Cu(I)-Catalyzed Reductive Aldol Cyclizations: Diastereo- and Enantioselective Synthesis of β -Hydroxylactones

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General Information

All reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. CH_2Cl_2 was distilled from CaH_2 . THF was distilled from sodium benzophenone ketyl. Anhydrous DMF was purchased from Aldrich. 'Petrol' refers to that fraction of light petroleum ether boiling in the range 40–60 °C. α,β -Unsaturated carboxylic acids used in the preparation of the cyclization substrates were obtained as follows: 3-(2-furyl)acrylic acid, 3,3-dimethylacrylic acid and 4-chlorocinnamic acid were purchased from Aldrich; 4-methoxycinnamic acid was purchased from Fluka; (*E*)-5-methylhex-2-enoic acid was prepared from a Wadsworth-Emmons reaction of isovaleraldehyde with triethyl phosphonoacetate, followed by hydrolysis of the resulting ethyl ester, according to literature procedures;¹ (*E*)-5-phenylpent-2-enoic acid was prepared analogously using hydrocinnamaldehyde (distilled before use) in place of isovaleraldehyde.¹ 4-Chlorocinnamoyl chloride was prepared from the reaction of 4-chlorocinnamic acid with thionyl chloride according to a literature procedure.² 3-Hydroxypropiophenone was prepared from ethyl benzoyl acetate according to a 3-step literature

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1. Hanessian, S.; Moitessier, N.; Cantin, L. D. *Tetrahedron* **2001**, 57, 6885–6900.
 2. Dimmock, J. R.; Kandepu, N. M.; Nazarali, A. J.; Motaganahalli, N. L.; Kowalchuk, T. P.; Pugazhenth, U.; Prisciak, J. S.; Quail, J. W.; Allen, T. M.; LeClerc, R.; Santos, C. L.; De Clercq E.; Balzarini, J. *J. Med. Chem.* **2000**, 43, 3933–3940.

procedure.³ Pyridine, Et₃N and crotonoyl chloride were distilled from CaH₂. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilen 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.⁴ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker DPX360 (360 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl₃ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ¹³C NMR spectra were recorded on a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl₃ at 77.0 ppm, d₆-DMSO at 39.5 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer using the electrospray (ES) positive ion mode at the EPSRC National Mass Spectrometry Service Centre, University of Wales Swansea, or on a Kratos MS50TC spectrometer using the fast atom bombardment (FAB) technique in the mass spectrometry laboratory at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the *ion* (i.e. the actual species being detected), *not* that of the neutral parent compound. Chiral HPLC analysis was performed on an Agilent 1100 instrument. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter.

Preparation of the Cyclization Substrates

General procedure A

Oxalyl chloride (1.21 equiv) was added dropwise over 2 min to a solution of the appropriate α,β-unsaturated carboxylic acid (1.10 equiv) and DMF (0.25 equiv) in CH₂Cl₂ (0.55 M with respect to

3. Yun, J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 5640–5644.

4. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

carboxylic acid) at 0 °C. The mixture was stirred at 0 °C until no more effervescence was observed (*ca.* 1 h). The resulting solution of acid chloride was then transferred to a solution of the appropriate hydroxyketone (1.0 equivalent), DMAP (0.05 equiv) and pyridine (4.0 equiv) in CH₂Cl₂ (1.0 M with respect to hydroxyketone) over 5 min *via* cannula, and the reaction was stirred at room temperature until TLC analysis showed the reaction to be complete. The reaction was partitioned between saturated aqueous NaHCO₃ solution and Et₂O. The organic layer was separated and washed with saturated aqueous NaHCO₃ solution (x 3), dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclization substrate.

General procedure B

This was identical to general procedure A, except that Et₃N (2.5 equiv) was used in place of pyridine.

3-Oxobutyl (*E*)-3-phenylpropenoate (1). A solution of cinnamoyl chloride (1.87 g, 11.0 mmol) in CH₂Cl₂ (20 mL) was added over 5 min to a solution of 4-hydroxy-2-butanone (0.91 mL, 10.0 mmol), DMAP (61 mg, 0.50 mmol), and Et₃N (2.1 mL, 15 mmol) in CH₂Cl₂ (30 mL) at 0 °C. The reaction was stirred at room temperature for 1 h before being quenched with saturated aqueous NaHCO₃ solution (50 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 30 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave the title compound as a white solid (1.64 g, 75%). m.p. 59-61 °C; IR (CHCl₃) 3062, 1705 (C=O), 1632 (C=C), 1577, 1311, 1164, 997, 776, 723, 688 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.63 (1H, d, *J* = 16.0 Hz, =CH), 7.49-7.44 (2H, m, ArH), 7.35-7.31 (3H, m, ArH), 6.37 (1H, d, *J* = 16.0 Hz, =CH), 4.43 (2H, t, *J* = 6.3 Hz, CH₂O), 2.80 (2H, t, *J* = 6.3 Hz, CH₂CH₂O), 2.17 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 205.5 (C), 166.5 (C), 144.8 (CH), 134.0 (C), 130.1 (CH), 128.6 (2 x CH), 127.8 (2 x CH), 117.4 (CH), 59.1 (CH₂), 42.1 (CH₂), 30.0 (CH₃); HRMS (FAB) Exact mass calcd for C₁₃H₁₅O₃ [M+H]⁺: 219.1016, found: 219.1017.

3-Oxobutyl (*E*)-3-(4-methoxyphenyl)propenoate (3a). The title compound was prepared according to general procedure B from 4-methoxycinnamic acid (1.96 g, 11.0 mmol) and 4-hydroxy-2-butanone (0.91 mL, 10.0 mmol) for a reaction time of 1 h and purified by column chromatography (20% EtOAc/petrol) to give a white solid (1.84 g, 74%). m.p. 72-74 °C; IR (CHCl₃) 2962, 1713 (C=O), 1634 (C=C), 1604, 1514, 1254, 1160, 1029, 984, 830 cm⁻¹;

^1H NMR (360 MHz, CDCl_3) δ 7.52 (1H, d, J = 16.0 Hz, =CH), 7.35 (2H, d, J = 8.7 Hz, ArH), 6.78 (2H, d, J = 8.7 Hz, ArH), 6.17 (1H, d, J = 16.0 Hz, =CH), 4.35 (2H, t, J = 6.3 Hz, CH_2O), 3.70 (3H, s, OCH_3), 2.74 (2H, t, J = 6.3 Hz, $\text{CH}_2\text{CH}_2\text{O}$), 2.11 (3H, s, $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 205.4 (C), 166.6 (C), 161.1 (C), 144.3 (CH), 129.4 (2 x CH), 126.6 (C), 114.7 (CH), 113.9 (2 x CH), 58.8 (CH_2), 54.9 (CH_3), 42.0 (CH_2), 29.8 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{14}\text{H}_{17}\text{O}_4$ $[\text{M}+\text{H}]^+$: 249.1122, found: 249.1126.

