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Bioreduction of α-Methylcinnamaldehyde Derivatives: Chemo-Enzymatic Asymmetric Synthesis of Lilial™ and Helional™

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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 [$(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (100 g/L), $Ce(SO_4)_2\cdot 4H_2O$ (4 g/L) in H_2SO_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-β-6TBDM, modified β-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 ($[\alpha]_D^{20}$) 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-methylpropenal (**1a**), (*E*)-3-(1,3-benzodioxole-5-yl)-2-methylpropenal (**2a**) and (*E*)-α-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-methylpropenal (**1a**): ^{1}H (360 MHz, $CDCl_3$) δ = 1.37 (s, 9H), 2.11 (s, 3H), 7.27 (s, 1H) 7.48-7.53 (m, 4H), 9.59 (s, CHO); ^{13}C (90 MHz, $CDCl_3$) δ = 10.96, 31.15, 34.89, 125.72, 130.07, 149.96, 195.70.

(*E*)-3-(1,3-Benzodioxole-5-yl)-2-methylpropenal (**2a**): ^{1}H (360 MHz, $CDCl_3$) δ = 2.07 (s, 3H), 6.05 (s, 2H), 6.9-7.08 (m, 3H) 7.16 (s, 1H), 9.53 (s, 1H); ^{13}C (90 MHz, $CDCl_3$) δ = 10.95, 101.62, 108.65, 109.62, 125.81, 129.44, 136.58, 148.09, 148.88, 149.75, 195.40.

(*E*)-α-Methylcinnamaldehyde (**3a**): ^{1}H (360 MHz, $CDCl_3$) δ = 2.10 (s, 3H), 7.28 (s, 1H), 7.39-7.56 (m, 5H), 9.61 (s, CHO); ^{13}C (90 MHz, $CDCl_3$) δ = 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™, Lilial™, *rac*-**1b**): ^{1}H (360 MHz, $CDCl_3$) δ = 1.11-1.12 (d, 3H, *J* = 6.8Hz), 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}C (90 MHz, $CDCl_3$) δ = 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™, Helional™, *rac*-**2b**): ^{1}H (360 MHz, $CDCl_3$) δ = 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}C (90 MHz, $CDCl_3$) δ = 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}H (360 MHz, $CDCl_3$) δ = 1.10-1,12 (d, 3H, *J* = 6.8Hz), 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* = 1.3Hz); ^{13}C (90 MHz, $CDCl_3$) δ = 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**)[1] was obtained by $NaBH_4$-reduction (1.5 equiv.) of *rac*-**3b** in MeOH at r.t. for 2h: ^{1}H (360 MHz, $CDCl_3$) δ = 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}C (90 MHz, $CDCl_3$) δ = 16.48, 37.76, 39.72, 67.52, 125.90, 128.28, 129.17, 140.66.

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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.

Compound	Column[a]	Conditions[b]	t_R [min]	
			1a-3a	**1b-3b**
1	A	E	8.23	5.45
2	A	E	8.99	5.78
3 [2]	A	E	3.80	3.10

[a] Column: A = Varian CP-1301, 6 % cyanopropyl-phenyl phase capillary column; [b] conditions: E = 14.5 psi H_2 at 180 °C, hold for 11 min.

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

Compound	Column[a]	Conditions[b]	t_R [min]	
			(*R*)	(*S*)
1b	C	G	29.45	29.73
2b	D	H	12.5	13.5
3b	B	F	11.8	12.7

[a] Column: B = Chiralcel OJ column (HPLC); C = Hydrodex-β-6TBDM, modified β-cyclodextrin capillary column (GC); D = Chiralcel OD-H column (HPLC); [b] 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_2 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

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