Bioreduction of $\alpha$-Methylcinnamaldehyde Derivatives: Chemo-Enzymatic Asymmetric Synthesis of Lilial$^{\text{TM}}$ and Helional$^{\text{TM}}$

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Electronic Supporting Information

Experimental

General

TLC plates were run on silica gel Merck 60 (F$_{254}$) and compounds were visualized by spraying with Mo-reagent [(NH$_4$)$_6$Mo$_7$O$_{24}$·4H$_2$O (100 g/L), Ce(SO$_4$)$_2$·4H$_2$O (4 g/L) in H$_2$SO$_4$ (10%)] or by UV (254 nm). Conversion and enantiomeric excess were determined via GC or HPLC analysis, respectively. GC analysis was carried out on a Varian 3800 gas chromatograph equipped with a FID detector using H$_2$ as carrier gas (14.5 psi), using an achiral stationary phase [for the determination of conversion (Varian CP-1301, 6 % cyanopropyl-phenyl phase capillary column, 30 m, 0.25 mm, 0.25 µm), column A] or a chiral stationary phase [for the determination of the enantiomeric excess (Hydrodex-$\beta$-6TBDM, modified $\beta$-cyclodextrin capillary column, 25 m x 0.25 mm), column B]. Temperature of the injector and detector were 180 and 250 °C, respectively, using a split ratio of 20:1. Chiral HPLC analyses were carried out on a Shimadzu system equipped with a Chiralcel OD-H column (column C, 0.46 x 25 cm) or a Chiralcel OJ column (column D, 0.46 x 25 cm) for the determination of the enantiomeric excess. NMR spectra were measured in CDCl$_3$ using a Bruker AMX spectrometer at 360 ($^1$H) and 90 ($^{13}$C) MHz. Chemical shifts are reported relative to TMS (δ = 0.00) and coupling constants ($J$) are given in Hz. Optical rotation values ([α]$_D^{20}$) were measured on a Perkin-Elmer polarimeter 341 at 589 nm (Na-line) in a 1 dm cuvette and are given in units of [(deg x mL)/(g x dm)].

$^{(E)}$-3-(4-tert-Butylphenyl)-2-methylpropanal (1a), $^{(E)}$-3-(1,3-benzodioxole-5-yl)-2-methylpropanal (2a) and $^{(E)}$-$\alpha$-methylcinnamaldehyde (3a) were provided by BASF (Ludwigshafen), NADH and

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NAD$^+$ were purchased from Biocatalytix/Codexis, glucose was obtained from Fluka and glucose dehydrogenase from Jülich Chiral Solutions.

\((E)-3\)-(4-tert-Butylphenyl)-2-methylpropanal (1a): \(^1\text{H}\) (360 MHz, CDCl$_3$) \(\delta = 1.37\) (s, 9H), 2.11 (s, 3H), 7.27 (s, 1H), 7.48-7.53 (m, 4H), 9.59 (s, CHO); \(^{13}\text{C}\) (90 MHz, CDCl$_3$) \(\delta = 10.96, 31.15, 34.89, 125.72, 130.07, 149.96, 195.70\).

\((E)-3\)-(1,3-Benzodioxole-5-yl)-2-methylpropanal (2a): \(^1\text{H}\) (360 MHz, CDCl$_3$) \(\delta = 2.07\) (s, 3H), 6.05 (s, 2H), 6.9-7.08 (m, 3H), 7.16 (s, 1H), 9.53 (s, 1H); \(^{13}\text{C}\) (90 MHz, CDCl$_3$) \(\delta = 10.95, 101.62, 108.65, 109.62, 125.81, 129.44, 136.58, 148.09, 148.88, 149.75, 195.40\).

\((E)-\alpha\)-Methylcinnamaldehyde (3a): \(^1\text{H}\) (360 MHz, CDCl$_3$) \(\delta = 2.10\) (s, 3H), 7.28 (s, 1H), 7.39-7.56 (m, 5H), 9.61 (s, CHO); \(^{13}\text{C}\) (90 MHz, CDCl$_3$) \(\delta = 10.94, 128.72, 129.57, 130.03, 135.16, 138.39, 149.80, 195.55\).

**General procedure for the synthesis of reference materials via catalytic hydrogenation**

\((E)-\)Alkene (1a-3a, 0.5 mmol) was dissolved in THF (10 mL) and hydrogenated under H$_2$ at atmospheric pressure and at room temperature employing Pd/C (10%, 5 mg) as catalyst. After the mixture was stirred overnight at room temperature, the reaction mixture was filtered through Celite and concentrated to yield racemic reference materials (rac-1b-3b) at 99% conversion. Thus were obtained:

- rac-3-(4-tert-Butylphenyl)-2-methylpropanal (Lysmeral\textsuperscript{TM}, Lilial\textsuperscript{TM}, rac-1b): \(^1\text{H}\) (360 MHz, CDCl$_3$) \(\delta = 1.11-1.12\) (d, 3H, \(J = 6.8\)Hz), 1.33 (s, 9H), 2.59-2.63 (m, 2H), 3.05-3.09 (m, 1H), 7.11-7.13 (d, 2H, \(J = 8.2\)), 7.32-7.35 (d, 2H, \(J = 8.2\)), 9.74-9.75 (d, CHO, \(J = 1.4\)); \(^{13}\text{C}\) (90 MHz, CDCl$_3$) \(\delta = 13.30, 31.37, 34.39, 36.16, 48.02, 125.41, 128.67, 204.62\).
- rac-3-(1,3-Benzodioxole-5-yl)-2-methylpropanal (Tropional\textsuperscript{TM}, Helional\textsuperscript{TM}, rac-2b): \(^1\text{H}\) (360 MHz, CDCl$_3$) \(\delta = 1.09-1.11\) (d, 3H, \(J = 6.8\)), 2.52-2.66 (m, 2H), 2.99-3.04 (m, 1H), 5.95 (s, 2H), 6.62-6.76 (m, 3H) 9.72 (s, CHO); \(^{13}\text{C}\) (90 MHz, CDCl$_3$) \(\delta = 13.18, 36.40, 48.22, 100.91, 108.25, 109.30, 121.94, 132.50, 146.11, 147.73, 204.41\).
- rac-2-Methyl-3-phenylpropanal (rac-3b): \(^1\text{H}\) (360 MHz, CDCl$_3$) \(\delta = 1.10-1.12\) (d, 3H, \(J = 6.8\)Hz), 2.59-2.73 (m, 2H), 3.09-3.14 (m, 1H), 7.18-7.34 (m, 5H), 9.74-9.75 (d, CHO, \(J = 1.3\)Hz); \(^{13}\text{C}\) (90 MHz, CDCl$_3$) \(\delta = 13.21, 36.65, 48.04, 126.42, 128.53, 129.02, 138.83, 204.39\).

Reference material for rac-2-methyl-3-phenylpropan-1-ol (rac-3c)\textsuperscript{1} was obtained by NaBH$_4$-reduction (1.5 equiv.) of rac-3b in MeOH at r.t. for 2h: \(^1\text{H}\) (360 MHz, CDCl$_3$) \(\delta = 0.95\) (d, 3H, \(J = 6.7\)), 1.96-1.98 (m, 1H), 2.45 (dd, 1H, \(J = 6\) and 13), 2.79 (dd, 1H, \(J = 5\) and 13), 3.46-3.58 (m, 2H), 7.20-7.30 (m, 5H, ArH); \(^{13}\text{C}\) (90 MHz, CDCl$_3$) \(\delta = 16.48, 37.76, 39.72, 67.52, 125.90, 128.28, 129.17, 140.66\).
Determination of conversion and enantiomeric excess. The conversion and enantiomeric excess were determined via GC or HPLC analysis, respectively.

Table 3. Determination of conversion via achiral GC-analyses.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Column&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conditions&lt;sup&gt;b&lt;/sup&gt;</th>
<th>1a-3a</th>
<th>1b-3b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A</td>
<td>E</td>
<td>8.23</td>
<td>5.45</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>E</td>
<td>8.99</td>
<td>5.78</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>E</td>
<td>3.80</td>
<td>3.10</td>
</tr>
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</table>

<sup>a</sup> Column: A = Varian CP-1301, 6 % cyanopropyl-phenyl phase capillary column; <sup>b</sup> conditions: E = 14.5 psi H<sub>2</sub> at 180 °C, hold for 11 min.

Table 4. Determination of enantiomeric excess via chiral GC- and HPLC-analyses.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Column&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Conditions&lt;sup&gt;b&lt;/sup&gt;</th>
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<th>1&lt;sub&gt;S&lt;/sub&gt;</th>
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<tr>
<td>1b</td>
<td>C</td>
<td>G</td>
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<td>29.73</td>
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<td>2b</td>
<td>D</td>
<td>H</td>
<td>12.5</td>
<td>13.5</td>
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<tr>
<td>3b</td>
<td>B</td>
<td>F</td>
<td>11.8</td>
<td>12.7</td>
</tr>
</tbody>
</table>

<sup>a</sup> Column: B = Chiralcel OJ column (HPLC); C = Hydrodex-β-6TBDM, modified β-cyclodextrin capillary column (GC); D = Chiralcel OD-H column (HPLC); <sup>b</sup> conditions: F = n-heptane/i-propanol 99:1 (isocratic) at 18 °C, flow 1 mL/min, ε = 190 nm, 205 nm, 215 nm; G = 14.5 psi H<sub>2</sub> at 130 °C, hold for 0 min, heat rate 1 °C/min to 165 °C, heat rate 20 °C/min to 180 °C, hold for 7 min; H = n-heptane/i-propanol 98:2 (isocratic) at 18 °C, 0-15 min: flow 1 mL/min, 15-20 min: flow 1.5 mL/min, ε = 205 nm, 235 nm, 285 nm.

References and Notes