3-Oxobutyl (E)-3-(4-chlorophenyl)propenoate (3b). A solution of 4-chlorocinnamoyl chloride (2.21 g, 11.0 mmol) in CH_2Cl_2 (20 mL) was added over 5 min to a solution of 4-hydroxy-2-butanone (0.91 mL, 10.0 mmol), DMAP (61 mg, 0.50 mmol), and Et_3N (2.1 mL, 15 mmol) in CH_2Cl_2 (30 mL) at 0 °C. The reaction

was stirred at room temperature for 2 h before being quenched with saturated aqueous NaHCO_3 solution (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification of the residue by column chromatography (30% EtOAc/petrol) gave the title compound as a white solid (2.02 g, 79%). m.p. 54–56 °C; IR (CHCl_3) 2968, 1713 ($\text{C}=\text{O}$), 1638, 1592, 1492, 1323, 1310, 1166, 922, 820 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.62 (1H, d, J = 16.0 Hz, =CH), 7.45 (2H, d, J = 8.5 Hz, ArH), 7.36 (2H, d, J = 8.5 Hz, ArH), 6.38 (1H, d, J = 16.0 Hz, =CH), 4.48 (2H, t, J = 6.2 Hz, CH_2O), 2.85 (2H, t, J = 6.2 Hz, $\text{CH}_2\text{CH}_2\text{O}$), 2.23 (3H, s, CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 205.6 (C), 166.5 (C), 143.6 (CH), 136.2 (C), 132.7 (C), 129.2 (2 x CH), 129.1 (2 x CH), 118.2 (CH), 59.4 (CH_2), 42.3 (CH_2), 30.2 (CH_3); HRMS (ES) Exact mass calcd for $\text{C}_{13}\text{H}_{14}\text{ClO}_3$ $[\text{M}+\text{H}]^+$: 253.0626, found: 253.0624.

3-Oxobutyl (E)-3-furan-2-ylpropenoate (3c). The title compound was prepared according to general procedure B from 3-(2-furyl)acrylic acid (1.52 g, 11.0 mmol) and 4-hydroxy-2-butanone (0.91 mL, 10.0 mmol) for a reaction time of 3 h and purified by

column chromatography (20% EtOAc/petrol) to give a yellow gum (1.23 g, 59%). IR (CHCl_3) 2963, 1713 ($\text{C}=\text{O}$), 1638 ($\text{C}=\text{C}$), 1361, 1305, 1263, 1209, 1160, 1018, 930 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.48 (1H, d, J = 1.8 Hz, CH), 7.42 (1H, d, J = 15.7 Hz, =CH), 6.61 (1H, d, J = 3.4 Hz, CH), 6.47 (1H, dd, J = 3.4, 1.8 Hz, CH), 6.28 (1H, d, J = 15.7 Hz, =CH), 4.45 (2H, t, J = 6.3 Hz, CH_2O), 2.83 (2H, t, J = 6.3 Hz, $\text{CH}_2\text{CH}_2\text{O}$), 2.21 (3H, s, CH₃); ^{13}C NMR (62.9 MHz, CDCl_3) δ 205.4 (C), 166.4 (C), 150.4 (C), 144.6 (CH), 131.1 (CH), 114.9 (CH), 114.8 (CH), 112.1 (CH), 59.0 (CH_2), 42.0 (CH_2), 29.9 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{11}\text{H}_{13}\text{O}_4$ $[\text{M}+\text{H}]^+$: 209.0809, found: 209.0812.

3-Oxobutyl (E)-5-methylhex-2-enoate (3d). The title compound was prepared according to general procedure A from (E)-5-methylhex-2-enoic acid (2.11 g, 16.5 mmol) and 4-hydroxy-2-butanone (1.36 mL, 15.0 mmol) for a reaction time of 12 h and purified by column chromatography (20% EtOAc/petrol) to give a pale yellow oil (1.63 g, 55%). IR (film) 2959, 1722 (C=O), 1653 (C=C), 1367, 1316, 1267, 1230, 1167, 1127, 1050 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 6.90 (1H, ddd, J = 15.4, 7.5, 7.5 Hz, =CH), 5.75 (1H, d, J = 15.4 Hz, =CH), 4.36 (2H, t, J = 6.3 Hz, CH_2O), 2.77 (2H, t, J = 6.3 Hz, $\text{CH}_2\text{CH}_2\text{O}$), 2.17 (3H, s, $\text{CH}_3\text{C}=\text{O}$), 2.07-2.02 (2H, m, $\text{CH}_2\text{CH}=\text{}$), 1.78-1.67 (1H, m, $(\text{CH}_3)_2\text{CH}$), 0.88 (6H, d, J = 6.6 Hz, $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 205.7 (C), 166.3 (C), 148.9 (CH), 121.7 (CH), 60.0 (CH_2), 42.3 (CH_2), 41.4 (CH_2), 30.2 (CH_3), 27.7 (CH), 22.2 (2 x CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{11}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 199.1329, found: 199.1332.

3-Oxobutyl (E)-5-phenylpent-2-enoate (3e). The title compound was prepared according to general procedure A from (E)-5-phenylpent-2-enoic acid (775 mg, 4.4 mmol) and 4-hydroxy-2-butanone (363 μL , 4.0 mmol) for a reaction time of 12 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow-orange oil (512 mg, 52%). IR (film) 3027, 2926, 1722 (C=O), 1653 (C=C), 1454, 1360, 1318, 1269, 1164, 701 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.32-7.29 (2H, m, ArH), 7.23-7.17 (3H, m, ArH), 7.00 (1H, ddd, J = 15.7, 6.8, 6.8 Hz, =CH), 5.83 (1H, dt, J = 15.7, 1.6 Hz, =CH), 4.40 (2H, t, J = 6.3 Hz, CH_2O), 2.81-2.75 (4H, m, $\text{CH}_2\text{CH}_2\text{O}$ and CH_2Ph), 2.56-2.49 (2H, m, $\text{CH}_2\text{CH}=\text{}$), 2.20 (3H, s, CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 205.7 (C), 166.3 (C), 148.7 (CH), 140.7 (C), 128.5 (2 x CH), 128.3 (2 x CH), 126.2 (CH), 121.3 (CH), 59.1 (CH_2), 42.3 (CH_2), 34.2 (CH_2), 33.9 (CH_2), 30.3 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{15}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 247.1329, found: 247.1335.

3-Oxobutyl 3-methylbut-2-enoate (3f). The title compound was prepared according to general procedure A from 3,3-dimethylacrylic acid (1.70 g, 16.5 mmol) and 4-hydroxy-2-butanone (1.37 mL, 15.0 mmol) for a reaction time of 12 h and purified by column chromatography (15% EtOAc/petrol) to give a pale yellow oil (2.10 g, 82%). IR (film) 2974, 2916, 1718 (C=O), 1652 (C=C), 1446, 1378, 1230, 1147, 1079, 851 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 5.54 (1H, br s, =CH), 4.54-4.49 (2H, m, CH_2O), 3.12-3.09 (2H, m, $\text{CH}_2\text{CH}_2\text{O}$), 2.57 (3H, s, $\text{CH}_3\text{C}=\text{C}$), 2.53 (3H, s, $\text{CH}_3\text{C}=\text{C}$), 2.29 (3H, s, $\text{CH}_3\text{C}=\text{O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 205.7 (C),

166.1 (C), 157.0 (C), 115.4 (CH), 58.2 (CH₂), 42.2 (CH₂), 30.0 (CH₃), 27.1 (CH₃), 19.9 (CH₃); HRMS (FAB) Exact mass calcd for C₉H₁₅O₃ [M+H]⁺: 171.1016, found: 171.1019.

