Supporting Information for

Bio-renewable Enantioselective Aldol Reaction in Natural Deep Eutectic Solvents.

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General Information: All reactions were carried out under argon. All reagents are commercially available and used without further purification. ¹H NMR (300 MHz, 400 MHz) and ¹³C NMR (75 MHz) spectra were obtained at 25 °C using CDCl₃ as solvent and chemical shifts are reported as δ values relative to TMS as internal standard. HPLC analyses were performed on equipped with a chiral column and automatic inyector, using mixtures of n-hexane/isopropyl alcohol (IPA) as mobile phase, at 25 °C. Analytical TLC was performed on silica gel plates and the spots were visualized under UV light (λ =254 nm). For flash chromatography we employed silica gel 60 (0.040-0.063 nm). For recycling experiments, an Edwards T-station equipped with a diaphragm pump 75 was used for water evaporation.

General procedure for the preparation of DES: The corresponding solid components of the desired DES in the correct proportion were placed in a 50 mL round-bottom flask. The resulting mixture was heated to 80 °C (from 1 to 3 h) under argon atmosphere with stirring until a clear colourless liquid was obtained.

General procedure for the aldol reaction in deep eutectic solvent: To around 1 mL of the corresponding solvent in a vessel under argon atmosphere, L-proline (0.035 g, 30 mol%) and the corresponding aldehyde (1 mmol) were added. Then the source of nucleophile was charged (5 mmol for the case of acetone and propanal, 1 mmol for cyclohexanone, 2 for the other ketones). The reaction mixture was stirred under argon atmosphere for 24 h to 5 days (see Table 1 and 2, Scheme 3 and text) at room temperature. Then, 2 mL of water were added and the mixture was extracted with ethyl acetate (3 \times 1 mL). The resulting organic phase was dried over anhydrous magnesium sulphate, and the solvent was evaporated under reduced pressure. The resulting crude material was purified by percolation through a small pad of silica gel with 1:1 ethyl acetate/hexane mixtures. In the case of using propanal, after extraction, the resulting organic phase was dried over anhydrous magnesium sulphate, and the solvent was evaporated under reduced pressure. The resulting crude was treated with sodium borohydride (5 mmol, 190 mg) in methanol (3 mL). The reaction mixture was stirred during 2 h at 0 °C. After reaction, phosphate buffer (2 mL) was added, and the mixture was extracted with ethyl acetate (3 \times 1 mL). The resulting organic phase was dried over anhydrous magnesium sulphate, and the solvent was evaporated under reduced pressure. The resulting crude material was purified by percolation through a small pad of silica gel with 1:1 ethyl acetate/hexane mixtures.

Recover and reuse of the catalyst and DES: To the corresponding solvent [aprox 3 mL: D-glucose (2.7 g) and D/L-malic acid (2.1 g)] were placed in a vessel under argon atmosphere. L-proline (0.175 g) and the corresponding aldehyde (5 mmol) were added. Then the source of nucleophile was charged (25 mmol). The reaction mixture was stirred under argon atmosphere for 24 h. Then, 10 mL of water was

added and the resulting organic upper layer was collected through a pipette for the gram scale procedure. The resulting organic phase was dried over anhydrous magnesium sulphate, and the solvent was evaporated under reduced pressure. The resulting crude material was purified recrystallization from ethyl acetate/hexane mixtures. The aqueous layer was evaporated under reduced pressure. Water traces were eliminated for the residue using a high-vacuum membrane pump system over 24 hours. Then, the flask containing the DES and L-proline was charged with a new batch of aldehyde and acetone.

Spectra data of aldol products

4-Hydroxy-4-(4-nitrophenyl)butan-2-one:[1]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ =2.22 (s, 3H), 2.86 (d, *J*(H,H)=2.9 Hz, 2H), 3.59 (d, *J*(H,H)= 3.3 Hz, 1H), 5.27 (dd, *J*(H,H)= 2.9, 3.3 Hz, 1H), 7.55 (d, *J*(H,H)= 8.8 Hz, 2H), 8.21 ppm (d, *J*(H,H)= 8.8 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ =30.5, 51.4, 68.7, 123.6, 126.3, 147.3, 149.8, 208.2 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel AS column at 254 nm (*n*-hexane/*i*-PrOH: 85/15, 1.0 mL/min), $t_{\rm R} = 16.8$ (major), $t_{\rm R} = 26.8$ (minor).



4-Hydroxy-4-(2-nitrophenyl)butan-2-one:[2]

¹H NMR (400 MHz, CDCl₃, 25 °C, TMS): δ =2.17 (s, 3H), 2.92-2.73 (m, 2H), 3.60 (br s, 1H), 3.82 (s, 3H), 5.41 (d, 1H, *J*(H,H)=8 Hz), 6.86 (d, 1H, *J*(H,H)=8 Hz), 6.97 (t, 1H, *J*(H,H)=8 Hz), 7.25 (t, 1H, *J*(H,H)=8 Hz), 7.44 ppm (d, 1H, *J*(H,H)= 8 Hz). ¹³C NMR (100 MHz, CDCl₃, 25 °C, TMS): δ = 30.5, 50.3, 55.2, 65.3, 110.2, 120.7, 126.2, 128.3, 130.9, 155.7 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel ADH column at 254 nm (*n*-hexane/*i*-PrOH: 98/2, 1.0 mL/min), $t_{\rm R} = 41.7$ (major), $t_{\rm R} = 45$ (minor).



