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Asymmetric bioreduction of substituted acenaphthenequinones using plant enzymatic systems: A novel strategy for the preparation of (+)- and (−)-mono hydroxyacenaphthenones

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Abstract

Regio- and enantioselective reduction of substituted acenaphthenequinones were conducted under mild reaction conditions using plant enzymatic systems. A screening of 15 plants allowed the selection of two suitable plants fulfilling enantiocomplementarity. The (+)- and (−)-mono hydroxyacenaphthenones were achieved with high conversion and good enantiomeric purity using peach (*Prunus persica* (L.) Batsch., conversion 98%, 71% ee) and carrot (*Daucus carota* L., conversion 95%, 81% ee), respectively.

Keywords: Bioreduction; Plant enzymes; Acenaphthenequinone; Chiral hydroxyacenaphthenone

As one of the most promising biocatalysts, plant enzymatic systems have been utilized in various organic reactions such as hydroxylation, glycosylation, hydrolysis, oxidation of alcohols, and reduction of ketones and olefins [1]. In the past decades, the biochemical potential of plant enzymes has been widely applied in the production of specific secondary metabolites, including drugs, flavors, pigments and agrochemicals [2]. However, it used to be regarded that plant enzyme systems, as well as other biocatalysts, were inefficient for reducing polycyclic aromatic ketones due to the highly sterically hindrance of such ketones [3,4].

As the unprecedented application of enzyme-catalyzed reactions in the field of organic synthesis, we have reported, for the first time, the baker's yeast-catalyzed reduction of substituted fluorenones with high enantioselectivity [5]. Afterwards, we have reported another example of reducing acenaphthenequinones to corresponding mono- and di-alcohols using baker's yeast whole-cell system [6]. These results indicate that even highly sterically hindered aromatic ketones can be reduced in the enzyme medium, as long as the mass-transfer limitation in the medium is overcome. As part of our continued interest in enzyme chemistry, we herein wish to report the first example of using plant enzyme systems as reducing agent for the enantioselective reduction of polycyclic aromatic ketones (Scheme 1).

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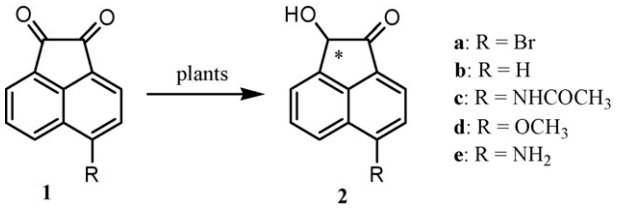

Scheme 1. Reduction of substituted acenaphthenequinones using plant enzyme systems.

Table 1
Rio- and enantioselective reduction of acenaphthenequinone (**1b**) catalysed by various plants[a]

Entry	Plant cells	Conv. (%)[b]	ee (%)[c]	$[\alpha]_D$[d]
1	Tomato (*Lycopersicon esculentum* Mill.)[e]	93	43	–
2	Cucumber (*Cucumis sativus* L.)[e]	68	<5	
3	Celeriac (*Apium graveolens* L. var. *rapaceum*)[f]	95	<5	
4	Grape (*Vitis vinifera* L.)[e]	15	Nd	
5	Garlic (*Allium sativum* L.)[g]	23	Nd	
6	Onion (*Allium cepa* L.)[g]	97	11	–
7	Apple (*Malus pumila* Mill.)[e]	88	33	+
8	Peach (*Prunus persica* (L.) Batsch.)[e]	98	71	+60.03
9	Aubergine (*Solanum melongena* L.)[e]	0	–	
10	Orange (*Citrus reticulata* Blanco.)[e]	87	19	+
11	Carrot (*Daucus carota* L.)[h]	95	81	−64.18
12	Kiwifruit (*Actinidia chinensis* Planch.)[e]	48	13	–
13	Pear (*Pyrus pyrifolia* (Burm.) Nak.)[e]	34	25	+
14	Persimmon (*Diospyros kaki* L.)[e]	37	23	–
15	Banana (*Musa paradisiaca* L.)[e]	12	nd	

[a] Reaction conditions: substrate (100 mg), water (100 mL), amount of plant (50 g), reaction time 3 days, at 30 °C.
[b] The conversion expressed as a percentage of the products in the reaction mixture on the basis of HPLC analysis.
[c] The ee were determined by HPLC using a chiralcel AD-H column. nd: yield was too low to determine ee.
[d] c 0.50–0.60, $CHCl_3$, 20 °C.
[e] Fruit.
[f] Stalk.
[g] Bulb.
[h] Root.

Acenaphthenequinone **1b** was chosen as the initial model to explore the feasibility of the reaction. The substrate was reduced by plants under typical conditions [7–9]. As shown in Table 1, among the selected plants, tomato (*Lycopersicon esculentum* Mill.), celeriac (*Apium graveolens* L. var. *rapaceum*), onion (*Allium cepa* L.), peach (*Prunus persica* (L.) Batsch.), and carrot (*Daucus carota* L.) were able to reduce **1b** and afforded mono hydroxyacenaphthenone **2b** in high conversions (>90%), while only peach (*Prunus persica* (L.) Batsch.) and carrot (*Daucus carota* L.) exhibited high enantioselectivity and gave **2b** with fairly good enantiomeric excesses (70–85%). The time-courses of the reactions catalyzed by carrot root and peach fruit are shown in Fig. 1. Both courses proceeded quickly in initial reaction time and the conversions increased over 80% after 36 h. Differing from baker's yeast which is able to reduce **1b** and afford mono- and di-alcohols (see our previous work [6]), plants can only reduce one carbonyl group of **1b** and give pure mono hydroxyl ketone **2b**. It means that, for the preparation of mono hydroxyacenaphthenone, the regioselective reaction catalyzed by carrot and peach has unique advantages, which does not require strict control of reaction time or addition of enzyme inhibitors [10,11].

Meanwhile, it should be noted that, as the biocatalyst of this reductive reaction, the various tested plants possess opposite stereochemical specificities (see Table 1). We can distinguish the predominant enantiomers of the products according to the data of HPLC and their positive or negative optical rotation, even if the absolute configuration of the chiral compound **2b** has not been determined. The most appropriate plants for further preparative syntheses were peach fruit and carrot root. The peach fruit reduced **1b** to chiral mono hydroxy-ketone (+)-**2b** with 71% ee (entry 8, $[\alpha]_D$ +60.03), whereas the carrot root exhibited an enantiocomplementarity behavior producing (−)-**2b** with 81% ee