3-Oxo-3-phenylpropyl propenoate (3g). Acryloyl chloride (0.37 mL, 4.4 mmol) was added dropwise over 1 min to a solution of 3-hydroxypropiofenone (601 mg, 4.0 mmol), DMAP (31 mg, 0.25 mmol), and Et₃N (0.84 mL, 6.0 mmol) in CH₂Cl₂ (30 mL) at 0 °C and the reaction was stirred at room temperature for 1.5 h. The reaction was partitioned between saturated aqueous NaHCO₃ solution (30 mL) and Et₂O (70 mL). The organic layer was washed with saturated aqueous NaHCO₃ solution (3 x 30 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/petrol) gave the title compound as white solid (527 mg, 65%). m.p. 38-40 °C; IR (CHCl₃) 2914, 1724 (C=O), 1686 (C=O), 1449, 1408, 1297, 1271, 1192, 984, 810 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.00-7.79 (2H, m, ArH), 7.62-7.57 (1H, m, ArH), 7.52-7.47 (2H, m, ArH), 6.40 (1H, dd, *J* = 17.3, 1.5 Hz, =CH), 6.11 (1H, dd, *J* = 17.3, 10.4 Hz, =CH), 5.83 (1H, dd, *J* = 10.4, 1.5 Hz, =CH), 4.63 (2H, t, *J* = 6.4 Hz, CH₂O), 3.38 (2H, t, *J* = 6.4 Hz, CH₂CH₂O); ¹³C NMR (62.9 MHz, CDCl₃) δ 196.7 (C), 165.8 (C), 136.4 (C), 133.2 (CH), 130.8 (CH₂), 128.5 (2 x CH), 128.0 (CH), 127.9 (2 x CH), 59.6 (CH₂), 37.2 (CH₂); HRMS (FAB) Exact mass calcd for C₁₂H₁₃O₃ [M+H]⁺: 205.0860, found: 205.0863.

3-Oxo-3-phenylpropyl (E)-but-2-enoate (3h). Crotonoyl chloride (0.53 mL, 5.5 mmol) was added dropwise over 1 min to a solution of 3-hydroxypropiofenone (751 mg, 5.0 mmol), DMAP (30 mg, 0.25 mmol) and pyridine (1.62 mL, 20 mmol) in CH₂Cl₂ (40 mL) at 0 °C and the reaction was stirred at room temperature for 16 h. The reaction was partitioned between saturated aqueous NaHCO₃ solution (30 mL) and Et₂O (70 mL). The organic layer was washed with saturated aqueous NaHCO₃ solution (3 x 30 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/petrol) gave the title compound (595 mg, 55%) as a white solid. m.p. 42-44 °C; IR (CHCl₃) 2968, 1719 (C=O), 1686 (C=O), 1658 (C=C), 1448, 1265, 1180, 1104, 1033, 970 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.00-7.96 (2H, m, ArH), 7.62-7.56 (1H, m, ArH), 7.51-7.46 (2H, m, ArH), 6.97 (1H, dq, *J* = 15.5, 6.9 Hz, =CH), 5.83 (1H, dq, *J* = 15.5, 1.7 Hz, =CH), 4.59 (2H, t, *J* = 6.4 Hz, CH₂O), 3.36 (2H, t, *J* = 6.4 Hz, CH₂CH₂O), 1.87 (3H, dd, *J* = 6.9, 1.7 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 196.7 (C), 165.9 (C), 144.7 (CH), 136.3 (C), 133.0 (CH), 128.3 (2 x CH), 127.7 (2 x CH), 122.1 (CH), 59.1 (CH₂), 37.1 (CH₂), 17.6 (CH₃); HRMS (FAB) Exact mass calcd for C₁₃H₁₅O₃ [M+H]⁺: 219.1016, found: 219.1022.

3-Oxo-3-phenylpropyl (E)-3-phenylpropenoate (3i). A solution of cinnamoyl chloride (733 mg, 4.4 mmol) in CH_2Cl_2 (35 mL) was added over 5 min to a solution of 3-hydroxypropioophenone (601 mg, 4.0 mmol), DMAP (27 mg, 0.20 mmol), and Et_3N (0.84 mL, 6.0 mmol) in CH_2Cl_2 (15 mL) at 0 °C. The reaction was stirred at room temperature for 1.5 h before being quenched with saturated aqueous NaHCO_3 solution (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (3 x 30 mL), and the combined organic layers were dried and concentrated *in vacuo*. Purification of the residue by column chromatography (15% EtOAc/petrol) gave the title compound as a white solid (897 mg, 80%). m.p. 68-70 °C; IR (CHCl_3) 2962, 1712 (C=O), 1685 (C=O), 1636 (C=C), 1449, 1331, 1312, 1170, 980, 768 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 8.02-7.99 (2H, m, ArH), 7.68 (1H, d, J = 16.0 Hz, =CH), 7.62-7.57 (1H, m, ArH), 7.53-7.47 (4H, m, ArH), 7.40-7.36 (3H, m, ArH), 6.42 (1H, d, J = 16.0 Hz, =CH), 4.68 (2H, t, J = 6.4 Hz, CH_2O), 3.41 (2H, t, J = 6.4 Hz, $\text{CH}_2\text{CH}_2\text{O}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 197.0 (C), 166.8 (C), 145.0 (CH), 136.6 (C), 134.2 (C), 133.3 (CH), 130.3 (CH), 128.8 (2 x CH), 128.6 (2 x CH), 128.0 (4 x CH), 117.7 (CH), 59.8 (CH_2), 37.5 (CH_2); HRMS (FAB) Exact mass calcd for $\text{C}_{18}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 281.1173, found: 281.1178.

2-Oxo-2-phenylethyl propenoate (3j). Acryloyl chloride (0.47 mL, 5.5 mmol) was added dropwise over 1 min to a solution of 2-hydroxyacetophenone (695 mg, 5.0 mmol), DMAP (30 mg, 0.25 mmol), and Et_3N (1.05 mL, 7.5 mmol) in CH_2Cl_2 (20 mL) at 0 °C and the reaction was stirred at room temperature for 1 h. The reaction was partitioned between saturated aqueous NaHCO_3 solution (30 mL) and Et_2O (70 mL). The organic layer was washed with saturated aqueous NaHCO_3 solution (3 x 30 mL), dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (20% EtOAc/petrol) gave the title compound as a yellow gum (670 mg, 70%). IR (CHCl_3) 2937, 1733 (C=O), 1703 (C=O), 1634 (C=C), 1598, 1404, 1228, 1179, 965, 755 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.96-7.93 (2H, m, ArH), 7.66-7.61 (1H, m, ArH), 7.53-7.49 (2H, m, ArH), 6.56 (1H, dd, J = 17.3, 1.4 Hz, =CH), 6.30 (1H, dd, J = 17.3, 10.4 Hz, =CH), 5.97 (1H, dd, J = 10.4, 1.4 Hz, =CH), 5.45 (2H, s, CH_2O); ^{13}C NMR (62.9 MHz, CDCl_3) δ 191.8 (C), 165.3 (C), 134.0 (C), 133.7 (CH), 131.9 (CH_2), 128.7 (2 x CH), 127.6 (2 x CH), 127.3 (CH), 65.9 (CH_2); HRMS (FAB) Exact mass calcd for $\text{C}_{11}\text{H}_{11}\text{O}_3$ $[\text{M}+\text{H}]^+$: 191.0703, found: 191.0708.