4-Hydroxy-4-(3-nitrophenyl)butan-2-one:[2]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): *δ*=2.21 (s, 3H), 2.69-2.96 (m, 2H), 3.39 (s, 1H), 5.12 (dd, 1H, *J*(H,H)=7.8, 4.5 Hz), 7.24 (d, 2H, *J*(H,H)=8.3 Hz), 7.48 ppm (d, 2H, *J*(H,H)=8.4 Hz,). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): 30.7, 51.5, 68.8, 120.7, 122.6, 129.5, 131.8, 144.7, 148.3, 208.8 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel ADH column at 254 nm (*n*-hexane/*i*-PrOH: 95/5, 1.0 mL/min), $t_R = 21.4$ (major), $t_R = 22.7$ (minor).



4-(4-Cyanophenyl)-4-hydroxybutan-2-one:[2]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): *δ*=2.21 (s, 3H), 2.83 (m, 2H), 5.05-5.24 (m, 1H), 7.47 (d, 2H, *J*(H,H)= 8.7 Hz), 7.63 ppm (d, 2H, *J*(H,H)=8.7 Hz). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): 29.4, 51.6, 68.9, 111.2, 118.8, 126.4, 132.4, 148.1, 208.7 ppm. The enantiomeric excess was determined by HPLC with a Chiralcel ODH column at 230 nm (*n*-

hexane/*i*-PrOH: 95/5, 1.0 mL/min), $t_R = 31.2$ (major), $t_R = 36.3$ (minor).



4-Hydroxy-4-(4-(trifluoromethyl)phenyl)butan-2-one:[2]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ =2.22 (s, 3H), 2.86 (d, *J*(H,H)=2.9 Hz, 2H), 3.59 (d, *J*(H,H)= 3.3 Hz, 1H), 5.27 (dd, *J*(H,H)= 2.9, 3.3 Hz, 1H), 7.55 (d, *J*(H,H)= 8.8 Hz, 2H), 8.21 ppm (d, *J*(H,H)= 8.8 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ =30.5, 51.4, 68.7, 123.6, 126.3, 147.3, 149.8, 208.2 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel AS column at 230 nm (*n*-hexane/*i*-PrOH: 92/8, 1.0 mL/min), $t_R = 8.6$ (major), $t_R = 10.8$ (minor).



4-(2-Chlorophenyl)-4-hydroxybutan-2-one:[1]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): *δ*=2.17 (s, 3H), 2.61-2.96 (m, 2H), 3.80 (br s, 1H), 5.46-5.55 (m, 1H), 7.14-7.28 ppm (m, 4H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): 30.5, 50.1, 66.5, 127.1, 127.2, 128.5, 129.5, 129.3, 209.0 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel AS column at 254 nm (*n*-hexane/*i*-PrOH: 98/2, 1.0 mL/min), $t_{\rm R} = 20.8$ (minor), $t_{\rm R} = 24.4$ (major).



4-Hydroxy-4-phenylbutan-2-one:[1]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ =2.21 (s, 3H), 2.83 (dd, 1H, *J*(H,H)=3.3, 17.7 Hz), 2.90 (dd, 1H, *J*(H,H)=9.0, 17.7 Hz), 5.16 (dd, 1H, *J*(H,H)=3.3, 9.0 Hz),), 7.29 ppm (m, 5H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): 30.8, 50.2, 69.8, 125.6, 128.6, 127.7, 128.5, 142.6, 209.3 ppm. The enantiomeric excess was determined by HPLC with a Chiralcel AS column at 210 nm (*n*-hexane/*i*-PrOH: 90/10, 1.0 mL/min), *t*_R = 11.5 (major), *t*_R = 14.1 (minor).



4-Hydroxy-4-(4-tolil)butan-2-one:[3]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): *δ*=2.20 (s, 3H), 2.35 (s, 3H), 2.82 (d, *J*(H,H)=3.0 Hz, 2H), 3.33 (br s, 1H), 5.12 (d, *J*(H,H)= 3.0 Hz, 1H), 7.17 (d, *J*(H,H)= 8.9 Hz, 2H), 7.26 ppm (d, *J*(H,H)= 8.9 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): *δ*=21.1, 30.8, 52.0, 69.7, 125.6, 128.2, 129.7, 137.4, 209.2 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel IA column at 280 nm (*n*-hexane/*i*-PrOH: 95/5, 1.0 mL/min), $t_{\rm R} = 10.5$ (minor), $t_{\rm R} = 12.6$ (major).



