Bioreduction of α-Acetoxymethyl Enones: Proposal for an $S_{N2'}$ Mechanism Catalyzed by Enereductase

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Abstract: (Z)-3-Acetoxymethyl-4-R-3-buten-2-ones (R = aryl, alkyl) and (Z)-3-methyl-4-R-3-buten-2-ones (R = aryl) were synthesized and submitted to reduction by the yeast *Saccharomyces cerevisiae* producing the (R)- and (S)-4-R-3-methylbutan-2-ones, respectively. This stereochemistry control strategy was applied in the syntheses of (R)- and (S)-Tropion/C24 with moderate to high enantiomeric excesses. Other (Z)-3-acetoxymethyl-4-phenyl-3-buten-2-ones showed similar behavior to the (Z)-3-acetoxymethyl counterpart, and the acylated Morita–Baylis–Hillman adduct 1-acetoxy-2-methylene-1-phenylbutan-3-one produced a mixture of products, with and without the acetoxy group, via three different reaction pathways. In addition to experiments employing whole cells, those in which isolated enereductases were used suggested that the main pathway through which the loss of the acetoxy group occurs during the biocatalytic cascade is an $S_{N2'}$-type reaction, rather than formal hydrogen addition followed by acetic acid elimination. Finally, related ethyl enones were reduced enantioselectively by the yeast *Candida albicans*, producing both (R)- and (S)-reduction products, depending on the presence of the acetoxy group in the starting material.

Keywords: biotransformation; enantioselectivity; enones; enzyme catalysis

Introduction

The asymmetric biocatalytic reduction of activated alkenes is a powerful tool in the production of small chiral molecules. The bioreduction of several α,β-unsaturated aldehydes, ketones, esters, nitroalkanes and nitriles using microorganisms or isolated Old Yellow Enzymes (OYEs) has been reported as the key step in the synthesis of commercially relevant compounds. In recent decades, considerable efforts have been made to understand the mechanisms by which OYEs catalyze these formal hydrogen additions.

Among activated alkenes, those with a leaving group at the β-position relative to the electron-withdrawing group are particularly interesting, because of their ability to undergo spontaneous elimination reactions. In recent years, different research groups have shown that these compounds participate in biocatalytic cascades involving alkene reduction, elimination to produce another activated alkene, and reduction of the newly formed C=C bond. For instance, reductions of β-chloroenals by *S. cerevisiae* or OYEs were shown to occur as follows: after the initial alkene reduction, dehydrohalogenations produced new enals that underwent further C=C reductions, forming saturated aldehydes. In another example, the reduction of polyhalogenated esters by enereductases resulted in dehalogenated esters, and when substrates bearing halogens in both the α- and β-positions were used, a clear distinction could be drawn between them: whereas β-halogens were lost in eliminations, those at the α position in relation to the electron-withdrawing group remained in the end products.

Recently, our research group showed that some α-chloromethyl and α-bromomethyl enones exhibit similar behavior by participating in reduction–elimination–reduction cascades to produce enantiomerically enriched saturated ketones as end products. However, in these experiments enones with electron donor groups bonded to their aromatic ring underwent rapid solvolysis and could not be reduced by the microorganisms. In an attempt to overcome this drawback, we studied the possibility of replacing the halide with a less effective leaving group. This article reports the
results obtained in the bioreduction of α-acetoxy-
methyl enones.

Results and Discussion

The α-acetoxy methyl enones used as substrates in this
study were prepared via three different routes. Com-
ponents 1a–f were prepared using 4-aryl-3-bromo-
methyl-3-buten-2-ones and 3-bromomethyl-3-nonanen-
2-one, as previously reported. Enones 1g and 1h
were prepared starting from Knoevenagel condensa-
tion to compounds 2g and 2h, followed by ester re-
duction to derivatives 3g and 3h and, finally, carboxyl
deprotection. Enones 1i and 1j were prepared by a 
TiCl₄-promoted reaction between methyl vinyl 
ketone and aromatic aldehydes, followed by substi-
tution of the allylic chloride by a hydroxy group, and its
acetylation (Scheme 1). Finally, enones 5h–j were
prepared by via aldol condensation between alde-
hydes and butanone (Scheme 2). The synthesis and 
biotransformation of analogous enones 5a–i was de-
scribed in a previous study.

The reduction of enones 1a–g by S. cerevisiae pro-
duced the corresponding (R)-α-methyl ketones in
moderate yields and high ees (Table 1). The stereo-
chemical outcome of these reductions is similar to 
that previously reported for α-halomethyl enones, in
which a reduction–elimination–reduction cascade is
proposed to be taking place. In this case, an OYE-
catalyzed reduction followed by acetic acid elimina-
tion produces an α-methylene ketone, which is then
reduced by an OYE to the corresponding α-methyl
ketone. The production of the (R)-isomer is consistent
with the flipped binding mode of α-methylene ketone
to the active site enzymes prior to hydride trans-
fer. These results can be contrasted with previous-
ly reported microbiological reductions of α-methylar-
lidenacetones, which produce the (S)-isomers of α-
methyl ketones via the same flipped binding mode.

In a previous study, we reported that chloro and 
bromo analogues of 1g, which contain an electron-
rich aromatic ring, underwent hydrolysis as the exclu-
sive reaction pathway when subjected to biotransfor-
mation conditions. It is important to note that 1g
did not produce its hydrolysis product during bio-
transformation, indicating that the acetox group is
a good balance between being a satisfactory leaving

group for the biocatalytic cascade and stable enough
for solvolysis.

Table 1. Biotransformation of enones 1a–g by S. cerevisiae.

<table>
<thead>
<tr>
<th>Enone</th>
<th>R</th>
<th>Time [h]</th>
<th>Product</th>
<th>Yield [%]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Ph</td>
<td>16</td>
<td>(R)-6a</td>
<td>58</td>
<td>96</td>
</tr>
<tr>
<td>1b</td>
<td>2-ClC₆H₄</td>
<td>8</td>
<td>(R)-6b</td>
<td>37</td>
<td>96</td>
</tr>
<tr>
<td>1c</td>
<td>4-ClC₆H₄</td>
<td>6</td>
<td>(R)-6c</td>
<td>71</td>
<td>98</td>
</tr>
<tr>
<td>1d</td>
<td>3-NO₂C₆H₄</td>
<td>8</td>
<td>(R)-6d</td>
<td>52</td>
<td>89</td>
</tr>
<tr>
<td>1e</td>
<td>3-NO₂C₆H₄</td>
<td>48</td>
<td>(R)-6e</td>
<td>44</td>
<td>91</td>
</tr>
<tr>
<td>1f</td>
<td>n-C₄H₉</td>
<td>6</td>
<td>(R)-6f</td>
<td>61</td>
<td>97</td>
</tr>
<tr>
<td>1g</td>
<td>4-MeOC₆H₄</td>
<td>48</td>
<td>(R)-6g</td>
<td>57</td>
<td>94</td>
</tr>
</tbody>
</table>

[a] Reactions performed with 0.5 mmol of substrate.
Given the positive results obtained in the biotransformation of 1a–g by S. cerevisiae, we opted to investigate the biotransformation of 1a by commercially available enereductases (EREDs). The results are shown in Table 2. EREDs 103, 110, 207 and P1A04 produced (R)-6a in 6 h of reaction with excellent conversions and ees. A low concentration of the proposed hydrogenation intermediate 9 was observed, whereas intermediate 10 was not detected. EREDs 112 and P1-H09 showed poorer conversions of 1a into (R)-6a; ERED 112 produced (R)-6a at high ee, whereas low ees of (R)-6a were obtained for ERED P1-H09. Finally, ERED P1-E01 resulted in a mixture of the hydrogenation product 9 and the biocatalytic cascade product (R)-6a, representing the only case, along with P1-H09, in which a significant amount of 9 was detected. In addition, it is noteworthy that only a small amount of 9 underwent elimination, producing 10 over the course of 24 h. Although significantly smaller amounts of 9 were produced in the reactions catalyzed by the other six enzymes, this compound also remained in the reaction medium in those cases. An authentic sample of compound 9 was synthesized to support its identification (Scheme 3).

Since the acetoxy group is an adequate leaving group for bioreduction cascades involving enones with electron-rich aromatic rings, enones 1h–j were selected for reduction by S. cerevisiae (Table 3). Thus, the ketones (R)-6h–j were obtained in yields of 30–47% and 90–95% ee. On the other hand, the reduction of enones 5h–j, which have no leaving group, produced the ketones (S)-6h–j with 13–64% yields and 75–97% ee.

To illustrate the synthetic potential of these biotransformations, both enantiomers of the chiral fragrance Tropional/C24 were prepared using enones 1j and 5j [Scheme 4, for the (R) enantiomer]. Bioreductions of 1j and 5j were scaled up to 5 mmol of substrate, and (R)- and (S)-6j were obtained with 63% and 73% yield, and 96% and 75% ee, respectively.

Table 2. Biotransformation of enone 1a by EREDs.