2-Oxo-2-phenylethyl (E)-but-2-enoate (3k). Crotonoyl chloride (0.53 mL, 5.5 mmol) was added dropwise over 1 min to a solution of 2-hydroxyacetophenone (695 mg, 5.0 mmol), DMAP (30 mg, 0.25 mmol), and pyridine (1.62 mL, 20 mmol) in CH_2Cl_2 (20 mL)

at 0 °C and the reaction was stirred at room temperature for 3 h. The reaction was partitioned between saturated aqueous NaHCO₃ solution (30 mL) and Et₂O (70 mL). The organic layer was washed with saturated aqueous NaHCO₃ solution (3 x 30 mL), dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/petrol) gave the title compound (512 mg, 50%) as a yellow gum. IR (CHCl₃) 2942, 1723 (C=O), 1707 (C=O), 1659 (C=C), 1450, 1373, 1291, 1180, 1107, 969 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.94-7.91 (2H, m, ArH), 7.62-7.57 (1H, m, ArH), 7.50-7.45 (2H, m, ArH), 7.11 (1H, dq, *J* = 15.6, 6.9 Hz, =CH), 6.00 (1H, dq, *J* = 15.6, 1.7 Hz, =CH), 5.39 (2H, s, CH₂O), 1.92 (3H, dd, *J* = 6.9, 1.7 Hz, CH₃C=); ¹³C NMR (62.9 MHz, CDCl₃) δ 192.3 (C), 165.6 (C), 146.3 (CH), 134.2 (C), 133.7 (CH), 128.7 (2 x CH), 127.7 (2 x CH), 121.6 (CH), 65.7 (CH₂), 18.1 (CH₃); HRMS (FAB) Exact mass calcd for C₁₂H₁₃O₃ [M+H]⁺: 205.0860, found: 205.0865.

2-Oxo-2-phenylethyl (E)-5-methylhex-2-enoate (3l). The title compound was

prepared according to general procedure A from (E)-5-methylhex-2-enoic acid (705 mg, 5.5 mmol) and 2-hydroxyacetophenone (695 mg, 5.0 mmol) for a reaction time of 3 h and purified by column chromatography (15% EtOAc/petrol) to give a colorless oil (646 mg, 52%). IR (film) 2957, 1730 (C=O), 1705 (C=O), 1654 (C=C), 1370, 1226, 1173, 1128, 981, 689 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.95-7.92 (2H, m, ArH), 7.63-7.58 (1H, m, ArH), 7.51-7.46 (2H, m, ArH), 7.08 (1H, ddd, *J* = 15.5, 7.5, 7.5 Hz, =CH), 5.98 (1H, dt, *J* = 15.5, 1.5 Hz, =CH), 5.40 (2H, s, CH₂O), 2.16-2.11 (2H, m, CH₂C=), 1.84-1.73 (1H, m, (CH₃)₂CH), 0.94 (6H, d, *J* = 6.7 Hz, (CH₃)₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 192.3 (C), 165.7 (C), 150.1 (CH), 134.2 (C), 133.7 (CH), 128.8 (2 x CH), 127.7 (2 x CH), 121.1 (CH), 65.8 (CH₂), 41.5 (CH₂), 27.7 (CH), 22.3 (2 x CH₃); HRMS (FAB) Exact mass calcd for C₁₅H₁₉O₃ [M+H]⁺: 247.1329, found: 247.1333.

2-Oxo-2-phenylethyl (E)-5-phenylpent-2-enoate (3m). The title compound was

prepared according to general procedure A from (E)-5-phenylpent-2-enoic acid (970 mg, 5.5 mmol) and 2-hydroxyacetophenone (695 mg, 5.0 mmol) for a reaction time of 3 h and purified by column chromatography (15% EtOAc/petrol) to yellow gum (711 mg, 48%). IR (CHCl₃) 3027, 2932, 1729 (C=O), 1703 (C=O), 1653 (C=C), 1597, 1450, 1227, 1171, 689 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.96-7.93 (2H, m, ArH), 7.65-7.60 (1H, m, ArH), 7.53-7.48 (2H, m, ArH), 7.34-7.29 (2H, m, ArH), 7.25-7.15 (4H, m, ArH and =CH), 6.04 (1H, dt, *J* = 6.0, 1.6 Hz, =CH), 5.42 (2H, s, CH₂O), 2.82 (2H, t, *J* = 7.8 Hz, PhCH₂), 2.62-2.56 (2H, m, CH₂CH=);

^{13}C NMR (62.9 MHz, CDCl_3) δ 192.2 (C), 165.6 (C), 149.8 (CH), 134.2 (C), 133.7 (CH), 128.7 (2 x CH), 128.4 (2 x CH), 128.2 (2 x CH), 127.7 (2 x CH), 126.1 (CH), 120.6 (CH), 65.8 (CH_2), 34.0 (CH_2), 33.9 (CH_2); HRMS (FAB) Exact mass calcd for $\text{C}_{19}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}]^+$: 295.1329, found: 295.1334.

Copper-Catalyzed Reductive Aldol Cyclizations

General Procedure C: Racemic Cyclizations

A solution of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (10.0 mg, 0.05 mmol) and DPPF (28.6 mg, 0.05 mmol) in THF (2 mL) was stirred for 15 min before TMDS (182 μL , 1.00 mmol) was added. The initially green solution was stirred until it became yellow (*ca.* 5 min), after which a solution of the substrate (1.00 mmol) in THF (2 mL + 1 mL rinse) was then added rapidly *via* cannula. The reaction was stirred at room temperature until complete consumption of the starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (1 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH_4Cl solution (20 mL). The mixture was extracted with CH_2Cl_2 (3 x 15 mL) and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclized product.