4-Hydroxy-4-(cyclohexyl)-butan-2-one:[3]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): *δ*=0.95-1.25 (m, 6h), 1.61-1.76 (m. 5H), 2.18 (s, 3H), 2.53 (m, 2H), 2.89 (br s, 1H), 3.82 (m, 1H) ppm. ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): *δ*=25.8, 26.2, 26.5, 28.1, 29.0, 30.7, 42.9, 47.7, 71.9, 210.7 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel AS column at 210 nm (*n*-hexane/*i*-PrOH: 90/10, 1.0 mL/min), $t_{\rm R} = 9.5$ (major), $t_{\rm R} = 11.3$ (minor).



anti-**3j**

2-[Hydroxy(4-nitrophenyl)methyl]cyclohexanone:[3]

¹H NMR (300 MHz, CDCl₃ CDCl₃, 25 °C, TMS): $\delta = \Box 1.28 \cdot 1.49$ (m, 1H), 1.52-1.73 (m, 3H), 1.79-1.83 (m, 1H), 2.06-2.14 (m, 1H), 2.21-2.31 (m, 1H), 2.33-2.50 (m, 1H), 2.54-2.63 (m, 1H), 3.12 (br s, 1H *syn*), 4.02 (br s, 1H *anti*), 4.88 (d, *J*(H,H)=8.4 Hz, 1H *anti*), 5.46 (s, 1H *syn*), 7.49 (d, *J*(H,H)=8.7 Hz, 2H), 8.19 ppm (d, *J*(H,H)=8.7 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃25 °C, TMS): δ =*anti* 24.6, 27.5, 30.6, 42.6, 57.1, 73.9, 123.5, 127.8, 147.4, 148.3, 214.6.

The enantiomeric excess was determined by HPLC with a Chiralcel ADH column at 254 nm (*n*-hexane/*i*-PrOH: 90/10, 1.0 mL/min), anti: $t_R = 19.1$ (minor), $t_R = 25.1$ (major), syn: $t_R = 15.0$ (minor), $t_R = 17.1$ (major).





2-[Hydroxy(4-(trifluoromethyl)phenyl)methyl]cyclohexanone:[4]

¹H NMR (300 MHz, CDCl₃ CDCl₃, 25 °C, TMS): $\delta = \Box 1.49 \cdot 1.83$ (m, 5H), 2.05-2.10 (m, 1H), 2.30-2.48 (m, 2H), 2.65-2.71 (m, 1H), 4.05 (d, *J*(H,H)=4.0 Hz, 1H), 5.35 (dd, *J*(H,H)=4.0, 8.2 Hz, 1H), 7.49 (d, *J*(H,H)=8.7 Hz , 2H), 8.19 ppm (d, *J*(H,H)=8.7 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): $\delta = anti 24.8, 27.8, 30.3, 42.6, 57.5, 70.3, 127.1, 128.1, 128.6, 129.1, 132.8, 139.0, 215.1 ppm.$

The enantiomeric excess was determined by HPLC with a Chiralcel AD column at 210 nm (*n*-hexane/*i*-PrOH: 90/10, 1.0 mL/min), anti: $t_R = 20.5$ (minor), $t_R = 26.3$ (major), syn: $t_R = 13.9$ (minor), $t_R = 16.2$ (minor).



anti-**3I**

2-[(2-Chlorophenyl)hydroxymethyl]cyclohexanone:[4]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): *δ*=1.49-1.83 (m, 5H), 2.05-2.10 (m, 1H), 2.30-2.48 (m, 2), 2.65-2.71 (m, 1H), 4.05 (d, *J*(H,H)=3.9 Hz, 1H), 5.35 (dd, *J*(H,H)=3.9, 8.1 Hz, 1H), 7.18-7.22 (m, 1H), 7.27-7.34 (m, 2H), 7.54-7.56 ppm (m, 1H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): *δ*=*anti* 25.0, 27.8, 30.6, 42.7, 57.6, 72.9, 123.4, 127.9, 128.5, 129.1, 132.5, 140.7, 215.2ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel ODH column at 280 nm (*n*-hexane/*i*-PrOH: 95/5, 1.0 mL/min), anti: $t_R = 8.5$ (major), $t_R = 10.8$ (minor), syn: $t_R = 6.4$ (minor), $t_R = 7.9$ (major).



anti-**3m**

2-[Hydroxy-(4-(fluorophenyl)methyl]-cyclohexanone:[5]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): $\delta = \Box 1.22 \cdot 2.08$ (m, 6H), 2.31-2.65 (m, 3H), 4.03 (br s, 1H), 4.77 (d, *J*(H,H)=8.4 Hz, 1H), 7.03 (d, *J*(H,H)=8.7 Hz , 2H), 7.33 ppm (d, *J*(H,H)=8.7 Hz , 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): $\delta = anti$ 24.6, 27.7, 30.7, 42.6, 57.4, 74.1, 115.2, 128.5, 136.5, 162.6, 215.4 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel ADH column at 210 nm (*n*-hexane/*i*-PrOH: 90/10, 0.3 mL/min), anti: $t_{\rm R}$ = 42.6 (minor), $t_{\rm R}$ = 47.3 (major), syn: $t_{\rm R}$ = 28.8 (minor), $t_{\rm R}$ = 32.9 (major).