<table>
<thead>
<tr>
<th>ERED</th>
<th>Time [h]</th>
<th>1a [%][a]</th>
<th>9 [%][b]</th>
<th>10 [%][c]</th>
<th>(R)-6a [%][c]</th>
<th>ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>103</td>
<td>6</td>
<td>4.4</td>
<td>1.9</td>
<td>n.d.</td>
<td>93.7</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>4.3</td>
<td>1.7</td>
<td>n.d.</td>
<td>94.0</td>
<td>94</td>
</tr>
<tr>
<td>110</td>
<td>6</td>
<td>0.8</td>
<td>1.1</td>
<td>n.d.</td>
<td>98.1</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>0.6</td>
<td>1.2</td>
<td>n.d.</td>
<td>98.2</td>
<td>95</td>
</tr>
<tr>
<td>112</td>
<td>6</td>
<td>58.9</td>
<td>0.7</td>
<td>n.d.</td>
<td>40.4</td>
<td>91</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>57.5</td>
<td>0.8</td>
<td>n.d.</td>
<td>41.7</td>
<td>90</td>
</tr>
<tr>
<td>207</td>
<td>6</td>
<td>7.0</td>
<td>3.5</td>
<td>n.d.</td>
<td>89.5</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>6.2</td>
<td>3.4</td>
<td>n.d.</td>
<td>90.4</td>
<td>94</td>
</tr>
<tr>
<td>P1-A04</td>
<td>6</td>
<td>n.d.</td>
<td>1.2</td>
<td>n.d.</td>
<td>98.8</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>n.d.</td>
<td>0.6</td>
<td>n.d.</td>
<td>99.4</td>
<td>99</td>
</tr>
<tr>
<td>P1-E01</td>
<td>6</td>
<td>n.d.</td>
<td>48.3</td>
<td>1.6</td>
<td>50.1</td>
<td>98</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>n.d.</td>
<td>43.5</td>
<td>2.6</td>
<td>53.9</td>
<td>98</td>
</tr>
<tr>
<td>P1-H09</td>
<td>6</td>
<td>45.8</td>
<td>15.7</td>
<td>0.5</td>
<td>37.7</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>42.3</td>
<td>12.5</td>
<td>0.9</td>
<td>40.6</td>
<td>36</td>
</tr>
</tbody>
</table>

[a] Conversion determined by GC.

Table 3. Biotransformations of enones 1h–j and 5h–j by S. cerevisiae.[a]

<table>
<thead>
<tr>
<th>Enone</th>
<th>Time [h]</th>
<th>Product</th>
<th>Yield [%][b,c]</th>
<th>ee [%][b,c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5h</td>
<td>72</td>
<td>(S)-6h</td>
<td>28 [13]</td>
<td>93 [-95]</td>
</tr>
<tr>
<td>1h</td>
<td>72</td>
<td>(R)-6h</td>
<td>30</td>
<td>90</td>
</tr>
<tr>
<td>5i</td>
<td>8</td>
<td>(S)-6i</td>
<td>46 [59]</td>
<td>97 [-95]</td>
</tr>
<tr>
<td>1i</td>
<td>48</td>
<td>(R)-6i</td>
<td>42</td>
<td>93</td>
</tr>
<tr>
<td>5j</td>
<td>8</td>
<td>(S)-6j</td>
<td>64</td>
<td>75</td>
</tr>
<tr>
<td>1j</td>
<td>72</td>
<td>(R)-6j</td>
<td>47</td>
<td>95</td>
</tr>
</tbody>
</table>

[a] Reactions performed with 0.5 mmol of substrate.
[b] Isolated yields.
[c] Yield and ee values in square brackets refer to those in ref.[11]
The enantiomerically enriched ketones were converted into the corresponding primary alcohols via a haloform reaction, followed by reduction of the mixed anhydride of the carboxylic acid formed in the reaction. The alcohols (R)- and (S)-11 were then transformed into (R)- and (S)-Tropional® with 94 and 75% ee respectively, via TEMPO-catalyzed oxidation. It is important to underscore that the asymmetric synthesis of Tropional® has been reported in the literature: both enantiomers of Tropional® have been synthesized by SAMP and RAMP hydrazone alkylations,[12] and (S)-Tropional® via OYE-catalyzed reduction of α,β-unsaturated aldehyde.[13]

Other α-acyloxymethyl enones were also investigated as substrates in the bioreduction cascade (Table 4). Good conversions were obtained for substrates 13a and 13b, which have 2 and 3 carbon alkyl chains, respectively, whereas reduced conversion was observed for substrate 13c and 13d, which contain 4 and 5 carbon alkyl chains, respectively. Poor conversions were also obtained for substrates 13e and 13f, in which benzoyl and Boc groups are bonded to the oxygen atom. However, the ee values were consistently high and in all cases the (R) isomer was the predominant product. These results corroborate the proposed biocatalytic pathway, whereby the stereogenic center of the final product is generated via the enymatic hydrogenation of the intermediate 3-benzyl-3-buten-2-one.

In light of the satisfactory results obtained with enones bearing terminal allylic acetoxy groups, we decided to study the biotransformation of the racemic acetylated Morita–Baylis–Hillman (MBH) adduct of benzaldehyde and 3-buten-2-one by S. cerevisiae. Initially, we expected this enone to follow a similar reaction pathway to that of the α-acetoxyethyl enones studied up to this point. In other words, a reduction–elimination sequence would lead to the formation of α-methylbenzyldieneacetone, which would then be reduced to (S)-3-methyl-4-phenyl-2-butanone [(S)-6a]. However, when 14 was reduced by S. cerevisiae, ketones (R)-6a and (1R,2R)-15 were isolated from the reaction medium (Scheme 5). The absolute configuration of 15 was determined by treating it with an alkaline solution of sodium hypobromite, which yielded 3-hydroxy-2-methyl-3-phenylpropanoic acid, and then methylating the acid with diazomethane. The relative configuration was determined as syn by comparing its 1H and 13C NMR spectra with the literature values,[14] and the absolute configuration was established by comparing its optical rotation with that of the literature sample.[15]

It is important to note that although substrate 14 was racemic, (1R,2R)-15 was produced at a high diastereomeric ratio (dr) from the onset of the reaction. This suggests that only one enantiomer of 14 is reduced to the product bearing the β-acetoxy group, as opposed to reduction of both enantiomers to 15 and elimination of only one diastereoisomer. Moreover, when the reaction was performed using a water/hexane biphasic system, three key intermediates were identified via GC/MS techniques in the re-
action medium: enone 1a, which is an isomer of 14, and enones 10 and 16 (Scheme 6). In this biphasic system, some reaction intermediates are removed from water to the organic solvent. This preliminarily suggests the three main reaction pathways involved in the reduction of 14: in addition to the reduction of (S)-14 to (1R,2R)-15, 14 can undergo isomerization in the reaction medium to produce 1a, and both 1a and 14 can be reduced via elimination of the acetoxy groups to produce different enantiomers of 6a. These diverging pathways also explain the production of (R)-6a with low ee in this biotransformation. In relation to the isomerization of 14 to 1a, it is known that acetates of MBH adducts from aromatic aldehydes producing 1-phenyl-1-hydroxy-2-methylidene-3-butanone, a diastereomeric mixture of 15, can act as an intermediate in the main reaction pathway of the biotransformation of 1a by S. cerevisiae. In another experiment using isolated EREDs, it seems reasonable to state that compound 9 is not the intermediate of the biotransformation of 1a, since 1a is converted to (R)-6a after 6 h by most EREDs (see Table 2).

In an attempt to study the elimination of the acetoxy group of (1R,2R)-15 to produce 16, pure (1R,2R)-15 was placed in an orbital shaker under the same biotransformation conditions for up to 96 h. Although some elimination occurred, it was sluggish, and (1R,2R)-15 remained in the reaction medium. This seems to indicate that (1R,2R)-15 is not an intermediate in the production of 16. In another experiment, a diastereomeric mixture of 15, obtained by reducing of 1-phenyl-1-hydroxy-2-methylidene-3-butanone with H2 and Pd/C followed by acetylation with Ac2O, was submitted to the same biotransformation conditions in an orbital shaker for up to 96 h. Once again, elimination was sluggish, and both diastereoisomers of 15 persisted in the reaction medium; preferential conversion of either syn- or anti-15 into 16 did not occur.

This prompted us to investigate the reactivity of a potential intermediate β-acetoxy ketone in the cell medium. Thus, when ketone 9, a possible (though not detected) intermediate of the reduction of 1a by S. cerevisiae, was submitted to biotransformation by this microorganism, a 97:3 mixture of hydrolysis product 8 and AcOH-elimination product 10 was obtained (Scheme 7).

Scheme 6. Suggested pathways for production of (R/S)-6a and (1R,2R)-15 in the biotransformation of (R/S)-14 by S. cerevisiae.

Scheme 7. Biotransformation of ketone 9 by S. cerevisiae.