(±)-(3R,4R)-3-Benzyl-4-hydroxy-4-methyltetrahydropyran-2-one (2). The title compound was prepared according to general procedure C from **1** (218 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (40% EtOAc/petrol) to give a yellow solid (158 mg, 72%). m.p. 79-80 °C; IR (CHCl_3) 3433 (OH), 2972, 1728 ($\text{C}=\text{O}$), 1496, 1455, 1394, 1258, 1140, 748, 701 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.38-7.30 (4H, m, ArH), 7.26-7.21 (1H, m, ArH), 4.52 (1H, ddd, J = 12.0, 7.4, 5.0 Hz, CH_2O), 4.26 (1H, ddd, J = 12.0, 6.6, 5.0 Hz, CH_2O), 3.34 (1H, dd, J = 14.6, 7.0 Hz, PhCH_2), 3.09 (1H, dd, J = 14.6, 4.2 Hz, PhCH_2), 2.70 (1H, dd, J = 7.0, 4.2 Hz, $\text{CHC}=\text{O}$), 2.40 (1H, br s, OH), 2.13-1.98 (2H, m, $\text{CH}_2\text{CH}_2\text{O}$), 1.42 (3H, s, CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 173.4 (C), 140.9 (C), 129.0 (2 x CH), 128.4 (2 x CH), 126.1 (CH), 71.1 (C), 64.7 (CH_2), 53.7 (CH), 38.3 (CH_2), 30.9 (CH_2), 28.8 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{13}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 221.1173, found: 221.1177.

(±)-(3R,4R)-4-Hydroxy-3-(4-methoxybenzyl)-4-methyltetrahydropyran-2-one (4a).

The title compound was prepared according to general procedure C from **3a** (248 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (40%

EtOAc/petrol) to give a yellow solid (153 mg, 61%). m.p. 82-84 °C; IR (film) 3451 (OH), 2969, 1727 (C=O), 1611, 1513, 1248, 1179, 1109, 1033, 825 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.24 (2H, d, *J* = 8.5 Hz, ArH), 6.83 (2H, d, *J* = 8.5 Hz, ArH), 4.51-4.44 (1H, m, CH₂O), 4.22 (1H, ddd, *J* = 11.3, 5.7, 5.7 Hz, CH₂O), 3.78 (3H, s, OCH₃), 3.27 (1H, dd, *J* = 14.6, 6.9 Hz, ArCH₂), 3.02 (1H, dd, *J* = 14.6, 3.6 Hz, ArCH₂), 2.62 (1H, app t, app *J* = 5.2 Hz, CHC=O), 2.25 (1H, br s, OH), 2.07-1.93 (2H, m, CH₂CH₂O), 1.39 (3H, s, CH₃COH); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.2 (C), 158.0 (C), 132.7 (C), 130.0 (2 x CH), 113.9 (2 x CH), 71.1 (C), 64.7 (CH₂), 55.2 (CH₃), 53.8 (CH), 38.3 (CH₂), 30.1 (CH₂), 28.9 (CH₃); HRMS (FAB) Exact mass calcd for C₁₄H₁₉O₄ [M+H]⁺: 251.1278, found: 251.1283.

(±)-(3*R*,4*R*)-3-(4-Chlorobenzyl)-4-hydroxy-4-methyltetrahydropyran-2-one

(4b). The title compound was prepared according to general procedure C from **3b** (253 mg, 1.00 mmol) for a reaction time of 24 h and purified by column

chromatography (40% EtOAc/petrol) to give a white solid (166 mg, 65%). m.p. 115-117 °C; IR (CHCl₃) 3433 (OH), 2972, 1728 (C=O), 1493, 1409, 1258, 1140, 1094, 1016, 818 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.26 (4H, s, ArH), 4.49 (1H, ddd, *J* = 11.5, 7.6, 4.9 Hz, CH₂O), 4.25 (1H, ddd, *J* = 11.5, 6.7, 4.9 Hz, CH₂O), 3.26 (1H, dd, *J* = 14.6, 7.2 Hz, ArCH₂), 3.01 (1H, dd, *J* = 14.6, 4.1 Hz, ArCH₂), 2.38 (1H, dd, *J* = 7.2, 4.1 Hz, CHC=O), 2.08 (1H, ddd, *J* = 14.5, 7.6, 4.9 Hz, CH₂CH₂O), 1.98 (1H, ddd, *J* = 14.5, 6.7, 4.9 Hz, CH₂CH₂O), 1.84 (1H, br s, OH), 1.41 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.0 (C), 139.4 (C), 132.0 (C), 130.4 (2 x CH), 128.6 (2 x CH), 71.2 (C), 64.7 (CH₂), 53.7 (CH), 38.4 (CH₂), 30.4 (CH₂), 28.9 (CH₃); HRMS (ES) Exact mass calcd for C₁₃H₁₆ClO₃ [M+H]⁺: 255.0782, found: 255.0782.

(±)-(3*R*,4*R*)-3-Furan-2-ylmethyl-4-hydroxy-4-methyltetrahydropyran-2-one **(4c).**

The title compound was prepared according to general procedure C from **3c** (208 mg, 1.00 mmol) for a reaction time of 30 h and purified by column chromatography (30%

EtOAc/petrol) to give a yellow gum (132 mg, 63%). IR (CHCl₃) 3440 (OH), 2973, 2930, 1730 (C=O), 1507, 1404, 1261, 1146, 1011, 736 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.29 (1H, br s, CH), 6.29 (1H, br s, CH), 6.13 (1H, br s, CH), 4.52-4.42 (1H, m, CH₂O), 4.24 (1H, ddd, *J* = 10.9, 5.5, 5.5 Hz, CH₂O), 3.30 (1H, dd, *J* = 15.8, 5.8 Hz, CH₂CHC=O), 3.12 (1H, dd, *J* = 15.8, 5.8 Hz, CH₂CH=O), 2.77 (1H, t, *J* = 5.8 Hz, CHC=O), 2.58 (1H, br s, OH), 2.07-1.99 (1H, m, CH₂CH₂O), 1.97-1.90 (1H, m, CH₂CH₂O), 1.30 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 172.6 (C), 153.6 (C), 140.8 (CH),

110.7 (CH), 106.8 (CH), 70.3 (C), 64.8 (CH₂), 50.5 (CH), 38.1 (CH₂), 28.2 (CH₃), 23.7 (CH₂); HRMS (FAB) Exact mass calcd for C₁₁H₁₅O₄ [M+H]⁺: 211.0965, found: 211.0971.

(±)-(3R,4R)-4-Hydroxy-4-methyl-3-(3-methylbutyl)tetrahydropyran-2-one (4d).

The title compound was prepared according to general procedure C from **3d** (198 mg, 1.00 mmol) for a reaction time of 18 h and purified by column chromatography (30% EtOAc/petrol) to give a colorless oil (146 mg, 73%). IR (film) 3444 (OH), 2956, 2870, 1727 (C=O), 1197, 1113, 1074, 932, 749, 560 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 4.42 (1H, ddd, *J* = 11.7, 5.8, 5.8 Hz, CH₂O), 4.18 (1H, ddd, *J* = 11.7, 5.8, 5.8 Hz, CH₂O), 2.68 (1H, br s, OH), 2.18 (1H, dd, *J* = 8.4, 2.8 Hz, CHC=O), 1.97 (2H, app t, app *J* = 6.0 Hz, CH₂CH₂O), 1.82-1.71 (1H, m, CH₂CHC=O), 1.67-1.58 (1H, m, CH₂CHC=O), 1.56-1.46 (2H, m, (CH₃)₂CHCH₂), 1.36 (3H, s, CH₃COH), 1.21-1.13 (1H, m, (CH₃)₂CH), 0.87 (6H, d, *J* = 6.3 Hz, (CH₃)₂CH); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.9 (C), 70.7 (C), 64.6 (CH₂), 51.8 (CH), 38.5 (CH₂), 37.6 (CH₂), 28.3 (CH₃), 28.1 (CH), 22.8 (CH₂), 22.5 (CH₃), 22.2 (CH₃); HRMS (FAB) Exact mass calcd for C₁₁H₂₁O₃ [M+H]⁺: 201.1486, found: 201.1491.