3-hydroxy(4-nitrophenyl)methyl)tetrahydro-4H-thiopyran-4-one:[6]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS):. *δ*=□2.48-2.55 (m, 1H), 2.65 (t, *J*(H,H)=12.2 Hz, 1H), 2.71-2.84 (m, 2H), 2.96-3.05 (m, 3H), 3.67 (br s, 1H), 5.05 (d, *J*(H,H)=7.9 Hz, 1H, *anti*), 5.52 (br s, 1H, *syn*),

7.55 (d, *J*(H,H)=8.8 Hz, 2H), 8.24 ppm (d, *J*(H,H)=8.8 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): *δ=anti* 30.7, 32.8, 44.7, 59.4, 73.1, 123.8, 127.7, 147.6, 147.7, 211.2 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel AD column at 280 nm (*n*-hexane/*i*-PrOH: 90/10, 1.0 mL/min), anti: $t_R = 38.6$ (minor), $t_R = 69.2$ (major). syn: $t_R = 29.6$ (mayor), $t_R = 59.4$ (minor).

2-[Hydroxy(4-nitrophenyl)methyl]cyclopentanone:[3]

¹H NMR (300 MHz, CDCl₃ CDCl₃, 25 °C, TMS): *δ*=□1.72-1.75 (m, 2H), 1.96-2.09 (m, 1H), 2.30-2.74 (m, 2H), 2.74 (d, *J*(H,H)=4.8 Hz, 1H, *syn*), 4.77 (br s, 1H, *anti*), 4.84 (d, *J*(H,H)=9.1 Hz, 1H, *syn*), 5.42 (s, 1H), 7.52 (d, *J*(H,H)=8.4 Hz, 2H), 8.21 ppm (d, *J*(H,H)=8.7 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): *δ*=*anti* 20.2, 22.2, 38.8, 56.0, 70.3, 123.6, 126.3, 147.0, 150.2, 219.6; *anti* 20.2, 26.7, 38.5, 55.0, 74.3, 123.5, 127.3, 147.2, 148.5, 219.7 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel AD column at 280 nm (*n*-hexane/*i*-PrOH: 96/4, 1.0 mL/min), *syn*: $t_{\rm R}$ = 31.4 (major), $t_{\rm R}$ = 46.0 (minor). *anti*: $t_{\rm R}$ = 55.9 (minor), $t_{\rm R}$ = 58.9 (major).

anti-3p

2-(-1-hydroxyundecyl)cyclopentan-1-one:[7]

¹H NMR (300 MHz, CDCl₃ CDCl₃, 25 °C, TMS): $\delta = \Box 0.83$ (t, J(H,H) = 6.6 Hz, 3H), 1.23 (br s, 2H), 1.36-2.29 (m, 22H), 4.03 ppm (dt, J(H,H) = 3, 6.6 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): $\delta = 14.1$, 20.6, 22.8, 26.0, 29.3, 29.4, 29.45, 29.5, 29.6, 31.8, 34.8, 39.1, 54.4, 96.5, 221.7 ppm. The enantiomeric excess was determined by HPLC with a Chiralcel IA column at 254 nm (*n*-hexane/*i*-PrOH: 99/1, 1.0 mL/min), *syn*: $t_R = 8.6$ (minor), $t_R = 10.5$ (major). anti: $t_R = 14.8$ (major), $t_R = 20.6$ (minor).



3,4-Dihydroxy-4-(4-nitrophenyl)butan-2-one:[8]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 2.02 (s, 3H), 3.03 (d, *J*(H,H)=4.3 Hz, 1H), 3.71 (d, *J*(H,H)=4.9 Hz, 1H), 4.60-4.91 (m, 1H), 5.08-5.11 (m, 1H), 7.62 (d, *J*(H,H)=8.4 Hz, 2H), 8.24 ppm (d, *J*(H,H)=8.9 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = 27.7, 74.3, 80.5, 123.7, 127.0, 146.3, 147.3, 207.2 ppm.

The enantiomeric excess was determined by HPLC with a Chiralcel ADH column at 254 nm (*n*-hexane/*i*-PrOH: 80/20, 0.8 mL/min), anti: $t_R = 10.5$ (minor), $t_R = 11.7$ (major), syn: $t_R = 13.4$ (mayor), $t_R = 17.1$ (minor).

4-hydroxy-3-methoxy-4-(4-nitrophenyl)butan-2-one:[8]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ = 2.16 (s, 3H), 3.20 (s, 1H), 3.32 (s, 3H), 3.70 (d, J(H,H)=6.2 Hz, 1H), 5.02 (d, J(H,H)=6.2 Hz, 1H), 7.56 (d, J(H,H)=8.8 Hz, 2H), 8.22 ppm (d, J(H,H)=8.8 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = \Box 27.5, 59.6, 73.3, 89.6, 123.4, 127.7, 146.7, 147.7, 209.9 ppm.