This result suggests two hypotheses: (i) when the C=O bond of 1a is hydrogenated by microbial OYEs, 9 undergoes rapid elimination in the intracellular medium before it can be hydrolyzed or (ii) 9 is not formed in the main bioreduction cascade pathway.

In order to assess hypothesis (ii), we performed biotransformations of 9 using commercially available EREDs; the results are presented in Table 5. All the EREDs studied exhibited significant difficulty in the biotransformation of 9. In general, 80–89% and 66–77% of 9 still remained after 6 and 24 h of reaction, respectively. The main products detected after 24 h of reaction were (R)-6a (4.3–12.5%), 10 (4–11%) and 8 (5–17%). The reduction catalyzed by ERED P1A04 showed an outlying behavior, with a higher quantity of 10 (22.3%) observed after 24 h. Based on these experiments using isolated EREDs, it seems reasonable to state that compound 9 is not the intermediate of the biotransformation of 1a, since 1a is converted to (R)-6a after 6 h by most EREDs (see Table 2).

In summary, the results of the experiment with S. cerevisiae and isolated EREDs indicate that 15 is not an intermediate in the main reaction pathway of the reduction of 14, and the same can be said for 9 in relation to the reduction of 1a. This means that the substrates 1a and 14 are not biotransformed via C=O bond hydrogenation followed by acetic acid elimination. An alternative to the hydrogenation–elimination sequence is an S_{n}^{2}-type reaction, involving a nucleophilic attack of the formal hydride from the flavin mononucleotide (FMNH_{2}) on the olefinic β-carbon and concomitant expulsion of the acetoxy group (Figure 1).

Thus, it seems that the main bioreduction cascade pathway for acetoxy enones 1a and 14 is not a hydro-
These are not the final page numbers!
as the corresponding methyl enone 16.[6d,e] On the other hand, the reduction of enone 17 mediated by isolated OYE3 produces (S)-23 in 89% ee, since OYE3 better tolerates the increased steric hindrance of the enone 17 compared to enone 16, via flipped binding mode of the substrate to the active site of the enzyme.[6d] Therefore, the reduction of 17 by microorganisms that have both OYE1-3 like S. cerevisiae produces 23 at low enantioselectivity. The yeast C. albicans has been shown to contain an estrogen binding protein (EBP) similar to S. cerevisiae OYEs,[20] and this enzyme, which possibly is similar to OYE3, may be involved in the reduction of 17 by C. albicans. Therefore, both ethyl enones 17 and 19 may fit in the active site of this enzyme via the flipped binding mode producing (S)-23 and (R)-23, respectively, as previously proposed for the corresponding methyl enones.[9] The same rationalization may be done for G. candidum, since this microorganism produces (S)-23 and (R)-23 at 90 and 97% ee from 17 and 19, respectively.

**Scheme 8.** Synthesis of enones 17, 19 and 22.

### Table 6. Microorganism screening for the biotransformation of ethyl enones 17, 19 and 22.[a]

<table>
<thead>
<tr>
<th>Microorganism</th>
<th>Enone</th>
<th>Time [h]</th>
<th>Conversion [%]</th>
<th>Ketone ee [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Saccharomyces cerevisiae</strong></td>
<td>17</td>
<td>72</td>
<td>68</td>
<td>(S)-23 50</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>24</td>
<td>100</td>
<td>(S)-23 14</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>48</td>
<td>100</td>
<td>(S)-23 9</td>
</tr>
<tr>
<td><strong>Saccharomyces boulardii</strong></td>
<td>17</td>
<td>72</td>
<td>5</td>
<td>n.d.</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>24</td>
<td>100</td>
<td>(S)-23 21</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>72</td>
<td>7</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Pichia kluveri</strong></td>
<td>17</td>
<td>72</td>
<td>3</td>
<td>n.d.</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>72</td>
<td>51</td>
<td>(R)-23 89</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>72</td>
<td>5</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Candida albicans</strong></td>
<td>17</td>
<td>48</td>
<td>100</td>
<td>(S)-23 97</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>24</td>
<td>100</td>
<td>(R)-23 83</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>48</td>
<td>100</td>
<td>(R)-23 93</td>
</tr>
<tr>
<td><strong>Candida parapsilosis</strong></td>
<td>17</td>
<td>72</td>
<td>6</td>
<td>n.d.</td>
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<tr>
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<td>19</td>
<td>48</td>
<td>100</td>
<td>(S)-23 40</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>72</td>
<td>9</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Trichosporon cutaneum</strong></td>
<td>17</td>
<td>72</td>
<td>14</td>
<td>n.d.</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>72</td>
<td>11</td>
<td>n.d.</td>
</tr>
<tr>
<td></td>
<td>22</td>
<td>72</td>
<td>5</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Kluveromyces marxianus</strong></td>
<td>17</td>
<td>72</td>
<td>7</td>
<td>n.d.</td>
</tr>
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<td></td>
<td>19</td>
<td>48</td>
<td>100</td>
<td>(S)-23 32</td>
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<td></td>
<td>22</td>
<td>72</td>
<td>10</td>
<td>n.d.</td>
</tr>
<tr>
<td><strong>Geotrichum candidum</strong></td>
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[a] Reactions performed with 0.1 mmol of substrate.
[b] The C=O bond reduction product was the only detected product.

**Conclusions**

Several α-acetoxyethyl enones were shown to take part in bioreduction cascades in which the substrate is reduced by an OYE with loss of the acetoxy group producing a new enone that is reduced by an OYE to form an enantiomerically enriched ketone. The acetoxy group is an adequate leaving group for bioreduc-
tion cascades involving the enones studied with electron-rich aromatic rings, avoiding hydrolysis that occurs with the corresponding α-halomethyl enones. This stereochemistry control strategy was applied to the syntheses of (R)- and (S)-Tropial@ with moderate to high enantiomeric excesses. Experiments performed using both S. cerevisiae and isolated EREDs suggest that the main biocatalytic cascade pathway for α-acetoxyethyl enones might not be a hydrogenation–elimination–hydrogenation sequence, but rather an allylic nucleophilic substitution followed by hydrogenation.

### Experimental Section

**General Methods**

Benzaldehyde, 2-chlorobenzaldehyde, 3-nitrobenzaldehyde, 4-nitrobenzaldehyde, hexanal, p-anisaldehyde, o-anisaldehyde, piperonal, 3,4-dimethoxybenzaldehyde, 3-buten-2-one, DABCO, bromine, trifluoroacetic acid, acetic anhydride, morpholine, disobutylaluminum hydride, ethyl acetooacetate, benzyl chloride, lithium aluminum hydride, TEMPO, iodo-benzene, propionic anhydride, valeric anhydride, hexanoic anhydride, benzoic anhydride, 3-pentanone, tert-butylicarbonate, methanesulfonyl chloride, DBU and methyl 3-oxopentanoate were purchased from Sigma–Aldrich. DMAP, sodium hydride and butyric anhydride were purchased from Fluka.

Fluroroacetic acid (1 mL, 13 mmol) and potassium carbonate, glacial acetic acid, sodium hydroxide, ethylene glycol, sulfuric acid and hydrochloric acid were purchased from Synth. Benzaldehyde and p-anisaldehyde were distilled before use; all the other reagents were used as received.

Yeast type II from Saccharomyces cerevisiae was purchased from Sigma (Lot BCBL8059V). All the EREDs used were from a Kit EREDs purchased from Codexis (Lot N15006).

Thin-layer chromatography (TLC) analyses were performed with precoated aluminum sheets (silica gel 60 Merck), and column chromatography was carried out on silica (200–400 mesh, Merck). Detection was performed by UV inspection (254 nm) for all compounds.

The method of GC/MS analyses was performed on an Agilent 7890A GC System with a Hewlett-Packard 5975C mass spectrometer (70 eV) using an HP-5MS fused silica capillary column (crosslinked 5% phenyl ethyl siloxane, 30 m × 0.25 m ID × 0.25 μm film thickness) and helium as a carrier gas (1 mL min⁻¹). The split ratio was 1:50. The injector temperature was kept 270°C and detector was kept at 280°C. The column temperature was held at 80°C for 3 min, increased to 230°C at a rate of 30°C min⁻¹, increased from 230°C to 280°C at a rate of 25°C min⁻¹, and then kept at 280°C for 5 min. 1 μL of a compound solution (1 mg mL⁻¹) in ethyl acetate was injected and the retention times (min) are reported for all compounds.

Chiral GC/FID analyses were obtained on an Agilent 6890 Series GC System using a Hydroxid chiral capillary column (30 m × 0.25 mm ID × 0.25 μm film thickness). Hydrogen was used as a carrier gas (1 mL min⁻¹), the injector temperature was 200°C and the detector temperature was 220°C. Three different methods were employed for the analysis of the bioreduction products. Method A: the column temperature was held at 80°C for 3 min, increased to 180°C at a rate of 3°C min⁻¹, and then kept at 180°C for 20 min. Method B: the column temperature was held at 80°C for 3 min, increased to 180°C at a rate of 1°C min⁻¹, and then kept at 180°C for 20 min. In all cases, 1 μL of a compound solution (1 mg mL⁻¹) in ethyl acetate was injected and the retention times (min) are reported for all compounds.

