The First Direct and Enantioselective Cross-Aldol Reaction of Aldehydes

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Supporting Information

General Information. Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.[1] Dimethylformamide was obtained from EM Science in a DriSolv™ container and used as supplied. Non-aqueous reagents were transferred under nitrogen via syringe or cannula. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator using an ice-water bath. Chromatographic purification of products was accomplished using forced-flow chromatography on ICN 60 32-64 mesh silica gel 63 according to the method of Still.[2] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching or by anisaldehyde stain.

^{1}H and ^{13}C NMR spectra were recorded on a Mercury 300 (300 MHz and 75 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz) and assignment. Data for ^{13}C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the UC Irvine Mass Spectral facility. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 and 6890 Series gas chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column or an ASTEC Chiraldex γ-BP (30 m x 0.25 mm) as noted. High performance liquid chromatography (HPLC) was performed on Hewlett-Packard 1100 Series chromatographs using a Chiralcel AD column (25 cm) and AD guard (5 cm) or a Chiralcel OJ column (25 cm) and OJ guard (5 cm) as noted.

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[1]Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd ed., Pergamon Press, Oxford, 1988.

(2*S*, 3*S*)-3-Hydroxy-2-methylpentanal (Table 2, entry 1). A suspension of freshly distilled propionaldehyde (3.61 mL, 50 mmol) and L-proline in 25.0 mL of dimethylformamide was stirred at 4 °C for 10 h. The resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (5:2 pentane : diethyl ether) afforded the title compound as a clear, colorless oil in 80% yield (2.31 g, 20 mmol), 99% ee, and 4:1 *anti*:*syn*. Analytical data for this compound are identical in every respect to the previously reported values, with the exception of optical rotation which has not been reported.[3] $[\alpha]_D = -14.7$ (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (obtained by the method of Yamamoto[4]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 °C isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 24.6 min, (2*R*, 3*R*) *anti* isomer t_r = 25.5 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 22.4 min.

(2*S*, 3*S*)-3-Hydroxy-2,5-dimethylhexanal (Table 2, entry 2). A solution of freshly distilled propionaldehyde (144 μL, 2.0 mmol) in 500 μL dimethylformamide pre-cooled to 4 °C was added slowly over the course of 2.5 h to a stirring suspension of isovaleraldehyde (107 μL, 1.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 500 μL dimethylformamide at 4 °C. After 16 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (20:7 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 88% yield (126 mg, 0.88 mmol), 97% ee and 3:1 *anti*:*syn*. IR (film) 3419, 2958, 2935, 2872, 1719, 1466, 1368, 1152, 1098, 1062, 1025, 976.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, J = 1.5 Hz, 1H, CHO); 3.89 (ddd, 1H, J = 9.9, 6.6, 2.7 Hz, 1H, **CH**OH); 2.44 (m, 1H, **CH**CH_3); 1.83 (m, 1H, **CH**$(CH_3)_2$); 1.47 (m, 1H, CH_2); 1.26 (m, 1H, CH_2); 1.14 (d, 3H, J = 7.2 Hz, **CH**$_3$CHCHO); 0.97 (d, 3H, J = 5.1 Hz, $(\mathbf{CH_3})_2$CH); 0.92 (d, 3H, J = 6.6 Hz, $(\mathbf{CH_3})_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 70.9, 52.8, 44.0, 34.5, 24.1, 21.8, 11.1; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_8H_{17}O_2$) requires *m/z* 145.1228, found *m/z* 145.1225; $[\alpha]_D = -33.6$ (c = 1.0,

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[2]Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978,** *43*, 2923.
[3] Mahrwald, R.; Costisella, B,; Guendogan, B. *Synthesis*, **1998**, 262.

$CHCl_3$). The product ratios were determined by GLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (obtained by the method of Yamamoto[4]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (100 °C isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 50.8 min, (2*R*, 3*R*) *anti* isomer t_r = 53.2 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 45.5 min.