The enantiomeric excess was determined by HPLC with a Chiralpak ODH column at 280 nm (*n*-hexane/*i*-PrOH: 90/10, 0.8 mL/min), $t_{\rm R} = 12.9$ (major), $t_{\rm R} = 15.7$ (minor).



2-Methyl-1-(4-nitrophenyl)propane-1,3-diol:[9]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): $\delta = \Box 0.78$ (d, *J*(H,H)=7.0 Hz, 3H), 2.01-2.06 (m, 1H), 2.74 (br s, 1H), 3.72-3.85 (m, 3H), 4.72 (d, *J*(H,H)=7.8 Hz, 1H *anti*), 7.54 (d, *J*(H,H)=8.7 Hz, 2H), 8.23 ppm (d, *J*(H,H)=8.7 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): $\delta = \Box 13.6$, 41.5, 67.4, 79.3, 123.6, 127.5, 147.4, 150.5 ppm.

The enantiomeric excess was determined by HPLC with a Chiralpak AD column at 210 nm (*n*-hexane/*i*-PrOH: 97/3, 1.0 mL/min), anti: $t_R = 89.6$ (major), $t_R = 94.5$ (minor); syn: $t_R = 79.3$ (major), $t_R = 85.3$ (minor).



anti-5b

2-Methyl-1-(2'-chlorophenyl)propane-1,3-diol:[10]

¹H NMR (300 MHz, CDCl₃, 25 °C, TMS): δ =0.87 (t, *J*(H,H)=7.2 Hz, 3H), 2.10-2.15 (m, 1H), 2.59-2.62 (m, 1H), 3.09 (d, *J*(H,H)=3.9 Hz, 1H), 3.72-3.78 (m, 2H), 5.13 (dd, *J*(H,H)=3.8 Hz, 7.2 Hz, 1H), 7.17-7.24 (m, 1H), 7.30-7.35 (m, 2H), 7.58-7.61 ppm (m, 1H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = \Box 13.6, 40.6, 67.4, 76.1, 127.1, 128.0, 128.6, 129.4, 132.4, 140.8 ppm.

The enantiomeric excess was determined by for the benzoylated product by HPLC with a Chiralpak AD column at 230 nm (*n*-hexane/*i*-PrOH: 97/3, 1.0 mL/min), anti: $t_R = 39.1$ (major), $t_R = 60.5$ (minor); syn: $t_R = 23.8$ (major), $t_R = 32.7$ (minor).



2-Methyl-1-(4-trifluromethylphenyl)propane-1,3-diol:[10]

¹H NMR (300 MHz, CDCl₃25 °C, TMS): δ =0.72 (d, *J*(H,H)=7.0 Hz, 3H), 2.01-2.03 (m, 1H), 2.89 (br s, 1H), 3.66-3.79 (m, 3H), 4.61 (d, *J*(H,H)=7.9 Hz, 1H *anti*), 5.04 (br s, 1H, *syn*) 7.45 (d, *J*(H,H)=8.1 Hz, 2H), 7.61 ppm (d, *J*(H,H)=8.1 Hz, 2H). ¹³C NMR (75 MHz, CDCl₃, 25 °C, TMS): δ = \Box 13.6, 41.4, 67.6, 79.9, 125.2, 126.9, 130.0, 147.2.

The enantiomeric excess was determined by HPLC with a Chiralpak AD column at 230 nm (*n*-hexane/*i*-PrOH: 97/3, 1.0 mL/min), anti: $t_{\rm R} = 28.5$ (major), $t_{\rm R} = 30.3$ (minor); syn: $t_{\rm R} = 18.3$ (major), $t_{\rm R} = 19.9$ (minor).

NMR spectra for aldol products























3h























anti-**3p**















AS, 85:15, 1ML





AS, 85:15 (Hx:iPrOH), 1.0 mL/min, HPLC2



Totals : 8.62899e4 1353.25888









ADH (98:02) 1 ML/MIN





ADH, 95:5 (Hexano:IPA), 1 mL/min, GPC





ADH, 95:5 (Hx:iPrOH), 1 mL/min, GPC



Totals : 1.04377e5 1905.64975






AS, 92:08 (Hx:iPrOH), 1 mL/min, GPC



#	[min]		[min]	[mAU*8]	[mAU]	8
1	8.464	vv	0.4901	1.28705e4	410.17987	47.3647
2	10.386	VB	0.5589	1.43026e4	335.82611	52.6353





AS, 98:02 (Hx:iPrOH), 1 mL/min, GPC





AS, 98:02 (Hx:iPrOH), 1 mL/min, GPC



Sorted By	:	Signal	
Multiplier	:	1.0000	
Dilution	:	1.0000	
Use Multiplier &	Dilution	Factor with	ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height (mAU)	Area %
1	20.793	вв	0.5280	369.73752	8.39188	19.2121
2	24.436	BB	0.9408	1554.76221	19.40345	80.7879