Chiral HPLC analyses were performed on a Shimadzu LC-20AT, using a Chiralcel OD-H column from Daicel. A hexane/3-propanol (99.5%/0.5%) mixture was used as eluent at a flow of 0.4 mL min⁻¹.

IR spectra were recorded on a FT-IR BOMEM MB-100 from Hartmann & Braun. Melting points were recorded on a Metler Toledo MP50 Melting Point System. Optical rotation measurements were recorded on a Perkin–Elmer 341 polarimeter with a sodium lamp. ESI-HR-MS analyses were performed on a Waters Xevo Q-Tof.

**General Procedure for the Preparation of α-Acetoxyethyl Enones 1a–f**

Trifluoroacetic acid (1 mL, 13 mmol) and potassium carbonate (1.52 g, 11 mmol) were added to a round-bottom flask containing (E)-3-bromomethyl-4-(aryl or alkyl)-3-buten-2-one (10 mmol) and acetone (10 mL) and the mixture was refluxed for 6 h. After this time, the mixture was cooled to room temperature and added to a separatory funnel containing water (100 mL). The product was extracted with ethyl acetate, the organic layer was washed with brine, and then dried over sodium sulfate. The solvent was removed under reduced pressure and then dichloromethane (50 mL) was added to the crude product. The solution was cooled to 0°C, and then acetic anhydride (1.135 mL, 12 mmol), triethylamine (1.67 mL, 12 mmol) and DMAP (122 mg, 1 mmol) were added to the mixture. The mixture was stirred at 0°C for 1 hour, and then water (100 mL) was added to the round-bottom flask. The mixture was further stirred at room temperature for 15 min, and then the organic layer was separated. The aqueous layer was extracted with dichloromethane, washed with brine, dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography.

(E)-3-Acetoxyethyl-4-phenyl-3-buten-2-one (1a): Following the general procedure, 1a was obtained as a colorless oil; yield: 79%. Rt (GC/MS): 5.98 min; MS-EL: m/z (%) = 218 (21) [M⁺], 176 (28), 175 (55), 159 (14), 158 (88), 157 (18), 143 (15), 133 (34), 130 (11), 129 (23), 117 (19), 116 (26), 115 (100), 103 (12), 77 (14); H NMR (CDCl₃, 250 MHz): δ = 2.08 (s, 3H), 2.48 (s, 3H), 4.94 (s, 2H), 7.35–7.48 (m, 5H), 7.79 (s, 1H); ¹³C NMR (CDCl₃, 62.5 MHz): δ = 20.9, 26.1, 58.5, 128.8, 129.5, 129.7, 134.3, 135.4, 145.0, 170.7, 198.3.
(E)-3-Acetoxyethyl-4-(2'-chlorophenyl)-3-buten-2-one (1b): Following the general procedure, 1b was obtained as a colorless oil; yield: 56%. Rt (GC/MS): 6.40 min; MS-EI: m/z (%) = 218 (14), 217 (100), 175 (27), 158 (11), 157 (76), 149 (12), 115 (24); IR (film): ν = 1741, 1677, 1435, 1371, 1238, 1029; 1H NMR (CDCl 3, 250 MHz): δ = 2.03 (s, 3H); 13C NMR (CDCl 3, 62.5 MHz): δ = 20.8, 26.2, 58.5, 127.0, 129.8, 130.2, 130.7, 132.9, 134.1, 137.0, 141.5, 170.5, 198.0; HR-MS-ESI*: m/z = 275.0471 [(M+Na)+], calcd: 275.0451.

(1e): Following the general procedure, 1e was obtained as a colorless solid; yield: 81%; mp 91.7–93.1 °C. Rt (GC/MS): 6.67 min; MS-EI: m/z (%) = 252 (2) [M]+, 211 (26), 210 (44), 209 (68), 194 (26), 192 (81), 151 (24), 149 (55), 116 (20), 115 (100), 114 (20), 75 (20), 70 (20); IR (KBr): ν = 1737, 1661, 1630, 1250, 1222; 1H NMR (CDCl 3, 300 MHz): δ = 2.34 (s, 3H), 4.90 (s, 2H), 7.27–8.32 (m, 4H), 8.28 (s, 1H); 13C NMR (CDCl 3, 75 MHz): δ = 26.1, 58.3, 129.1, 130.8, 132.7, 135.8, 135.9, 143.5, 170.6, 198.0; HR-MS-ESI*: m/z = 275.0457 [(M+Na)+], calcd: 275.0451.

Preparation of Ethyl (Z)-2-(2'-Methyl-1,3'-dioxolan-2'-yl)-3-(4'-methoxyphenyl)propenoate (2g) Morpholine (862 μL, 10 mmol) was slowly added to a round-bottom flask containing ethyl acetocacetate (1.276 mL, 10 mmol), p-anisaldehyde (1.36 g, 10 mmol) and glacial acetic acid (1.144 mL, 20 mmol). The reaction mixture was stirred for 24 h, and then ethyl acetate was added to the mixture. The solution was washed with water, and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was used in the next step without purification.

The Knoevenagel adduct was dissolved in toluene (20 mL), and ethylene glycol (1.118 mL, 20 mmol) and p-toluenesulfonic acid (344 mg, 2 mmol) were added to the round-bottom flask. The mixture was refluxed for 6 h with water removal by means of a Dean–Stark apparatus. Then, the mixture was added to a separatory funnel, and washed with water, 10% sodium bicarbonate and brine. The organic layer was dried over sodium sulfate, the solvent was removed under reduced pressure and the product was purified by column chromatography (90:10 hexane/ethyl acetate).

Preparation of (E)-2-(2'-Methyl-1,3'-dioxolan-2'-yl)-3-(4'-methoxyphenyl)propen-1-ol (3g)

Diisobutylaluminum hydride (2M in toluene, 6 mL, 12 mmol) was slowly added to a round-bottom flask containing compound 2g (1.46 g, 5 mmol) and CH 2Cl 2 (10 mL) at 0°C under a nitrogen atmosphere. The mixture was stirred for 6 h at 0°C, and then ethyl acetate (10 mL) was added to the round-bottom flask. The reaction was stirred for 30 min, and then water (1 mL) was added to the round-bottom flask. The mixture was further stirred for 10 min, and then a 10% sodium hydroxide solution (1 mL) was added to the round-bottom flask. The mixture was further stirred for 1 hour. After 1 hour, the solid mass was separated by filtration, the organic layer was washed with water and brine, and then dried over sodium sulfate. The organic solvent was removed under reduced pressure, and the product was purified by column chromatography (85:15 hexane/ethyl acetate). Product 3g was obtained as a colorless oil; yield: 668 mg (53%). Rt (GC/MS): 6.56 min; MS-EI: m/z (%) = 206 (53), 163 (40), 146 (34), 145 (100), 121 (37), 115 (21), 108 (72), 103 (25), 91 (27), 77 (26), 55 (40); IR (film): ν = 3386, 1602, 1512, 1257, 1179; 1H NMR (CDCl 3, 400 MHz): δ = 1.60 (s, 3H), 2.46 (brs, 1H), 3.81 (s, 3H), 3.97–4.05 (m, 2H), 4.28 (br, 2H), 6.86–6.90 (m, 4H), 7.35–7.38 (m, 2H); 13C NMR (CDCl 3, 125 MHz): δ = 24.4, 55.3, 58.6, 64.7, 110.6, 113.8, 128.6, 129.0, 130.4, 137.8, 159.1.

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Preparation of (E)-3-Acetoxymethyl-3-(4′-methoxy-phenyl)-3-buten-2-one (1g)

Compound 3g (500 mg, 2 mmol), THF (2 mL) and 10% HCl (1 mL) were stirred for 10 h in a round-bottom flask. The product was extracted with diethyl ether, the organic layer was washed with 10% sodium bicarbonate and dried over magnesium sulfate. The solvent was removed under reduced pressure, and then dichloromethane (10 mL) was added to the crude product. The solution was cooled to 0°C, and then acetic anhydride (227 µL, 2.4 mmol), triethylamine (334 µL, 2.4 mmol) and DMAP (24 mg, 0.2 mmol) were added to the mixture. The mixture was stirred at 0°C for 1 hour, and then water (10 mL) was added to the round-bottom flask. The mixture was further stirred at room temperature for 15 min, and then the organic layer was separated. The aqueous layer was extracted with dichloromethane, washed with brine, dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (95:5 hexane/ethyl acetate). Product was obtained as a colorless oil; yield: 468 mg (37%).

Preparation of Ethyl (Z)-2-(2′-Methyl-1′,3′-dioxolan-2′-yl)-3-(2′-methylphenyl)propenoate (2h)

Following the procedure for preparation of 2g and using o-anisaldehyde (1.36 g, 10 mmol), the product 2h was obtained as a colorless oil; yield: 1.837 g (63%).