(2*S*, 3*S*)-3-Cyclohexyl-3-hydroxy-2-methylpropanal (Table 2, entry 3). A solution of freshly distilled propionaldehyde (72 μL, 1.0 mmol) in 500 μL dimethylformamide pre-cooled to 4 °C was added slowly over the course of 20 h to a stirring suspension of cyclohexane carboxaldehyde (242 μL, 2.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 500 μL dimethylformamide at 4 °C. After 22 hours, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (20:7 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 87% yield (148 mg, 0.87 mmol), 99% ee and 93:7 *anti* : *syn*. IR (film) 3438, 2928, 2853, 1722, 1450, 1396, 1376, 1314, 1186, 1112, 1063, 975.8, 893.2, 847.5 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, 1H, *J* = 2.1 Hz, CHO); 3.53 (dd, 1H, *J* = 7.2, 4.8 Hz, C**H**OH); 2.58 (m, 1H, C**H**CH_3); 1.8-1.0 (br m, 11H, cyclohexyl); 1.10 (d, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 77.1, 49.2, 40.7, 30.3, 26.73, 26.69, 26.68, 26.4, 11.4; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{10}H_{19}O_2$) requires *m/z* 171.1385, found *m/z* 171.1386. $[\alpha]_D$ = –5.1 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the corresponding 4-cyclohexyl-2,2,5-trimethyl-[1,3]dioxane (obtained by $NaBH_4$ reduction followed by acetonide protection of the 1,3-diol according to the method of Goto *et al.*[5]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 °C isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 17.8 min, (2*R*, 3*R*) *anti* isomer t_r = 18.7 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 21.0, 22.2 min.

Determination of the absolute stereochemistry of (2*S*, 3*S*)-3-Cyclohexyl-3-hydroxy-2-methylpropanal by correlation to (2*S*, 3*S*)-3-cyclohexyl-3-hydroxy-2-methylpropionic

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[4] Furuta, K.; Shimizu, S.; Miwa, S.; Yamamoto, Y. *J. Org. Chem.* **1989**, *54*, 1481.
[5] Kitamura, M.; Isobe, Y.; Ichikawa, Y.; Goto, T. *J. Am. Chem. Soc.* **1984**, *106*, 3252.

acid methyl ester. A stirring solution of (2*S*, 3*S*)-3-cyclohexyl-3-hydroxy-2-methylpropanal (77 mg, 0.45 mmol) in 3.0 mL of ethanol was treated sequentially with a solution of $AgNO_3$ (123 mg, 0.73 mmol) in 2.0 mL of water and a solution of NaOH (123 mg, 3.1 mmol) in 3.0 mL of 2:1 ethanol:water. After stirring for 4 hours, the mixture was filtered through celite, and the filter cake was rinsed with several portions of ethyl acetate. The filtrate was then washed with 1N HCl and the aqueous layer was back-extracted with ethyl acetate. The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was then dissolved in 8.0 mL of methanol and trimethylsilyldiazomethane (2.0 M in hexane) was added until a yellow color persisted. Excess diazomethane was quenched by the dropwise addition of acetic acid. The resulting colorless solution was then diluted with ether, washed successively with 10% $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (5–10% ethyl acetate in hexanes, linear gradient) afforded a 71% yield (63 mg, 0.32 mmol) of (2*S*, 3*S*)-3-cyclohexyl-3-hydroxy-2-methylpropionic acid methyl ester; $[\alpha]_D$ = +5.1 (c = 1.05, $CHCl_3$) (lit.[6] $[\alpha]_D$ = – 8.1 (c = 1.05, $CHCl_3$) for (2*R*, 3*R*)-3-cyclohexyl-3-hydroxy-2-methylpropionic acid methyl ester).

(2*S*, 3*S*)-3-Hydroxy-2-methyl-3-phenyl-propionaldehyde (Table 2, entry 4). A solution of freshly distilled propionaldehyde (72 μL, 1.0 mmol) in 500 μL dimethylformamide pre-cooled to 4 °C was added slowly over the course of 16 h to a stirring suspension of benzaldehyde (1.02 mL, 10 mmol), L-proline (11.5 mg, 0.10 mmol) and 4.5 mL dimethylformamide at 4 °C. After 16 hours, the resulting solution was diluted with ethyl acetate and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and then concentrated. Flash chromatography (4:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil in 81% yield (132 mg, 0.81 mmol), 99% ee and 3:1 *anti*:*syn*. Analytical data for this compound are identical in every respect to the previously reported with the exception of optical rotation which has not been reported.[3] $[\alpha]_D$ = +9.1 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel AD and AD guard

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[6] Meyers, A. I.; Yamamoto, Y. *J. Am. Chem. Soc.* **1981**, *103*, 4278.

column (1.0 % isopropanol/hexanes, 1 mL/min); (2*S*, 3*S*) *anti* isomer t_r = 147.5 min, (2*R*, 3*R*) *anti* isomer t_r = 161.1 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 173.0, 200.0 min.