Totals : 1924.49973 27.79534



AS, 90:10, 1

Injection Date	: 02/09/2015 14:04:14
Sample Name	: RG1532F Location : Vial 2
Acq. Operator	· UDIC 2
Acq. Method	: C:\HPCHEM\2\METHODS\C5.M
Last changed	: 02/09/2015 14:03:00 by RG
	(modified after loading)
Analysis Method	: C:\HPCHEM\2\METHODS\C5.M
Last changed	: 21/04/2015 18:07:24 by JW
DADT C, Sig	=210,8 Ret=360,100 (RG/RG1532F.D)
mAU -	
10100000	
1400 -	2 S
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1200 -	A A A A A A A A A A A A A A A A A A A
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	00 m
1000 -	$\overline{\Lambda}$
800 -	
-	
600 -	
	v v
400	
400 -	
200 -	
-	
1 1	
0	5 10 15 20
	Area Percent Report
=======================================	
Sorted By	: Signal
Multiplier	: 1.0000
Dilution	: 1.0000
Sample Amount	: 1.00000 [ng/ul] (not used in calc.)
Use Multiplier	& Dilution Factor with ISTDs
Signal 1: DAD1 (C. Sig=210.8 Ref=360.100
	-,,,,,, .
Peak RetTime Ty	pe Width Area Height Area
# [min]	[min] [mAU*s] [mAU] %
2 13 810 VV	0.4331 3.7779784 1269.69678 51.8064 0.4034 3.5145164 1047 60461 48 1036
2 13.010 VD	0.1224 2.2142TC1 T041.0040T 40.1220
Totals :	7.29248e4 2317.30139



AS 90/10 HEX/IPA 1ml/min HPLC2





IA 95/05 1.0 ml/min HPLC2





IA 95/05 1.0 ml/min HPLC2

Injection Date	: 08/09/2015 12:25:55
Sample Name	: RG1542HY Location : Vial 3
Acq. Operator	: RG
Acq. Instrument	: HPLC 2 Inj Volume : 15 µl
Acq. Method	: C:\HPCHEM\2\METHODS\C1.M
Last changed	: 08/09/2015 11:55:25 by RG
	(modified after loading)
Analysis Method	: C:\HPCHEM\2\METHODS\C1.M
Last changed	: 03/06/2015 20:03:47 by RG
DADTE, Sig-	-280, 10 Rel-300, 100 (RG1842H1.D)
mAU _	29
	Ŕ
-	
200 -	
]	
150 -	
-	
-	
-	
100 -	
-	
	D
	22
50	9
50 -	\wedge
]	
0 -	MMM I I I
	0
	<u>-</u>
0	5 10 15
	Auto Deveryb Deveryb
	Area Percent Report
Sorted By	: Signal
Multiplier	5
P/2	: 1.0000
Dilution	: 1.0000 : 1.0000
Sample Amount	: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.)
Sample Amount Use Multiplier &	: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) ≿ Dilution Factor with ISTDs
Sample Amount Use Multiplier &	: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) & Dilution Factor with ISTDs
Sample Amount Use Multiplier &	: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) & Dilution Factor with ISTDs
Sample Amount Use Multiplier & Signal 1: DAD1 H	: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) & Dilution Factor with ISTDs 2, Sig=280,16 Ref=360,100
Signal 1: DAD1 H	: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) Multion Factor with ISTDs E, Sig=280,16 Ref=360,100 Ne Width Area Height Area
Signal 1: DAD1 F Peak RetTime Typ	: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) & Dilution Factor with ISTDs E, Sig=280,16 Ref=360,100 pe Width Area Height Area [min] [mAU*s] [mAU] %
Signal 1: DAD1 F Peak RetTime Typ # [min]	: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) & Dilution Factor with ISTDs E, Sig=280,16 Ref=360,100 pe Width Area Height Area [min] [mAU*s] [mAU] %
Signal 1: DAD1 F Peak RetTime Typ # [min] 	<pre>: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) & Dilution Factor with ISTDs E, Sig=280,16 Ref=360,100 pe Width Area Height Area [min] [mAU*s] [mAU] % </pre>
Signal 1: DAD1 F Peak RetTime Typ # [min] 	<pre>: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) & Dilution Factor with ISTDs E, Sig=280,16 Ref=360,100 pe Width Area Height Area [min] [mAU*s] [mAU] % 0.6806 2249.93433 51.40871 13.4973 0.9250 1.44195e4 234.62718 86.5027</pre>
Signal 1: DAD1 H Peak RetTime Typ # [min] 	<pre>: 1.0000 : 1.0000 : 1.00000 [ng/ul] (not used in calc.) & Dilution Factor with ISTDs ; Sig=280,16 Ref=360,100 pe Width Area Height Area [min] [mAU*s] [mAU] % 0.6806 2249.93433 51.40871 13.4973 0.9250 1.44195e4 234.62718 86.5027</pre>