Preparation of (E)-2-(2′-Methyl-1′,3′-dioxolan-2′-yl)-3-(2′-methylphenyl)-2-propen-1-ol (3h)

Following the procedure for preparation of 3g and using 2h (1.46 g, 5 mmol), the product 3h was obtained as a colorless oil; yield: 292 (10) [M]+, 277 (10), 277 (61), 219 (21), 165 (20), 89 (11), 87 (100); IR (film): ν = 1722, 1489, 1465, 1372, 1251, 1200, 1116, 1030, 755; 1H NMR (CDCl3, 500 MHz): δ = 2.65 (t, 3H), J = 7.25 Hz, 1.77 (s, 3H), 3.82 (s, 3H), 3.97–4.03 (m, 4H), 4.15 (q, 2H, J = 7.25 Hz), 6.83–7.29 (m, 4H), 7.22 (s, 1H); 13C NMR (CDCl3, 125 MHz): δ = 13.9, 25.6, 55.5, 60.7, 64.5, 108.1, 110.5, 120.3, 124.2, 126.8, 128.8, 129.7, 136.1, 157.2, 168.4.

Preparation of (E)-3-Acetoxymethyl-3-(2′-methoxy-phenyl)-3-buten-2-one (1h)

Following the procedure for preparation of 1g and using 3h (375 mg, 1.5 mmol), the product 1h was obtained as a colorless oil; yield: 338 mg (91%).

Preparation of (E)-4-(3′,4′-Dimethoxyphenyl)-3-hydroxymethyl-3-buten-2-one (4i)

Titanium chloride (660 µL, 6 mmol) was added to a mixture of 3-buten-2-one (1 mL, 12 mmol) and 3,4-dimethoxybenzaldehyde (1.66 g, 10 mmol) and dichloromethane (50 mL). The mixture was stirred at room temperature under a nitrogen atmosphere for 72 h, and then quenched with a 10% sodium bicarbonate solution at 0°C. The organic layer was separated, washed with brine and then dried over sodium sulfate. The solvent was removed under reduced pressure, and then the residue was dissolved in acetic acid (10 mL). Trifluoroacetic acid (1 mL, 13 mmol) and potassium carbonate (1.52 g, 11 mmol) were added to the round-bottom flask and the mixture was refluxed for 3 h. After this time, the mixture was cooled to room temperature and added to a separatory funnel containing water (100 mL). The product was extracted with ethyl acetate, the organic layer was washed with brine, and then dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (80:20 hexane/ethyl acetate). Product 4i was obtained as a colorless solid; yield: 843 mg (36%); mp 76.5–81.5°C. RT (GC/MS): 7.18 min; MS: m/z (%): 236 (100) [M]+, 221 (11), 128 (10), 205 (11), 193 (20), 187 (16), 176 (21), 175 (64), 162 (15), 161 (35), 160 (11), 151 (20), 147 (14), 139 (17), 138 (48), 133 (11), 131 (13), 103 (10), 91 (15), 89 (11), 77 (19), 55 (26); 1H NMR (CDCl3, 250 MHz): δ = 2.47 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.15 (q, 2H, J = 7.25 Hz), 6.83–7.29 (m, 4H), 7.22 (s, 1H); 13C NMR (CDCl3, 62.5 MHz): δ = 1.39, 25.6, 55.5, 60.7, 64.5, 108.1, 110.5, 120.3, 124.2, 126.8, 128.8, 129.7, 136.1, 157.2, 168.4.

Preparation of (E)-3-Acetoxyethylmethyl-4-(3′,4′-dimethoxyphenyl)-3-buten-2-one (1i)

Acetic anhydride (343 µL, 3.6 mmol), triethylamine (501 µL, 3.6 mmol) and DMAP (37 mg, 0.3 mmol) were added to a round-bottom flask containing 4i (3 mmol) and dichloromethane (15 mL). The mixture was stirred at 0°C for 1 hour, and then water was added to the round-bottom flask. The mixture was further stirred at room temperature for 15 min, and then the organic layer was separated. The aqueous layer was extracted with dichloromethane, washed with brine, dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (95:5 hexane/ethyl acetate). Product 1i was obtained as a pale yellow solid; yield: 843 mg (36%); mp 76.5–81.5°C. RT (GC/MS): 7.18 min; MS: m/z (%): 236 (100) [M]+, 221 (11), 128 (10), 205 (11), 193 (20), 187 (16), 176 (21), 175 (64), 162 (15), 161 (35), 160 (11), 151 (20), 147 (14), 139 (17), 138 (48), 133 (11), 131 (13), 103 (10), 91 (15), 89 (11), 77 (19), 55 (26); 1H NMR (CDCl3, 250 MHz): δ = 2.47 (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.50 (s, 2H), 6.90–7.14 (m, 4H), 7.21 (s, 1H); 13C NMR (CDCl3, 62.5 MHz): δ = 25.6, 56.0, 57.4, 111.1, 128.3, 127.3, 138.3, 143.6, 149.0, 150.5, 201.0.
Preparation of (E)-3-Hydroxymethyl-4-(3,4-methylenedioxyphenyl)-3-buten-2-one (4j)

Following the procedure for preparation of 4i and using 3,4-methylenedioxybenzaldehyde (4.50 g, 30 mmol) the product 4j was obtained in yield: 3.49 g (53%); mp 75.1–75.9 °C. Rt (GC/MS): 6.91 min; MS-EI: m/z (%) = 220 (100) [M]+, 202 (27), 177 (29), 160 (38), 159 (73), 147 (74), 135 (33), 122 (40), 103 (26), 91 (40), 89 (32), 65 (21), 63 (22); 1H NMR (CDCl3, 600 MHz): δ = 2.46 (s, 3H), 4.46 (d, 2H, J = 6.60 Hz), 6.02 (s, 2H), 6.86–7.06 (m, 3H), 7.56 (s, 1H); 13C NMR (CDCl3, 125 MHz): δ = 25.6, 57.3, 101.6, 108.6, 109.7, 125.0, 128.5, 138.5, 143.2, 148.1, 149.0, 201.1.

Preparation of (E)-3-Acetoxyethyl-4-(3,4-methylenedioxyphenyl)-3-buten-2-one (1i)

Following the procedure for preparation of 1i and using 4j (15 mmol) the product 1j was obtained as a pale yellow solid; yield: 3.587 g (91%); mp 105.9–109.2 °C. Rt (GC/MS): 6.12 min; MS-EI: m/z (%) = 236 (23), 176 (21), 161 (12), 135 (100), 131 (13), 77 (11); 1H NMR (CDCl3, 500 MHz): δ = 2.10 (s, 3H), 2.46 (s, 3H), 4.95 (s, 2H), 6.03 (s, 2H), 6.85–6.96 (m, 3H), 7.69 (s, 1H); 13C NMR (CDCl3, 100 MHz): δ = 21.0, 26.0, 58.5, 101.6, 108.7, 109.3, 125.1, 128.2, 133.8, 145.1, 148.2, 149.2, 170.8, 198.1.

Preparation of (E)-3-Methyl-4-(2'-methoxyphenyl)-3-buten-2-one (5h)

Glacial acetic acid (10 mL) and butanone (1.8 mL, 20 mmol) were added to a round-bottom flask containing 2-methoxybenzaldehyde (1.36 g, 10 mmol). Under stirring, sulfuric acid (2 mL) was added dropwise and the mixture was stirred at room temperature for 16 h. Then, the reaction mixture was neutralized with 10% sodium hydroxide and extracted with diethyl ether. The organic layer was washed with brine and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the product was purified by column chromatography (95:5 hexane/ethyl acetate). Product 5h was obtained as a colorless oil; yield: 1.001 g (55%). Rt (GC/MS): 5.52 min; MS-EI: m/z (%) = 190 (3) [M]+, 159 (100), 132 (16), 131 (18), 115 (10), 91 (22); 1H NMR (CDCl3, 250 MHz): δ = 1.99 (s, 3H, J = 1.25 Hz), 2.47 (s, 3H), 3.87 (s, 3H), 6.9–7.36 (m, 4H), 7.7 (br, 1H); 13C NMR (CDCl3, 100 MHz): δ = 13.1, 25.9, 55.5, 110.5, 120.2, 124.9, 130.1, 130.3, 135.7, 137.7, 157.4, 200.6.

Preparation of (E)-4-(3,4'-Dimethoxyphenyl)-3-methyl-3-buten-2-one (5i)

Following the procedure for preparation of 5h and using 3,4-dimethoxybenzaldehyde (1.66 g, 10 mmol), the product 5i was obtained as a pale yellow oil; yield: 845 mg (38%). Rt (GC/MS): 6.55 min; MS-EI: m/z (%) = 220 (100) [M]+, 219 (34), 205 (65), 190 (11), 189 (64), 177 (27), 162 (11), 147 (11), 146 (32), 131 (16), 115 (13), 103 (12), 91 (15); 1H NMR (CDCl3, 500 MHz): δ = 2.09 (d, 3H, J = 1.00 Hz), 2.46 (s, 3H), 3.92 (s, 3H), 6.92 (d, 1H, J = 7.00 Hz), 6.98 (d, 1H, J = 1.50 Hz), 7.07 (dd, 1H, J = 1.50, 7.00 Hz), 7.47 (br, 1H); 13C NMR (CDCl3, 100 MHz): δ = 13.0, 25.8, 55.9, 111.0, 12.9, 123.4, 128.7, 136.1, 139.8, 148.7, 149.6, 200.2.