(2*S*, 3*S*)-3-Hydroxy-2,4-dimethylpentanal (Table 2, entry 5). A solution of freshly distilled propionaldehyde (1.81 mL, 25.0 mmol) in 12.5 mL dimethylformamide pre-cooled to 4 °C was added slowly over the course of 20 h to a stirring suspension of isobutyraldehyde (4.54 mL, 50 mmol), L-proline (288 mg, 2.5 mmol) and 12.5 mL dimethylformamide at 4 °C. After 30 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions of dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (20:7 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 82% yield (2.65 g, 20.6 mmol), >99% ee and 96:4 *anti*:*syn*. Analytical data for this compound are identical in every respect to the previously reported values with the exception of optical rotation which has not been reported.[3] $[\alpha]_D = -17.9$ (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (obtained by the method of Yamamoto[4]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 °C isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 31.8 min, (2*R*, 3*R*) *anti* isomer t_r = 33.9 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 29.4, 29.8 min.

Determination of the absolute stereochemistry of (2*S*, 3*S*)-3-Hydroxy-2,4-dimethylpentanal by correlation to (2*S*, 3*S*)-3-hydroxy-2,4-dimethylpentanoic acid methyl ester. A stirring solution of (2*S*, 3*S*)-3-hydroxy-2,4-dimethylpentanal (101 mg, 0.63 mmol) in 3.0 mL of ethanol was treated sequentially with a solution of $AgNO_3$ (170 mg, 1.0 mmol) in 2.0 mL of water and a solution of NaOH (171 mg, 4.3 mmol) in 3.0 mL of 2:1 ethanol:water. After stirring for 4 hours, the mixture was filtered through celite, and the filter cake was rinsed with several portions of ether. The filtrate was then washed with 1N HCl and the aqueous layer was back-extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was then dissolved in 8.0 mL of methanol, and trimethylsilyldiazomethane (2.0 M in hexane) was added until a yellow color persisted. Excess diazomethane was quenched by the dropwise addition of acetic acid. The resulting colorless solution was then diluted with ether, washed successively with 10% $NaHCO_3$ and brine, dried

over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (5–25% ether in pentane, linear gradient) afforded a 39% yield (47 mg, 0.25 mmol) of (2*S*, 3*S*)-3-hydroxy-2,4-dimethylpentanoic acid methyl ester; $[\alpha]_D$ = +7.6 (c = 0.85, $CHCl_3$) (lit.[7] $[\alpha]_D$ = +11.1 (c = 0.85, $CHCl_3$).

(2*S*)-2-[(1*S*)-1-hydroxy-2-methylpropyl]hexanal (Table 2, entry 6). A solution of freshly distilled hexanal (120 μL, 1.0 mmol) in 500 μL dimethylformamide was added slowly over the course of 24 h to a stirring suspension of isobutyraldehyde (272 μL, 3.0 mmol), L-proline (11.5 mg, 0.10 mmol) and 500 μL dimethylformamide at room temperature. After 24 h, the resulting solution was diluted with diethyl ether and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions dichloromethane. The organic layers were combined, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. Flash chromatography (7:3 pentane:diethyl ether) afforded the title compound as a clear, colorless oil in 80% yield (127 mg, 0.80 mmol), 98% ee and 96:4 *anti* : *syn*. IR (film) 3458, 2960, 2934, 2874, 2725, 1720, 1467, 1328, 1220, 1146, 1024, 991.2, 959.9, 901.1, 775.6 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.75 (d, 1H, *J* = 3.3 Hz, CHO); 3.56 (dd (apparent q), 1H, *J* = 6.0, 5.7 Hz, **CH**OH); 2.46 (dddd, 1H, *J* = 8.4, 5.7, 5.7, 3.3 Hz, **CH**CH_2); 1.99 (d, 1H, *J* = 6.0 Hz, OH); 1.82 (m, 1H, **CH**$(CH_3)_2$); 1.70 (m, 1H, CH**CH**$_2$); 1.58 (m, 1H, CH**CH**$_2$); 1.30 (m, 4H, CH_2CH_2CH3); 0.97 (d, 3H, *J* = 6.6 Hz, $CH(CH_3)_2$); 0.93 (d, 3H, *J* = 6.6 Hz, $CH(CH_3)_2$); 0.90 (dd (apparent t), 3H, *J* = 6.6, 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.1, 76.7, 54.9, 31.3, 29.5, 26.7, 23.2, 20.0, 17.1, 14.2; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{10}H_{21}O_2$) requires *m/z* 173.1541, found *m/z* 173.1540; $[\alpha]_D$ = –15.4 (c = 1.0, $CHCl_3$). The product ratios were determined by GLC analysis of the acetal derived from 2,2-dimethylpropane-1,3-diol (obtained by the method of Yamamoto[4]) using a Bodman Chiraldex β-DM (30 m x 0.25 mm) column (110 °C isotherm, 23 psi); (2*S*, 3*S*) *anti* isomer t_r = 97.8 min, (2*R*, 3*R*) *anti* isomer t_r = 102.7 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 94.4, 96.5 min.

