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Asymmetric hydrolysis of α-alkylated cyclohexanone enol acetates by the cultured cells of *Marchantia polymorpha*

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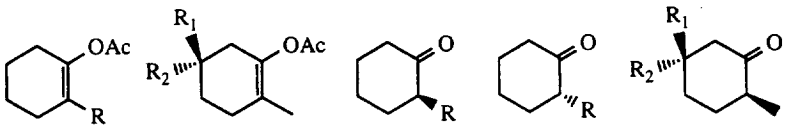
Abstract: The cultured suspension cells of *Marchantia polymorpha* hydrolyzed cyclohexanone enol acetates with 2-alkyl groups to afford optically active ketones. The stereoselectivity of the protonation of the enol intermediate was reversed when the chain length of alkyl substituents was increased. © 1997 Published by Elsevier Science Ltd

Asymmetric protonation of compounds with a prochiral center is a useful method for the production of chiral synthons for organic synthesis.[1] Recently, a new type of enzymatic hydrolysis has been reported, the hydrolysis of enol esters with discrimination of its enantiotopic faces to afford optically active α-substituted ketones.[2,3] We have now investigated the enantioface selective hydrolysis of enol esters, such as 2-alkylated cyclohexanone enol acetates, by the cultured cells of *Marchantia polymorpha*.



1: R=Me
2: R=Et
3: R=Pr
4: R=Pnt

5: R_1=H, R_2=*i*-Pr
6: R_1=*i*-Pr, R_2=H

7: R=Me
8: R=Et

9: R=Pr
10: R=Pnt

11: R_1=H, R_2=*i*-Pr
12: R_1=*i*-Pr, R_2=H

The substrate, **1–6** (each 30 mg)[4–6] was administered to the flask containing the cultured suspension cells of *M. polymorpha* (30 g) in MSK-2 medium[7] (120 ml), and the cultures were incubated at 25°C for 5 h. The yields and enantiomeric excesses of products were determined by GLC of the product.[8–10] It was confirmed that neither non-enzymatic hydrolysis nor racemization of the product occurred under the incubation conditions. 2-Methylcyclohexenyl acetate (**1**) was hydrolyzed to give 2-methylcyclohexanone (**7**) in over 99% yield. The positive curve in the circular dichroism spectrum of **7** indicates its configuration at the 2-position of **7** to be *S* (>99% *e.e.*), as shown in Table 1.[8] Hydrolyses of enol acetates, **5** and **6**, having a stereogenic center at the C-5 position gave the corresponding ketones and the preferred configurations at the 2-position of the products were *S*, identical to the case of the hydrolysis of **1**. Enol acetates, **2–4**, were also hydrolyzed to the corresponding ketones, **8–10**. However, the ethyl group at the 2-position of the enol acetate markedly reduced the enantiomeric excess of the products, compared to the case of the methyl group. On the other hand, in the cases of the enol acetates, **3** and **4**, having propyl and pentyl groups, respectively, the circular dichroism curves of the corresponding products, **9** and **10**, were negative; the preferred configurations of these ketones were therefore *R*. These results demonstrate that the chain elongation (C≥3) of the *n*-alkyl group at the 2-position reverses the stereoselectivity of the protonation of their enol intermediates.

Thus, asymmetric hydrolysis of 2-alkylated cyclohexanone enol acetates with the cultured cells of *M. polymorpha* has been realized with discrimination of the enantiotopic faces of the C=C double bond of the corresponding enol intermediate, and optically active α-substituted ketones were prepared.

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Table 1. Hydrolysis of enol acetates by the cultured cells of *M. polymorpha*

Substrate	Product	Conversion / %	E.e. / %	Preferred config.[b]
1	**7**	>99	>99	*S*
2	**8**	>99	25	*S*
3	**9**	99	30	*R*
4	**10**	73	43	*R*
5	**11**	99	72 [a]	*S*
6	**12**	>99	36 [a]	*S*

a) Diastereomeric excess.
b) Preferred configuration at the α-position to the carbonyl group of the product.

It was also shown that in the hydrolysis of substrates with a longer side chain (C≥3) at the 2-position, the protonation occurred from the other side of the C=C double bond, compared with the case of the substrates having short side chains. It was reported that the enantioselectivity in the hydrolyses using a kind of yeast as biocatalyst became higher with the chain elongation of the alkyl group at the 2-position,[2] therefore the results obtained here apparently indicate that the enzyme from *M. polymorpha* cell cultures differs from that of the yeast. Recently, Matsumoto *et al.* have reported the existence of an enantioselectivity-promoting factor in yeast.[11] The change in stereoselectivity of the protonation due to chain elongation may indicate the existence of such a factor, the existence of two different enzymes with opposite stereoselectivities, or the turning over of the enantiotopic face of the substrate in the active site of a enzyme. The enzymes which catalyze the hydrolysis of enol esters in *M. polymorpha* are now being purified and characterized.

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4. Cyclohexanone enol acetates, **1–6**, were prepared by treatment of their corresponding ketones, **7–12**, with perchloric acid and acetic anhydride.[5] (1*S*,4*S*)-Carvomenthone (**11**) and (1*S*,4*R*)-isocarvomenthone (**12**) were prepared from (*S*)-(+)- and (*R*)-(−)-carvones ($[\alpha]_D^{25}$ +57.1 (neat) and −60.1 (neat), respectively) by reduction with zinc powder.[6]
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8. Retention times for the products in the GLC with a capillary column (0.25 mm × 25 m) coated by CP cyclodextrin β 236M-19 (column temp, 100°C; flow rate of N_2, 50 ml min^{-1}) were as follows: (*S*)- and (*R*)-**7**, 11.8 and 12.8 min; (*S*)- and (*R*)-**8**, 12.7 and 12.9 min; (*S*)- and (*R*)-**9**, 27.7 and 27.9 min; (*S*)- and (*R*)-**10**, 72.1 and 72.8 min. The CD data of the products were **7**: $[\theta]_{288}$ +952 (c 0.10, MeOH) {lit.:[9] $[\theta]_{288}$ −987 for *R* enantiomer}; **8**: $[\theta]_{287}$ +520 (c 0.01, MeOH) {lit.:[10] $[\theta]_{287}$

+2200}; **9**: $[\theta]_{287}$ −775 (c 0.15, MeOH) {lit.:[10] $[\theta]_{287}$ +2480 for *S* enantiomer}; **10**: $[\theta]_{291}$ −947 (c 0.04, MeOH).

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