(±)-(3R,4R)-4-Hydroxy-4-methyl-3-(3-phenylpropyl)tetrahydropyran-2-one (4e).

The title compound was prepared according to general procedure C from **3e** (246 mg, 1.00 mmol) for a reaction time of 18 h and purified by column chromatography (30% EtOAc/petrol) to give a yellow solid (151 mg, 61%). Slow evaporation of a CDCl₃ solution was found to give colorless crystals suitable for X-ray diffraction. m.p. 98-100 °C; IR (CHCl₃) 3443 (OH), 2929, 1728 (C=O), 1454, 1403, 1259, 1204, 1138, 749, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.30-7.26 (2H, m, ArH), 7.22-7.16 (3H, m, ArH), 4.43 (1H, ddd, *J* = 11.6, 5.8, 5.8 Hz, CH₂O), 4.18 (1H, ddd, *J* = 11.6, 5.8, 5.8 Hz, CH₂O), 2.67 (3H, br t, *J* = 7.5 Hz, PhCH₂ and OH), 2.25 (1H, dd, *J* = 8.3, 2.4 Hz, CHC=O), 2.11-1.85 (2H, m, CH₂CH=O), 1.96 (2H, app t, app *J* = 6.0 Hz, CH₂CH₂O), 1.74-1.66 (2H, m, PhCH₂CH₂), 1.34 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.7 (C), 141.9 (C), 128.2 (2 x CH), 128.1 (2 x CH), 125.5 (CH), 70.6 (C), 64.6 (CH₂), 51.3 (CH₂), 51.3 (CH), 37.5 (CH₂), 35.8 (CH₂), 30.7 (CH₂), 28.2 (CH₃), 24.6 (CH₂); HRMS (FAB) Exact mass calcd for C₁₅H₂₁O₃ [M+H]⁺: 249.1486, found: 249.1489.

(±)-(3R,4R)-4-Hydroxy-4-methyl-3-iso-propyltetrahydropyran-2-one (4f). The title compound was prepared according to general procedure C from **3f** (170 mg, 1.00 mmol) for a reaction time of 30 h and purified by column chromatography (30% EtOAc/petrol)

to give a white solid (106 mg, 62%). Slow evaporation of a CDCl_3 solution was found to give colorless crystals suitable for X-ray diffraction. m.p. 76-78 °C; IR (CHCl_3) 3440 (OH), 2972, 1712 (C=O), 1471, 1404, 1274, 1215, 1167, 1129, 1071 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 4.56 (1H, ddd, $J = 11.3, 7.8, 6.1$ Hz, CH_2O), 4.23 (1H, ddd, $J = 11.3, 5.1, 5.1$ Hz, CH_2O), 2.32 (1H, d, $J = 1.9$ Hz, CHCH=O), 2.32-2.23 (1H, m, $(\text{CH}_3)_2\text{CH}$), 1.97 (1H, br s, OH), 1.92-1.85 (2H, m, $\text{CH}_2\text{CH}_2\text{O}$), 1.40 (3H, s, CH_3COH), 1.24 (3H, d, $J = 7.0$ Hz, $(\text{CH}_3)_2\text{CH}$), 1.08 (3H, d, $J = 6.8$ Hz, $(\text{CH}_3)_2\text{CH}$); ^{13}C NMR (62.9 MHz, CDCl_3) δ 171.6 (C), 70.7 (C), 64.7 (CH_2), 56.8 (CH), 37.0 (CH_2), 29.4 (CH_3), 26.4 (CH), 24.5 (CH_3), 19.3 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_9\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 173.1172, found: 173.1178.

(±)-(3R,4R)-4-Hydroxy-3-methyl-3-phenyltetrahydropyran-2-one (4g). The title compound was prepared according to general procedure C from **3g** (204 mg, 1.00 mmol) for a reaction time of 20 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (146 mg, 71%). m.p. 109-110 °C; IR (CHCl_3) 3439 (OH), 2988, 1712 (C=O), 1409, 1307, 1263, 1207, 1049, 980, 701 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.43-7.39 (4H, m, ArH), 7.36-7.30 (1H, m, ArH), 4.71 (1H, ddd, $J = 11.3, 10.4, 4.4$ Hz, CH_2O), 4.48-4.42 (1H, m, CH_2O), 3.03 (1H, q, $J = 7.1$ Hz, CHC=O), 2.48 (1H, ddd, $J = 15.3, 10.4, 5.7$ Hz, $\text{CH}_2\text{CH}_2\text{O}$), 2.13-2.06 (2H, m, $\text{CH}_2\text{CH}_2\text{O}$ and OH), 1.10 (3H, d, $J = 7.1$ Hz, CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 173.9 (C), 144.7 (C), 128.5 (2 x CH), 127.3 (CH), 124.3 (2 x CH), 74.2 (C), 65.4 (CH_2), 46.0 (CH), 38.0 (CH_2), 9.3 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{12}\text{H}_{15}\text{O}_3$ $[\text{M}+\text{H}]^+$: 207.1016, found: 207.1021.

(±)-(3R,4R)-3-Ethyl-4-hydroxy-3-phenyltetrahydropyran-2-one (4h). The title compound was prepared according to general procedure C from **3h** (218 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (109 mg, 50%). m.p. 143-144 °C; IR (CHCl_3) 3349 (OH), 2973, 1705 (C=O), 1446, 1208, 1147, 1126, 1098, 1063, 757 cm^{-1} ; ^1H NMR (360 MHz, CDCl_3) δ 7.45-7.48 (4H, m, ArH), 7.36-7.29 (1H, m, ArH), 4.62 (1H, ddd, $J = 11.5, 8.4, 4.9$ Hz, CH_2O), 4.41 (1H, app dt, $J = 11.5, 5.6$ Hz, CH_2O), 2.77 (1H, dd, $J = 8.6, 2.7$ Hz, CHC=O), 2.53 (1H, br s, OH), 2.41 (1H, ddd, $J = 14.4, 8.4, 5.4$ Hz, $\text{CH}_2\text{CH}_2\text{O}$), 2.12 (1H, app dt, $J = 14.4, 5.4$ Hz, $\text{CH}_2\text{CH}_2\text{O}$), 1.84-1.72 (1H, m, CH_3CH_2), 1.36-1.25 (1H, m, CH_3CH_2), 0.94 (3H, t, $J = 7.4$ Hz, CH_3); ^{13}C NMR (62.9 MHz, CDCl_3) δ 173.3 (C), 145.2 (C), 128.7 (2 x CH), 127.4 (CH), 124.3 (2 x CH), 75.5 (C), 65.1 (CH_2), 52.7 (CH), 39.2 (CH_2), 18.5 (CH_2), 13.9 (CH_3); HRMS (FAB) Exact mass calcd for $\text{C}_{13}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}]^+$: 221.1173, found: 221.1179.