Preparation of (E)-3-Methyl-4-(3,4'-methylenedioxyphenyl)-3-buten-2-one (5j)

Following the procedure for preparation of 5h and using piperonal (3.0 g, 10 mmol), the product 5j was obtained as a pale yellow solid; yield: (2.615 g (64%); mp 91.9–94.0 °C. Rt (GC/MS): 6.20 min; MS-EI: m/z (%) = 204 (100) [M]+, 203 (60), 189 (33), 161 (16), 160 (12), 159 (52), 131 (41), 103 (65), 102 (13), 77 (28), 51 (10); 1H NMR (CDCl3, 600 MHz): δ = 2.05 (d, 3H, J = 1.80 Hz), 2.43 (s, 3H), 6.01 (s, 2H), 6.85 (d, 1H, J = 7.80 Hz), 6.94 (dd, 1H, J = 1.20, 7.80 Hz), 6.96 (d, 1H, J = 1.20 Hz), 7.42 (br, 1H); 13C NMR (CDCl3, 125 MHz): δ = 13.0, 25.8, 51.0, 104.8, 108.4, 129.6, 130.0, 136.3, 139.6, 147.8, 148.0, 200.1.

General Procedure for the Biotransformation of 1a–j and 5h–j by Saccharomyces cerevisiae

The yeast Saccharomyces cerevisiae, type II (5.0 g of lyophilized cells), was added to distilled water at 40–42°C (50 mL) in a 125 mL Erlenmeyer flask. The substrate (0.5 mmol) was adsorbed in filter paper (approximately 2 cm² per mg of substrate) and added in small pieces to the cell suspension. The mixture was stirred in an orbital shaker at 30°C and 180 rpm and monitored by GC/MS. After the appropriate amount of time, the reaction mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by column chromatography. The cr values were obtained by chiral GC/FID analysis and the results are provided in Table 1 and Table 2. Spectral data for 6a–g matched those already reported elsewhere.[9]

R) and (S)-3-Methyl-4-(2'-methoxyphenyl)-2-butanone [R]- and (S)-6h: Following the general procedure, the reduction of 6h afforded (R)-6h and the reduction of 5h gave (S)-6h as a colorless oil. Optical rotation of the R isomer: [α]D20 = −43 (c 1.95, CHCl3); lit [10] [α]D20 +57.3 (c 1.1, CHCl3) for the S-isomer. Rt (GC/MS): 4.95 min; Rt (GC/FID, Method B): 57.25 min (R-isomer), 57.88 min (S-isomer); MS-EI: m/z (%) = 192 (36) [M]+, 121 (100), 108 (15), 91 (52); 1H NMR (CDCl3, 250 MHz): δ = 1.05 (d, 3H, J = 6.75 Hz), 2.10 (s, 3H), 2.56 (dd, 1H, J = 6.75, 13.00 Hz), 2.89 (sx, 1H, J = 6.75 Hz), 3.00 (dd, 1H, J = 6.75, 13.00 Hz), 3.82 (s, 3H), 6.82–7.20 (m, 4H); 13C NMR (CDCl3, 150 MHz): δ = 16.0, 28.6, 33.9, 46.8, 55.2, 110.2, 120.3, 127.6, 128.0, 130.9, 157.5, 212.6.

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Preparation of 4-Phenyl-3-hydroxymethyl-2-butanone (8)

Lithium aluminum hydride (114 mg, 3 mmol) was added to a solution of 7 (792 mg, 3 mmol) in THF (3 mL) under a nitrogen atmosphere. The mixture was stirred for 3 h, and then the mixture was cooled to 0°C. Water (0.2 mL) was slowly added to the mixture, and then 10% sodium hydroxide (0.5 mL) was added. After ten minutes, water (0.5 mL) was added and the mixture was heated to room temperature and stirred for 30 min. The solid was filtered and the product was extracted with diethyl ether. The organic layer was washed with brine and then the solvent was removed under reduced pressure. THF (5 mL) and 10% hydrochloric acid (5 mL) were added to the residue, and the mixture was stirred for 16 h. Water was added to the round-bottom flask, and the product was extracted with ethyl acetate. The organic layer was washed with 10% sodium bicarbonate, brine, and dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (90:10 hexane/ethyl acetate). Product 8 was obtained as a colorless oil; yield: 279 mg (52%).

Preparation of 3-Acetoxyethyl-4-phenyl-2-butanone (9)

Triethylamine (167 µL, 1.2 mmol), acetic anhydride (115 µL, 1.2 mmol) and DMAP (12 mg, 0.1 mmol) were added to a solution of 8 (178 mg, 1 mmol) in dichloromethane (5 mL) at 0°C. The mixture was stirred at 0°C for 1 h, and then water (10 mL) was added to the round-bottom flask. The mixture was further stirred at room temperature for 15 min, and then the organic layer was separated. The aqueous layer was extracted with dichloromethane, washed with brine, dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (95:5 hexane/ethyl acetate). Product 9 was obtained as a colorless oil; yield: 186 mg (85%).

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The mixture was stirred for 1 hour. Then, most of the dioxane/water mixture was evaporated under reduced pressure, the residue was diluted with water, and extracted with dichloromethane. The aqueous layer was acidified, and then extracted with dichloromethane. The organic layer from the second extraction was dried over sodium sulfate and the solvent was removed under reduced pressure to afford the corresponding acids. The residue was dissolved in THF (6 mL) and kept under a nitrogen atmosphere. The solution was cooled to 0°C, and then ethyl chlororformate (343 µL, 3.6 mmol) and triethylamine (501 µL, 3.6 mmol) were added to the mixture, which was stirred for 30 min. Triethylammonium chloride was removed by filtration, and then sodium borohydride (555 mg, 15 mmol) was added to the mixture. Methanol was slowly added to the mixture until considerable gas evolution started (adding too much methanol affords the methyl ester), and then the reaction mixture was stirred for 1 hour. After that, the reaction was quenched with water and the product was extracted with dichloromethane. The organic layer was washed with 10% hydrochloric acid, 10% sodium bicarbonate, brine and dried over sodium sulfate. The organic solvent was removed under reduced pressure, and the product was purified by column chromatography (80:20 hexane/ethyl acetate). Product (R)-11 was obtained as a colorless oil; yield: 421.2 mg (72%); 94% ee. Optical rotation: [α]26° = -9.1 (c 3.98, CHCl3); lit.[12] [α]26° = -11.0 (c 1.07, CHCl3); Rt (GC/MS): 5.66 min; Rt (HPLC): 46.27 min.

Preparation of (R)- and (S)-2-methyl-3-(3,4'-methylenedioxyphenyl)propanal – (R)-Tropical® and (S)-Tropical® [(R)- and (S)-12]

TEMPO (15.6 mg, 0.1 mmol) was added to a solution of (R)- or (S)-11 (96 mg, 0.5 mmol) and PhI(OAc)2 (161 mg, 0.5 mmol) in dry dichloromethane (5 mL). The mixture was stirred for 3 h, and then the solvent was removed under reduced pressure. The product was purified by column chromatography (95:5 hexane/ethyl acetate) giving (R)-12 in 68% and (S)-12 in 65% yield. Enantiomerics excesses of the aldehydes were measured by reducing a small sample of (R)- or (S)-12 with sodium borohydride in ethanol, and then analyzing the produced alcohols by chiral HPLC. Optical rotation of the R isomer: [α]26° = +2.9 (c 3.81, CHCl3); lit.[12] [α]26° = +3.3 (c 0.98, CHCl3); optical rotation of the S isomer: [α]26° = -2.5 (c 3.49, CHCl3); lit.[12] [α]26° = -2.8 (c 1.07, CHCl3); Rt (GC/MS): 5.35 min; MS-EI: m/z (%): 192 (34) [M]+, 135 (100), 122 (10), 77 (17); 1H NMR (CDCl3, 500 MHz); δ = 1.08 (d, 3H, J = 7.00 Hz), 2.53 (dd, 1H, J = 7.00, 14.00 Hz), 2.61 (sxd, 1H, J = 1.50, 7.00 Hz), 3.00 (dd, 1H, J = 7.00, 14.00 Hz), 5.92 (s, 2H), 6.61 (dd, 1H, J = 1.50, 7.50 Hz), 6.65 (d, 1H, J = 1.50 Hz), 6.73 (d, 1H, J = 7.50 Hz), 9.69 (d, 1H, J = 1.50 Hz); 13C NMR (CDCl3, 125 MHz); δ = 13.2, 36.4, 48.2, 100.9, 108.2, 109.3, 121.9, 132.5, 146.1, 147.7, 204.4.

