and as shown in Tables 1 and 2 enantioselectivities and catalytic efficiencies that are unique in the area. In the course of these studies we developed a sensitive continuous UV assay for the detection of retro-aldol activity that will facilitate the identification of new catalysts of this reaction.

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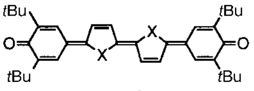
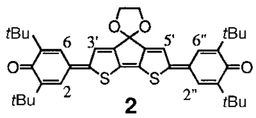
The First Heterotriquinone and Dicyanoheterotriquinone Methide That Undergo a Five-Stage Amphoteric Redox Reaction[**]

Kazuko Takahashi,* Satoshi Fujita, Kimio Akiyama, Misao Miki, and Kazunori Yanagi

In recent years heterocycle-incorporated conjugated molecules possessing interesting electrochemical and optical properties have been widely developed in the field of fundamental molecular and supramolecular chemistry.[1] We have recently synthesized heteroquaterphenoquinones **1a–d**, which exhibit an intense absorption band in the near-IR (NIR) region and undergo amphoteric redox reactions.[2] However, these quinones exist in a flexible conformation in solution at around room temperature, and afford unstable anion radicals on electrochemical reduction. Furthermore, they have relatively weak electron-accepting abilities, which are sometimes unfavorable when these quinones are to be employed as functional molecules such as electron-accepting or electron-transporting mediators, and as functional units in supramolecular electric systems that can be modulated by external electrical stimulation.[3] To create a new type of organic redox system that does not have these disadvantages, we have now designed and synthesized the novel heterotriquinone **3** and the novel dicyanoheterotriquinone methide **4**, as the first heterotriquinonoid systems. On the grounds of the enhanced conjugation between the three terminal electron-withdrawing groups, each of these compounds should have a rigid conformation and thus exhibit strong electron-accepting properties, which should facilitate the formation of stable radical anions and radical trianions. Indeed, we have found that **4** exhibits very characteristic electrochemical behavior and strong electron-accepting ability; it undergoes a novel amphoteric five-stage one-electron redox reaction.



1a : X = O, **1b** : X = S
1c : X = Se, **1d** : X = NMe



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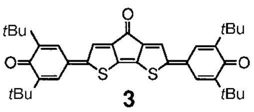

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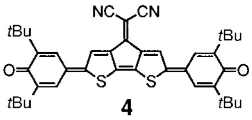
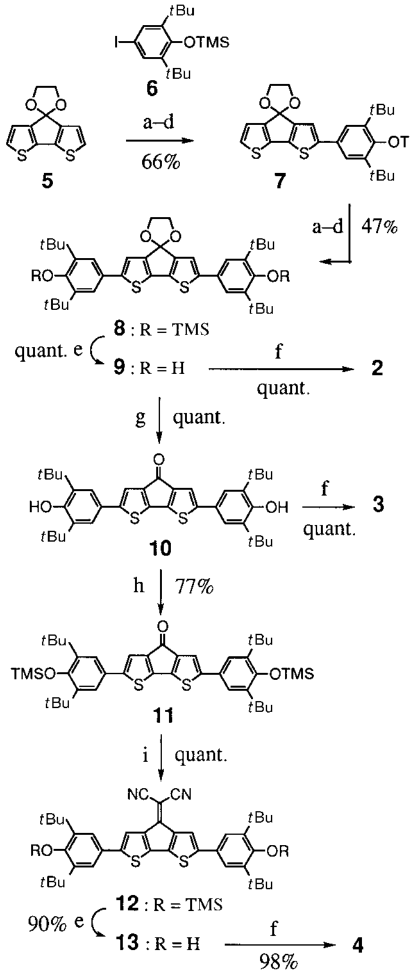


4

The heterotriquinone **3**, the dicyanoheterotriquinone methide **4**, and the ethylenedioxy derivative **2** (a reference compound for **3** and **4**) were synthesized according to the routes shown in Scheme 1, starting from the reaction of **5**[4]



Scheme 1. Reagents and conditions: a) BuLi (1.0 equiv), diethyl ether, 0 °C, 1 h; b) $ZnCl_2$ (1.0 equiv), THF, 0 °C, 1.5 h; c) $[PdCl_2(PPh_3)_2]$ (0.5 equiv), THF, DIBAH (0.1 equiv), room temperature, 15 min; d) **6** (1.0 equiv), THF, room temperature, 1 h; e) TBAF (2 equiv), THF, 0 °C, 2 min; f) PbO_2 (10 equiv), CH_2Cl_2, room temperature, 30 min; g) conc. HCl/THF (1/10), room temperature, 1 h; h) *N,O*-bistrimethylsilylacetamide (BSA) (ca. 1.2 equiv), CH_3CN, 75 °C, 1 h; i) $CH_2(CN)_2$ (1.2 equiv), benzene/piperidine (cat.), reflux, 22 h.

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