AS, 90:10, 1

Injection Date : 02/0 Sample Name : RG15 Acq. Operator : RG Acq. Instrument : HPLC Acq. Method : C:\H Last changed : 02/0 (mod Analysis Method : C:\H Last changed : 21/0 DAD1 C, Sig=210,8 Refe	9/2015 13:04:28 34 2 PCHEM\2\METHODS\C5.M 9/2015 13:02:08 by RG ified after loading) PCHEM\2\METHODS\C5.M 4/2015 18:07:24 by JW =360,100 (RG\RG1534.D)	Location : Vial 2 Inj Volume : 8 µl
mAU	9.355	
800 600 400 200 0		~
0	5 10	15
	Area Percent Report	
Sorted By Multiplier Dilution Sample Amount Use Multiplier & Dilut	: Signal : 1.0000 : 1.0000 : 1.00000 [ng/ul] ion Factor with ISTDs	(not used in calc.)
Signal 1: DAD1 C, Sig=:	210,8 Ref=360,100	
Peak RetTime Type Wid # [min] [min 1 9.355 VV 0.3 2 10.942 VB 0.4	th Area Height n] [mAU*s] [mAU] 	Area % - 7 49.3111 3 50.6889
Totals :	9.37515e4 2934.54810	D





AS 90/10 1.0 ml/min HPLC2





HPLC 2 ADH 90/10 1.0ml/min





HPLC 2 ADH 90/10 1.0ml/min





AD, 90:10 (Hx:iPrOH), 0.5 mL/min, HPLC2





AD, 90:10 (Hx:iPrOH), 0.5 mL/min, HPLC2







ODH, 95:05 (Hx:iPrOH), 1 mL/min, HPLC2





anti-**3I**

55% ee

ODH, 95:05 (Hx:iPrOH), 1 mL/min, HPLC2







anti-3m

ADH, 90:10 (Hx:iPrOH), 0.3 mL/min, HPLC2







ADH, 90:10, 1 mL/min, GPC



Totals :

1.46039e4 183.90912



anti-3n

AD 90/10 , 1 ML/MIN GPC



Totals : 3405.85446 33.34747



AD, 96/04-1ML/MIN, GPC

Injection Date : 23/01/2015 11:02:07 Sample Name : RG1503 Acq. Operator : RG Acq. Instrument : HPLC-GPC Acq. Method : C:\HPCHEM\1\METHODS\AO.M Last changed : 23/01/2015 10:59:47 by RG Analysis Method : C:\HPCHEM\1\METHODS\RG.M Last changed : 23/07/2015 18:37:52 by PZ DAD1 E, Sig=280,16 Ref=360,100 (RG\RG1503.D)	Seq. Line : Location : Inj : Inj Volume :	: 1 : Vial 1 : 1 : 8 µl	
mAU - 300 - 250 -	28-280		
200 -		38.982	52.0088.782
100			
0 10 20	30	40	50
Area Percent Report			
Sorted By : Signal Multiplier : 1.0000 Dilution : 1.0000 Use Multiplier & Dilution Factor with ISTDs			
Signal 1: DAD1 E, Sig=280,16 Ref=360,100			
Peak RetTime Type Width Area Height # [min] [min] [mAU]*s] [mAU] 1 1 28.280 VB 0.8802 1.95906e4 330.19925 2 38.982 BB 1.3077 1.93565e4 196.08130 3 48.782 BV 1.3990 1.87075e4 189.955593	Area % 25.4740 25.1695 3 24.3257 25 220		
4 52.005 VB 1.5218 1.92498e4 163.46898 Totals : 7.69045e4 879.70546	5 25.0308		







RAC-30

IA, 99:01 (Hx:iPrOH), 1 mL/min, HPLC2





anti-30

IA, 99:01 (Hx:iPrOH), 1 mL/min, HPLC2





ADH 80/20 0.8 ml/min HPLC2







ODH 90/10 1ML

Injection Date	:	02/10/2015 13:33:41					
Sample Name	:	RG1800R2	L	ocation	:	Vial	1
Acq. Operator	:	RG					
Acq. Instrument	:	HPLC 2	Inj	Volume	:	8 µl	
Acq. Method	:	C:\HPCHEM\2\METHODS\C6 1 60.M	-				
Last changed	:	02/10/2015 11:54:49 by RG					
		(modified after loading)					
Analysis Method	:	C:\HPCHEM\2\METHODS\C6 1 60.M					
Last changed	:	15/09/2015 10:06:37 by JW					





ODH 90/10 1ML

Injection Date	:	02/10/2015 12:33:30					
Sample Name	:	RG1801Q	L	ocation	:	Vial	2
Acq. Operator	:	RG					
Acq. Instrument	:	HPLC 2	Inj	Volume	:	8 µl	
Acq. Method	:	C:\HPCHEM\2\METHODS\C6 1 60.M					
Last changed	:	02/10/2015 11:54:49 by RG					
		(modified after loading)					
Analysis Method	:	C:\HPCHEM\2\METHODS\C6 1 60.M					
Last changed	:	15/09/2015 10:06:37 by JW					
							===