General Procedure for the Acylation of 8 with Different Anhydrides: Preparation of 13a–e

Triethylamine (167 µL, 1.2 mmol), the acid anhydride (1.2 mmol) and DMAP (12 mg, 0.1 mmol) were added to a solution of (E)-4-phenyl-3-hydroxymethyl-3-buten-2-one (8.176 mg, 1 mmol) in dichloromethane (5 mL) at 0°C. The mixture was stirred at 0°C for 1 hour, and then water (10 mL) was added to the round-bottom flask. The mixture was further stirred at room temperature for 15 min, and then the organic layer was separated. The aqueous layer was extracted with dichloromethane, washed with brine, dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (95:5 hexane/ethyl acetate).

(E)-4-Phenyl-3-propanoyloxymethyl-3-buten-2-one (13a):
Following the general procedure, 13a was obtained as a colorless oil; yield: 145 mg (62%). Rt (GC/MS): 6.32 min; MS-EI: m/z (%) = 232 (11) [M]+, 176 (24), 175 (100), 159 (12), 158 (71), 157 (17), 133 (24), 129 (18), 116 (17), 115 (65), 57 (66); 1H NMR (CDCl3, 500 MHz); δ = 0.96 (t, 3H, J = 7.50 Hz), 2.35 (q, 2H, J = 7.50 Hz), 2.48 (s, 3H), 4.95 (s, 2H), 7.38–7.45 (m, 5H), 7.79 (s, 1H); 13C NMR (CDCl3, 125 MHz); δ = 13.4, 19.2, 26.1, 27.5, 58.4, 128.9, 129.7, 134.3, 135.5, 144.9, 174.1, 198.3; HR-MS-ESI*: m/z = 233.1194 (M+H)+, calculated: 233.1178.

(E)-3-Butanoyloxymethyl-4-phenyl-3-buten-2-one (13b):
Following the general procedure, 13b was obtained as a colorless oil; yield: 213 mg (87%). Rt (GC/MS): 6.64 min; MS-EI: m/z (%) = 246 (6) [M]+, 176 (20), 175 (100), 158 (43), 157 (11), 133 (16), 129 (11), 116 (12), 115 (43), 71 (45); 1H NMR (CDCl3, 500 MHz); δ = 0.96 (t, 3H, J = 7.50 Hz), 1.67 (sx, 2H, J = 7.50 Hz), 2.32 (t, 2H, J = 7.50 Hz), 2.48 (s, 3H), 4.94 (s, 2H), 7.37–7.44 (m, 5H), 7.88 (s, 1H); 13C NMR (CDCl3, 125 MHz); δ = 13.7, 18.5, 26.1, 36.1, 58.3, 128.8, 129.5, 129.7, 134.3, 135.5, 144.9, 173.3, 198.3; HR-MS-ESI*: m/z = 247.1329 (M+H)+, calculated: 247.1334.

(E)-4-Phenyl-3-pentanoyloxymethyl-3-buten-2-one (13c):
Following the general procedure, 13c was obtained as a colorless oil; yield: 192 mg (74%). Rt (GC/MS): 6.94 min; MS-EI: m/z (%) = 260 (4) [M]+, 176 (19), 175 (100), 158 (36), 133 (14), 116 (11), 115 (36), 85 (40), 57 (43); 1H NMR (CDCl3, 500 MHz); δ = 0.92 (t, 3H, J = 7.50 Hz), 1.36 (sx, 2H, J = 7.50 Hz), 1.62 (q, 2H, J = 7.50 Hz), 2.34 (t, 2H, J = 7.50 Hz), 2.48 (s, 3H), 4.94 (s, 2H), 7.38–7.44 (m, 5H), 7.79 (s, 1H); 13C NMR (CDCl3, 125 MHz); δ = 13.9, 18.5, 26.1, 36.1, 58.3, 128.8, 129.5, 129.7, 134.3, 135.5, 144.9, 173.3, 198.3; HR-MS-ESI*: m/z = 261.1478 (M+H)+, calculated: 261.1491.

(E)-4-Phenyl-3-hexanoyloxymethyl-3-buten-2-one (13d):
Following the general procedure, 13d was obtained as a colorless oil; yield: 166 mg (60%). Rt (GC/MS): 7.32 min; MS-EI: m/z (%) = 274 (4) [M]+, 176 (18), 175 (100), 158 (33), 133 (13), 116 (10), 115 (29), 99 (28), 71 (23); 1H NMR (CDCl3, 500 MHz); δ = 0.90 (t, 3H, J = 7.00 Hz), 1.30–1.33

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Preparation of (E)-3-Benzoyloxymethyl-4-phenyl-3-buten-2-one (13e):
Following the general procedure, 13e was obtained as a colorless oil; yield: 104 mg (37%). 

\[ \text{(E)} - \text{3-Benzoyloxymethyl-4-phenyl-3-buten-2-one (13e) in dichloromethane (25 mL) at 0}^\circ \text{C} \]

Triethylamine (880 mg, 5 mmol), acetic anhydride (567 mg, 5 mmol), and DMAP (60 mg, 0.5 mmol) were added to a solution of 1-phenyl-1-hydroxy-2-methylidene-3-butanone (13f) \( (s, 3H), 4.94 (s, 2H), 7.38–7.44 (m, 5H), 7.78 (s, 1H); 13C NMR (CDCl\textsubscript{3}, 150 MHz): } \delta = 129.8, 130.0, 133.0, 134.3, 135.3, 145.1, 166.3, 198.2; HR-MS-ESI\textsuperscript{+}; \text{m/z} = 275.1635 (M + H\textsuperscript{+})\textsuperscript{+}; calculated: 275.1647.

Yeast from Saccharomyces cerevisiae, type II (20.0 g of lyophilized cells), was added to distilled water at 40–42°C (200 mL) in a 125 mL Erlenmeyer flask. The substrate (2.0 mmol) was adsorbed in filter paper (approximately 2 cm\textsuperscript{2} per mg of substrate) and added in small pieces to the cell suspension. The reaction mixture was stirred in an orbital shaker at 30°C and 180 rpm and monitored by GC/MS. After the appropriate amount of time, the reaction mixture was extracted with ethyl acetate, the organic phase was washed with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by column chromatography (95:5 hexane/ethyl acetate).

Product (1R,2R)-1-Acetoxy-1-phenyl-2-methyl-3-butanone (1[1R,2R]-15)

Yeast from Saccharomyces cerevisiae, type II (20.0 g of lyophilized cells), was added to distilled water at 40–42°C (200 mL) in a 125 mL Erlenmeyer flask. The substrate (2.0 mmol) was adsorbed in filter paper (approximately 2 cm\textsuperscript{2} per mg of substrate) and added in small pieces to the cell suspension. The reaction mixture was stirred in an orbital shaker at 30°C and 180 rpm and monitored by GC/MS. After the appropriate amount of time, the reaction mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by column chromatography (95:5 hexane/ethyl acetate).

Preparation of (E)-2-Benzylidene-3-oxobutyl tert-Butyl Carbonate (13f)

Boc\textsubscript{2}O (262 mg, 1.2 mmol) and DMAP (12 mg, 0.1 mmol) were added to a solution of (E)-4-phenyl-3-hydroxymethyl-3-buten-2-one \( (8, 176 \text{ mg, 1 mmol}) \) in dichloromethane (5 mL) at 0°C. The mixture was stirred at 0°C for 1 hour, and then water (10 mL) was added to the round-bottom flask. The mixture was further stirred at room temperature for 15 min, and then the organic layer was separated. The aqueous layer was extracted with dichloromethane, washed with brine, dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (95:5 hexane/ethyl acetate). Product 13f was obtained as a colorless solid; yield: 103 mg (37\%); mp 130.5–134.2°C. 

\[ \text{Rt (GC/MS): 6.80 min; MS-ESI: m/z}\textsuperscript{+} (\%) = 220 (100), 219 (51), 175 (12), 159 (24), 158 (26), 117 (12), 116 (19), 115 (48), 57 (42); 1\text{H NMR (CDCl}_3, 500 MHz): } \delta = 2.52 – 2.53 (2H), 5.20 (2H), 7.38–8.02 (m, 10H), 7.86 (s, 1H). 13C NMR (CDCl\textsubscript{3}, 150 MHz): \delta = 26.2, 59.1, 128.4, 128.9, 129.5, 129.7, 129.8, 130.0, 133.4, 135.3, 145.1, 166.3, 198.2; HR-MS-ESI\textsuperscript{+}; \text{m/z} = 281.1161 (M + H\textsuperscript{+})\textsuperscript{+}; calculated: 281.1178.