(±)-(3*R*,4*R*)-3-Benzyl-4-hydroxy-3-phenyltetrahydropyran-2-one (4i). The title compound was prepared according to general procedure C from **3i** (280 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (30% EtOAc/petrol) to give a 10:1 inseparable diastereomeric mixture of products as a white solid (134 mg, 47%). (NMR data reported for major isomer): m.p. 180-182 °C; IR (CHCl₃) 3478 (OH), 2992, 1713 (C=O), 1447, 1377, 1317, 1262, 1200, 1050, 755 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.49-7.31 (5H, m, ArH), 7.23-7.12 (3H, m, ArH), 7.02-7.00 (2H, m, ArH), 4.64 (1H, ddd, *J* = 11.5, 8.5, 4.9 Hz, CH₂O), 4.43 (1H, app dt, *J* = 11.5, 5.5 Hz, CH₂O), 3.24 (1H, dd, *J* = 7.7, 2.5 Hz, CHC=O), 3.09 (1H, dd, *J* = 14.0, 7.7 Hz, PhCH₂), 2.78 (1H, dd, *J* = 14.0, 2.5 Hz, PhCH₂), 2.47 (1H, ddd, *J* = 14.3, 8.5, 5.5 Hz, CH₂CH₂O), 2.14 (1H, app dt, *J* = 14.8, 5.2 Hz, CH₂CH₂O), 2.00 (1H, br s, OH); ¹³C NMR (62.9 MHz, d₆-DMSO) δ 173.1 (C), 146.8 (C), 141.5 (C), 128.5 (2 x CH), 127.8 (2 x CH), 126.8 (CH), 125.4 (CH), 125.2 (2 x CH), 75.0 (C), 64.8 (CH₂), 53.0 (CH), 38.8 (CH₂), 30.7 (CH₂); HRMS (FAB) Exact mass calcd for C₁₈H₁₉O₃ [M+H]⁺: 283.1329, found: 283.1335.

(±)-(3*R*,4*R*)-4-Hydroxy-3-methyl-4-phenyltetrahydrofuran-2-one (4j). The title compound was prepared according to general procedure C from **3j** (190 mg, 1.00 mmol) for a reaction time of 13 h and purified by column chromatography (30% EtOAc/petrol) to give a white solid (132 mg, 69%). m.p. 67-69 °C; IR (film) 3458 (OH), 2983, 1767 (C=O), 1449, 1385, 1188, 1112, 1021, 957, 763 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.51-7.36 (5H, m, ArH), 4.42 (1H, d, *J* = 10.0 Hz, CH₂O), 4.36 (1H, d, *J* = 10.0 Hz, CH₂O), 3.06 (1H, q, *J* = 7.1 Hz, CHC=O), 2.51 (1H, br s, OH), 1.23 (3H, d, *J* = 7.1 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 177.5 (C), 139.2 (C), 129.0 (2 x CH), 128.5 (CH), 125.1 (2 x CH), 79.9 (C), 78.0 (CH₂), 45.3 (CH), 6.9 (CH₃); HRMS (FAB) Exact mass calcd for C₁₁H₁₃O₃ [M+H]⁺: 193.0860, found: 193.0864.

(±)-(3*R*,4*R*)-3-Ethyl-4-hydroxy-4-phenyltetrahydrofuran-2-one (4k). The title compound was prepared according to general procedure C from **3k** (204 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow gum (148 mg, 72%). IR (CHCl₃) 3465 (OH), 2970, 1764 (C=O), 1380, 1279, 1182, 1120, 1024, 763, 701 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.54-7.51 (2H, m, ArH), 7.45-7.32 (3H, m, ArH), 4.33 (2H, s, CH₂O), 2.89 (1H, t, *J* = 6.9 Hz, CHC=O), 2.69 (1H, br s, OH), 1.94-1.82 (1H, m, CH₃CH₂), 1.70-1.54 (1H, m, CH₃CH₂), 0.92 (3H, t, *J* = 7.5 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 177.3 (C), 139.8 (C),

128.8 (2 x CH), 128.3 (CH), 125.0 (2 x CH), 80.1 (C), 78.5 (CH₂), 51.9 (CH), 17.1 (CH₂), 12.3 (CH₃); HRMS (FAB) Exact mass calcd for C₁₂H₁₅O₃ [M+H]⁺: 207.1016, found: 207.1023.

(±)-(3*R*,4*R*)-4-Hydroxy-3-(3-methylbutyl)-4-phenyltetrahydrofuran-2-one (4l).

The title compound was prepared according to general procedure C from **3l** (246 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow solid (161 mg, 65%). m.p. 67-69 °C; IR (CHCl₃) 3458 (OH), 2956, 1766 (C=O), 1448, 1366, 1174, 1125, 1025, 761, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.53-7.50 (2H, m, ArH), 7.46-7.42 (2H, m, ArH), 7.39-7.34 (1H, m, ArH), 4.33 (2H, s, CH₂O), 2.92 (1H, t, *J* = 6.8 Hz, CHC=O), 2.53 (1H, br s, OH), 1.89-1.79 (1H, m, CH₂CH=O), 1.64-1.52 (1H, m, CH₂CH=O), 1.49-1.29 (2H, m, (CH₃)₂CHCH₂), 1.10-0.99 (1H, m, (CH₃)₂CH), 0.81 (3H, d, *J* = 6.5 Hz, CH₃), 0.76 (3H, d, *J* = 6.5 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 177.3 (C), 139.7 (C), 128.8 (2 x CH), 128.3 (CH), 125.0 (2 x CH), 80.2 (C), 78.4 (CH₂), 50.4 (CH), 36.3 (CH₂), 27.8 (CH), 22.2 (2 x CH₃), 21.5 (CH₂); HRMS (FAB) Exact mass calcd for C₁₅H₂₁O₃ [M+H]⁺: 249.1486, found: 249.1490.

(±)-(3*R*,4*R*)-4-Hydroxy-4-phenyl-3-(3-phenylpropyl)tetrahydrofuran-2-one (4m).

The title compound was prepared according to general procedure C from **3m** (294 mg, 1.00 mmol) for a reaction time of 24 h and purified by column chromatography (20% EtOAc/petrol) to give a yellow solid (178 mg, 60%). m.p. 103-105 °C; IR (CHCl₃) 3447 (OH), 2930, 1770 (C=O), 1496, 1449, 1147, 1027, 966, 761, 700 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.52-7.38 (5H, m, ArH), 7.25-7.13 (3H, m, ArH), 7.02-7.00 (2H, m, ArH), 4.35 (1H, d, *J* = 10.2 Hz, CH₂O), 4.32 (1H, d, *J* = 10.2 Hz, CH₂O), 2.97 (1H, t, *J* = 6.7 Hz, CHC=O), 2.63 (1H, br s, OH), 2.52 (2H, t, *J* = 7.5 Hz, PhCH₂), 1.94-1.52 (4H, m, PhCH₂CH₂CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 177.1 (C), 141.6 (C), 139.6 (C), 128.9 (2 x CH), 128.3 (5 x CH), 125.8 (CH), 125.0 (2 x CH), 80.1 (C), 78.5 (CH₂), 50.1 (CH), 35.5 (CH₂), 28.7 (CH₂), 23.2 (CH₂); HRMS (FAB) Exact mass calcd for C₁₉H₂₁O₃ [M+H]⁺: 297.1486, found: 297.1490.