Area Percent Report

Sorted By	:	Signal		
Multiplier	:	1.0000		
Dilution	:	1.0000		
Sample Amount	:	1.00000	[ng/ul]	(not used in calc.)
Use Multiplier	& Dilution	Factor with	ISTDs	

Signal 1: DAD1 A, Sig=254,4 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	12.898	BB	0.5977	7.02440e4	1798.39258	78.2572
2	15.702	BB	0.8335	1.22000e4	215.81902	13.5917
3	28.722	BB	0.9333	1601.35779	20.49984	1.7840
4	36.024	PB	1.1219	5715.10986	60.62152	6.3671
Total	ls :			8.97605e4	2095.33296	



AD, 97:03 (Hx:iPrOH), 1 mL/min, HPLC2





ADH, 97:03 (Hx:iPrOH), 1 mL/min, HPLC2





AD, 97:03, 1 mL/min, GPC

Injection Date : 09/03/2015 13:32:40 Seq. Line : 1
Sample Name : RG154997 Location : Vial 11
Acq. Operator : RG Inj : 1
Acq. Instrument : HPLC-GPC Inj Volume : 7 µl
Different Inj Volume from Sequence ! Actual Inj Volume : 8 µl
Acq. Method : C:\HPCHEM\1\MBTHODS\RG.M
Last changed : $09/03/2015 13:31:32$ by RG
Analysis Method : C:\HPCHEM\1\METHODS\KG.M
DAD ID. Sio=230.100 (FSRG154297.D)
mAll -
1400 -
1200-
<u>0 10 20 30 40 50 60</u>
Area Percent Report
Sorted By · Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs
Signal 1: DAD1 D, Sig=230,16 Ref=360,100
Deale Detwine Width Dura Height Dura
fear retrine type width Area Height Area
π [maxe] [maxe] [maxe =] [maxe] =
1 23.674 VB 0.7621 7822.98682 148.13287 9.8614
2 32.580 BB 1.2633 1.63134e4 186.36140 20.5641
3 39.397 VB 1.2937 2.97849e4 326.07205 37.5459
4 61.133 BB 1.5638 2.54081e4 194.78745 32.0286
Tetele . 7 02202e4 055 25270
10tals: //33433et 000.000/0



anti-5b'

AD, 97:03, 1 mL/min, GPC





AD 97/03 1 ml/min HPLC2

Injection Date	:	21/09/2015 12:51:28					
Sample Name	:	RG1551V8	L	ocation	:	Vial	51
Acq. Operator	:	RG					
Acq. Instrument	:	HPLC 2	Inj	Volume	:	7 µl	
Acq. Method	:	C:\HPCHEM\2\METHODS\C3 1 60.M	-				
Last changed	:	21/09/2015 12:51:58 by RG					
		(modified after loading)					
Analysis Method	:	C:\HPCHEM\2\METHODS\C3 1 60.M					
Last changed cOLUMNA 2	:	30/03/2015 14:08:24 by RG					





Sorted By	:	Signal		
Multiplier	:	1.0000		
Dilution	:	1.0000		
Sample Amount	:	1.00000	[ng/ul]	(not used in calc.)
Use Multiplier	& Dilution	Factor with	ISTDs	

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Туре	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.021	VB	0.6149	1154.50525	28.12388	10.8056
2	22.306	PV	0.6362	1061.09180	24.94789	9.9313
3	33.020	BV	0.9216	3920.74097	61.02012	36.6962
4	34.643	VB	1.0266	4547.98730	59.98472	42.5669
Tota	ls :			1.06843e4	174.07660	



AD 97/03 1 ml/min HPLC2

```
_____
Injection Date : 21/09/2015 13:58:09
         : RG1550PURO-V7-20
Sample Name
                                     Location : Vial 52
Acq. Operator : RG
Acq. Instrument : HPLC 2
Acq. Method : C:\HPCH
                                    Inj Volume : 7 µl
           : C:\HPCHEM\2\METHODS\C3_1_60.M
Last changed
           : 21/09/2015 12:51:58 by RG
             (modified after loading)
Analysis Method : C:\HPCHEM\2\METHODS\C3_1_60.M
Last changed
           : 30/03/2015 14:08:24 by RG
cOLUMNA 2
```



Area Percent	Report	

Sorted By	:	Signal		
Multiplier	:	1.0000		
Dilution	:	1.0000		
Sample Amount	:	1.00000	[ng/ul]	(not used in calc.)
Use Multiplier	& Dilution	Factor with	ISTDs	

Signal 1: DAD1 D, Sig=230,16 Ref=360,100

Peak #	RetTime [min]	Туре	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.057	PB	0.6536	4775.55615	109.76529	14.7372
2	22.312	BV	0.6903	2654.88940	57.96550	8.1929
3	32.847	BB	1.1166	2.49743e4	335.43155	77.0699
Total	ls :			3.24048e4	503.16233	
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