(2*S*, 3*S*)-2-Benzyl-3-hydroxy-4-methylpentanal (Table 2, entry 7). A solution of freshly distilled hydrocinnamaldehyde (132 μL, 1.0 mmol) in 500 μL dimethylformamide was added slowly over the course of 24 h to a stirring suspension of isobutyraldehyde (272 μL, 3.0

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[7] Oppolzer, W.; Starkemann, C.; Rodriguez, I.; Bernardinelli, G. *Tet. Lett.* **1991**, *32*, 61.

mmol), L-proline (11.5 mg, 0.10 mmol) and 500 μL dimethylformamide at room temperature. After 26 h, the resulting solution was diluted with ethyl acetate and washed successively with water and brine. The combined aqueous layers were back-extracted with 3 portions dichloromethane. The organic layers were combined, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. Flash chromatography (3:1 hexanes:ethyl acetate) afforded the title compound as a clear, colorless oil in 75% yield (155 mg, 0.75 mmol), 91% ee and 95:5 *anti* : *syn*. IR (film) 3466, 3086, 3063, 3028, 2962, 2932, 2834, 2733, 1950, 1875, 1806, 1722, 1604, 1496, 1454, 1390, 1368, 1244, 1180, 1136, 1049, 1031, 993.0, 964.3, 849.7, 800.6, 739.8, 700.2 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.83 (d, 1H, J = 2.1 Hz, CHO); 7.27 (m, 5H, Ar-H); 3.43 (ddd, 1H, J = 6.6, 6.6, 4.5 Hz, **CH**OH); 3.06 (dd, 1H, J = 13.2, 7.8 Hz, $PhCH_2$); 2.92 (dd, 1H, J = 13.2, 6.9 Hz, $PhCH_2$); 2.81 (m, 1H, **CH**CH_2); 2.15 (d, 1H, J = 6.0 Hz, OH); 1.90 (m, 1H, **CH**$(CH_3)_2$); 0.96 (d, 3H, J = 6.6 Hz, CH(**C**$H_3)_2$); 0.92 (d, 3H, J = 7.2 Hz, CH(**C**$H_3)_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.6, 129.2, 128.9, 128.6, 126.8, 76.9, 55.8, 33.4, 32.0, 19.7, 18.2; HRMS (CI) exact mass calcd for $[M + H]^+$ ($C_{13}H_{19}O_2$) requires *m/z* 207.1385, found *m/z* 207.1386; $[\alpha]_D$ = –7.9 (c = 1.0, $CHCl_3$). The product ratios were determined by HPLC analysis of the corresponding alcohol (obtained by $NaBH_4$ reduction) using a Chiracel OJ and OJ guard column (1.0 % ethanol/hexanes, 1 mL/min); (2*S*, 3*S*) *anti* isomer t_r = 7.5 min, (2*R*, 3*R*) *anti* isomer t_r = 9.4 min, (2*R*, 3*S*) and (2*S*, 3*R*) *syn* isomers t_r = 6.3, 6.9 min.