Preparation of 1-Acetoxy-1-phenyl-2-methylidene-3-butanone (14)

Triethylamine \( (880 \text{ mg, 5 mmol}) \), acetic anhydride \( (567 \text{ mg, 6 mmol}) \) and DMAP \( (60 \text{ mg, 0.5 mmol}) \) were added to a solution of 1-phenyl-1-hydroxy-2-methylidene-3-butanone \( (880 \text{ mg, 5 mmol}) \) in dichloromethane \( (25 \text{ mL}) \) at 0°C. The mixture was stirred at 0°C for 1 hour, and then water \( (10 \text{ mL}) \) was added to the round-bottom flask. The mixture was further stirred at room temperature for 15 min, and then the organic layer was separated. The aqueous layer was extracted with dichloromethane, washed with brine, dried over sodium sulfate. The solvent was removed under reduced pressure and the product was purified by column chromatography (95:5 hexane/ethyl acetate). Product 14 was obtained as a colorless oil; yield: 918 mg (84\%). 

\[ \text{Rt (GC/MS): 5.40 min; MS-ESI: m/z}\textsuperscript{+} (\%) = 176 (24), 175 (100), 115 (24), 105 (20), 97 (23), 77 (10); 1\text{H NMR (CDCl}_3, 500 MHz): } \delta = 2.09 (s, 3H), 2.31 (s, 3H), 6.07 (d, 1H, J = 1.00 Hz), 6.22 (bs, 1H), 6.74 (bs, 1H), 7.27–7.38 (5H, 5H); 13C NMR (CDCl\textsubscript{3}, 100 MHz): \delta = 21.1, 26.2, 72.5, 125.2, 127.5, 128.2, 128.4, 138.2, 147.8, 169.4, 197.3.

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Preparation of 1-Phenyl-2-methylideno-3-pentanone (19)

LiAlH₄ (380 mg, 10 mmol) was added to a solution of 18 (2.64 g, 10 mmol) in dry THF (10 mL) under an N₂ atmosphere. The mixture was stirred for 3 h at room temperature and after that the mixture was cooled to 0°C. Water (0.5 mL) was slowly added and 10% NaOH solution (1 mL) was also slowly added. After 10 min, water (2 mL) was added and the mixture was heated to room temperature. After the mixture had been stirred for 30 min, MgSO₄ was added and the resulting mixture was filtered. 10% HCl solution (10 mL) was added to the filtrate and the resulting mixture was stirred for 16 h. After that, the reaction product was extracted with EtOAc, the organic phase was washed with 10% NaHCO₃ solution, brine and dried with MgSO₄. The solvent was removed under reduced pressure giving an oil that was treated with benzene (10 mL). MsCl (851 μL, 11 mmol) and DBU (3.29 mL, 22 mmol). The resulting mixture was refluxed for 2 h and then water (10 mL) was added and the mixture stirred for 10 min. The organic phase was washed three times with water, brine and dried with Na₂SO₄. After the removing the solvent under reduced pressure, the product was purified by column chromatography (hexane/EtOAc, 95:5) giving 19 as a colorless oil; yield: 1.05 g (60%). Rt (GC/MS): 4.58 min; MS-EI: m/z (%) = 174 (50) [M⁺], 173 (26), 146 (10), 145 (84), 118 (10), 117 (100), 116 (28), 115 (82), 91 (36), 65 (11), 57 (15); ¹H NMR (CDCl₃, 250 MHz): δ = 0.86 (t, 3H, J = 7.25 Hz), 2.71 (q, 2H, J = 7.25 Hz), 3.60 (s, 2H), 5.60 (s, 1H), 6.07 (s, 1H), 7.15–7.29 (m, 5H); ¹³C NMR (CDCl₃, 62.5 MHz): δ = 8.31, 13.0, 30.8, 128.4, 128.8, 129.7, 136.0, 137.2, 137.8, 138.2, 201.9.

Preparation of Methyl (Z)-2-(2’-Ethyl-1’,3’-dioxolan-2’-yl)-3-phenylpropanoate (20)

Morpholine (2.585 mL, 30 mmol) was slowly added to a round-bottom flask containing methyl 3-oxopentanoate (3.790 mL, 30 mmol), benzaldehyde (3.060 mL, 30 mmol) and glacial acetic acid (3.430 mL, 60 mmol). The reaction mixture was stirred for 24 h, and then ethyl acetate was added to the mixture. The solution was washed with water, and the organic layer was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was dissolved in toluene (60 mL). Ethylene glycol (3.355 mL, 60 mmol) and p-toluene sulfonic acid (517 mg, 3 mmol) were added to the round-bottom flask. The mixture was refluxed for 6 h with water removal by means of a Dean–Stark apparatus. Then, the mixture was added to a separatory funnel, and washed with water, 10% sodium bicarbonate and brine. The organic layer was dried over sodium sulfate, the solvent was removed under reduced pressure and the product was purified by column chromatography (hexane/EtOAc, 95:5) giving 20 as a colorless oil; yield: 6.084 g (77%). Rt (GC/MS): 6.29 min; MS-EI: m/z (%) = 234 (15), 233 (100), 121 (37), 103 (38), 102 (10), 101 (39), 57 (12).

Preparation of (E)-2-(2’-Ethyl-1’,3’-dioxolan-2’-yl)-3-phenyl-2-propen-1-ol (21)

Disobutylaluminum hydride (2M in toluene, 24 mL, 48 mmol) was slowly added to a solution of compound 20...
Preparation of (E)-2-Acetoxymethyl-1-phenyl-1-penten-3-one (22)

10% Hydrochloric acid (10 mL) was added to a solution of 21 (2.34 g, 10 mmol) in THF (10 mL). The reaction mixture was refluxed for 2 h, and then the water was added to the round-bottom flask and the product was extracted with ethyl acetate. The organic layer was washed with water and brine and then dried over sodium sulfate. The solvent was removed under reduced pressure, and the product was purified by column chromatography (85:15 hexane/ethyl acetate). Product 21 was obtained as a colorless oil; yield: 2.704 g (58%). Rt (GC/MS): 6.34 min; MS-EI m/z 232 (79) [M]+, 190 (24), 189 (40), 173 (12), 172 (79), 161 (53), 143 (100), 133 (51), 128 (10), 117 (51), 116 (21), 115 (85), 103 (11), 77 (12), 57 (46); 1H NMR (CDCl3, 600 MHz): δ = 0.97 (t, 3H, J = 7.20 Hz), 1.90 (q, 2H, J = 7.80 Hz), 2.71 (brs, 1H), 3.97–4.03 (m, 4H), 4.25 (s, 2H), 6.89 (s, 1H), 7.25–7.41 (m, 5H); 13C NMR (CDCl3, 62.5 MHz): δ = 7.8, 29.9, 58.7, 64.7, 112.5, 127.4, 129.0, 129.9, 136.1, 138.2.

Preparation of (R)- and (S)-1-Phenyl-2-methyl-3-pentanone [(R)- and (S)-23]

Substrate 17 or 19 (1.0 mmol) was adsorbed in filter paper (approximately 2 cm² per mg of substrate) and added in small pieces to a suspension of Candida albicans (10 g, wet mass) in water (50 mL) in a 250 mL Erlenmeyer flask. The reaction mixture was stirred in an orbital shaker at 30°C and 180 rpm and monitored by GC/MS. After 48 h, the reaction mixture was extracted with ethyl acetate, the organic layer was washed with brine, dried over sodium sulfate and the solvent was removed under reduced pressure. The product was purified by column chromatography (95:5 hexane/ethyl acetate). Product (S)-23 was obtained as a colorless oil; yield: 139.3 mg (79%); 95% ee. Product (R)-23 was obtained as a colorless oil; yield: 126.5 mg (72%); 93% ee. Optical rotation of the R isomer: [α]23D = -65.1 (c 3.86, CHCl3); Optical rotation of the S isomer: [α]23D = +63.0 (c 3.20, CHCl3); lit.[2] [α]23D = +7.0 (c 1.10, CHCl3); Rt (GC/MS): 4.40 min; Rt (GC/FID, Method A): 22.43 min (S isomer), 23.66 min (R isomer); MS-ESI m/z (%): 176 (20) [M]+, 147 (39), 119 (28), 91 (100), 57 (36); 1H NMR (CDCl3, 600 MHz): δ = 0.97 (t, 3H, J = 7.20 Hz), 1.79 (t, 3H, J = 7.20 Hz), 2.25 (dq, 1H, J = 7.20, 17.40 Hz), 2.34 (dq, 1H, J = 7.20, 17.40 Hz), 2.57 (dd, 1H, J = 7.20, 13.80 Hz), 2.84 (sx, 1H, J = 7.20 Hz), 2.97 (dd, 1H, J = 7.20, 13.80 Hz), 7.12–7.28 (m, 5H). 13C NMR (CDCl3, 62.5 MHz): δ = 7.6, 16.6, 35.2, 39.3, 47.9, 126.2, 128.4, 128.9, 139.9, 214.8.

Acknowledgements


References


Bioreduction of α-Acetoxyethyl Enones: Proposal for an S$_{N}$2′ Mechanism Catalyzed by Enereductase


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