General Procedure D: Enantioselective Cyclizations

A solution of Cu(OAc)₂·H₂O (2.0 mg, 0.01 mmol) and the chiral ligand (0.01 mmol) in THF (1 mL) was stirred for 15 min before TMDS (35 μL, 0.20 mmol) was added. The solution was stirred for 5 min, after which a solution of the substrate (0.20 mmol) in THF (0.5 + 0.5 mL rinse) was then added rapidly *via* cannula. The reaction was stirred at room temperature until complete consumption of the

starting material as observed by TLC analysis. The reaction was quenched by the addition of 1 M HCl (0.5 mL), and the mixture was stirred for 1 h before being diluted with saturated aqueous NH₄Cl solution (10 mL). The mixture was extracted with CH₂Cl₂ (3 x 10 mL) and the combined organic layers were dried (MgSO₄) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/petrol) afforded the cyclized product.

(3R,4R)-3-Benzyl-4-hydroxy-4-methyltetrahydropyran-2-one (2) (Table 2, entry 4).

The title compound was prepared according to general procedure D using **1** (44 mg, 0.20 mmol) and (*R*)-3,5-di-*i*Pr-MeOBIPHEP (**8**) (9.2 mg, 0.01 mmol) for a reaction time of 24 h to give the enantioenriched product **2** (28 mg, 64% yield). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); *t_r* (minor) = 13.5 min, *t_r* (major) = 18.6 min; 77% ee; $[\alpha]_D^{22}$ -35.1 (c. 0.47, CHCl₃).

(3R,4R)-3-(4-Chlorobenzyl)-4-hydroxy-4-methyltetrahydropyran-2-one (4b)

(Table 2, entry 8). The title compound was prepared according to general procedure D using **1** (51 mg, 0.20 mmol) and (*R*)-3,5-xyl-MeO-BIPHEP (**7**) (6.9 mg, 0.01 mmol) for a reaction time of 24 h to give the enantioenriched product **4b** (36 mg, 71% yield). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 225 nm, 25 °C); *t_r* (minor) = 14.2 min, *t_r* (major) = 15.6 min; 83% ee; $[\alpha]_D^{21}$ -46.9 (c. 0.96, CHCl₃).

(3S,4S)-4-Hydroxy-4-methyl-3-(3-phenylpropyl)tetrahydropyran-2-one (4e)

(Table 2, entry 13). The title compound was prepared according to general procedure D using **3e** (49 mg, 0.20 mmol) and (*S*)-SEGPPOS (**9**) (6.1 mg, 0.01 mmol) for a reaction time of 16 h to give the enantioenriched product **4e** (32 mg, 68% yield). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); *t_r* (minor) = 11.9 min, *t_r* (major) = 13.7 min; 80% ee; $[\alpha]_D^{21}$ +2.2 (c. 0.90, CHCl₃).

(3R,4R)-4-Hydroxy-4-phenyl-3-(3-phenylpropyl)tetrahydrofuran-2-one (4m)

(Table 2, entry 14). The title compound was prepared according to general procedure D from **3m** (59 mg, 0.20 mmol) and (*R*)-3,5-xyl-MeO-BIPHEP (**7**) (6.9 mg, 0.01 mmol) for a reaction time of 24 h give the enantioenriched product **4m** (30 mg, 51%).

Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (95:5 hexanes:isopropanol, 0.8 mL/min, 210 nm, 25 °C); t_r (major) = 30.4 min, t_r (minor) = 32.7 min; 49% ee; $[\alpha]_D^{24}$ -11.1 (c. 0.90, CHCl₃).

Stereochemical Determinations

Relative Stereochemistries of δ -Valerolactones

- The relative (and absolute) stereochemistry of the δ -valerolactone **4b** was determined by X-ray crystallography (*vide infra*).
- The relative stereochemistry of the δ -valerolactone **4e** was determined by X-ray crystallography. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 270977.

- The relative stereochemistry of the δ -valerolactone **4f** was determined by X-ray crystallography. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 270978.

- The crystal structures of **4e** and **4f** showed the δ -valerolactone rings to possess twist-boat and half-chair conformations respectively in the solid state. A NOESY experiment on the lactone **2** showed a diagnostic nOe between the methine proton and one of the protons of the methylene group adjacent to the ring oxygen, indicating the methine proton to be pseudoaxial (1,3-dipseudoaxial nOe). A further nOe between the methine proton and the protons of the methyl group indicated the methyl group to be pseudoequatorial, thus confirming the relative stereochemistry to be as shown.

Note: Although we have depicted the lactone **2** in a twist-boat conformation, the alternative half-chair conformation does not change the stereochemical analysis.

- The relative stereochemistries of the remaining δ -valerolactones **4a**, **4c**, **4d** and **4g-i** were assigned by analogy.

Relative Stereochemistries of γ -Butyrolactones

- The relative stereochemistries of the γ -butyrolactones **4j** and **4l** were assigned by NOESY experiments, which displayed the following enhancements:

- The relative stereochemistries of the remaining γ -butyrolactones **4k** and **4m** were assigned by analogy.

Absolute and Relative Stereochemistry of **4b**

The absolute sense of stereochemical induction in the asymmetric cyclizations of substrate **3b** (and by inference, of substrates **1**, **3e**, and **3m**, Table 2) was determined as follows:

From the above reaction (Table 2, entry 7), a small quantity of the lactone **4b** (7.3 mg, 76% ee) was recrystallized from Et₂O/petrol to give colorless crystals (2.2 mg). These crystals were dissolved in CH₂Cl₂, and an aliquot of the resulting solution was analyzed by HPLC using a Chiralpak AD-H column (85:15 hexanes:isopropanol, 0.8 mL/min, 225 nm, 25 °C); *t_r* (major) = 13.9 min, *t_r* (minor) = 15.5 min, which showed an increase of enantiomeric purity to 97% ee. After concentration of the

solution *in vacuo*, the remaining solid was dissolved in the minimum quantity of boiling Et₂O (*ca.* 0.5 mL), and petrol (*ca.* 1.5 mL) was very gently layered on top. The next day, crystals suitable for X-ray diffraction were obtained. Crystal structure data deposited at the Cambridge Crystallographic Data Center; Deposition Number: CCDC 277908.

The Flack parameter was found to be 0.02(5), which allowed a definitive assignment of the absolute configuration as that depicted above. Note – there is disorder associated with the methylene carbons C5 and C6 in the lactone ring (see CIF file for details).

COC(=O)COC(=O)C=Cc1ccccc1

Isolated as a 10:1 mixture
of diastereoisomers