A Catalytic Asymmetric Bioorganic Route to Enantioenriched Tetrahydro- and Dihydropyranones

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SUPPORTING INFORMATION

General: Melting points were determined in a capillary and are uncorrected. NMR spectra were recorded on a Bruker DPX-400, a Bruker AVANCE AV400, a Bruker DPX-500 or a Bruker AMX-500 spectrometer. The experiments were performed at 400 MHz for ¹H and 100 MHz for ¹³C, except where otherwise specified. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane with the undeuterated solvent resonance as the internal standard. IR spectra were recorded on a Perkin-Elmer Paragon 1000 FT-IR spectrometer. Selected absorption bands are reported in wavenumbers (cm⁻¹). Mass spectra (*m/z*) and HRMS were recorded on a Micromass GCT in Chemical Ionization (NH₃, CI), Electron Impact (EI⁺) or Field Ionization (FI) mode or on a Micromass AutoSpec (CI⁺). Optical rotations were determined on a Perkin-Elmer 241 polarimeter in a 1 dm cell. Concentrations are given in g/100ml. Microanalyses were performed by 'Elemental Microanalysis Limited', Devon. Thin layer chromatography (TLC) was performed using Merck aluminium foil backed sheets pre-coated with Kieselgel 60F₂₅₄. Column chromatography refers to chromatography on Merck Silica gel C60 (40–60 μm). Biphasic antibody-catalyzed reactions were carried out in Oak Ridge Teflon[®] centrifuge tubes (10 or 30 ml) and agitated in a Nickel Electro NE5-28 shaking bath at room temperature.

Preparation of β-hydroxyenones (±)-1a–l

General procedure: To a solution of lithium di-isopropylamide [prepared by dropwise addition of *n*-butyllithium (5.6 ml, 11.2 mmol) to a solution of di-isopropylamine (1.65 ml, 11.3 mmol) in dry THF (15 ml) at 0 °C] at –78 °C was added the enone (1.32 ml, 11.3 mmol) in dry THF (7.5 ml) *via* cannula. The reaction was allowed to stir at –78 °C for 30 min for aldols **1a**, 20 min for aldols **1f**, **g** and **j** or 15 min for aldol

1b, 1c, 1e, 1i and 1l. The aldehyde (1.22 g, 7.5 mmol) in dry THF (7.5 ml) was then added *via* cannula, and the mixture allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 15 min for aldols **1a-1l**. The reaction was quenched by the addition of saturated aqueous ammonium chloride (50 ml) and allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate (3×50 ml). The combined organic fractions were dried (MgSO_4), filtered under suction and the solvent removed *in vacuo*. The residue was then purified by column chromatography to yield the desired β -hydroxyenone.

(E)-1-Hydroxy-1-(4-methoxyphenyl)-hex-4-en-3-one 1a

Prepared from 3-penten-2-one (2.80 g, 33.2 mmol) and anisaldehyde (3.02 g, 22.2 mmol) according to the general procedure. The crude product was purified by column chromatography on silica (hexane:ethyl acetate 9:1 to 2:1) to yield **1a** (3.22 g, 66%) as a pale yellow solid (mp $35.5\text{--}36.5\text{ }^{\circ}\text{C}$); R_f (hexane:ethyl acetate, 1:1) = 0.34; δ_{H} (CDCl_3) 1.92 (3H, dd, $J = 6.9, 1.6\text{ Hz}$), 2.91 (1H, dd, $J = 16.0, 4.4\text{ Hz}$), 2.95 (1H, dd, $J = 16.0, 8.0\text{ Hz}$), 3.52 (1H, br d, $J = 2.7\text{ Hz}$), 3.81 (3H, s), 5.08–5.21 (1H, m), 6.14 (1H, dq, $J = 15.8, 1.6\text{ Hz}$), 6.84–6.94 (3H, m), 7.31 (2H, d, $J = 8.7\text{ Hz}$, m); δ_{C} (CDCl_3) 18.4, 48.0, 55.3, 69.7, 113.9 (2C), 126.9 (2C), 132.1, 135.2, 144.4, 159.0, 200.3; ν_{max} (CHCl_3) 3513, 3019, 2400, 1686, 1662, 1628, 1614, 1515, 1442, 1250, 1222 and 1036; m/z (HRMS, ESI $^-$) found 219.1024 ($[\text{M}-\text{H}]^-$), $\text{C}_{13}\text{H}_{15}\text{O}_3$ requires 219.1021.

(E)-1-Hydroxy-1-(4-methoxyphenyl)-hept-4-en-3-one 1b

Prepared from anisaldehyde (0.19 ml, 1.53 mmol) and hex-3-en-2-one (0.21 g, 2.14 mmol) according to the general procedure. The crude product was purified by column chromatography on silica (hexane:ethyl acetate 3:1) to yield **1b** (0.2 g, 0.86 mmol, 56%) as a colourless oil. R_f (hexane:ethyl acetate, 1:1) = 0.35; δ_{H} (CDCl_3) 1.02 (3H, t, $J = 7.3\text{ Hz}$), 2.27 (2H, q, $J = 7.3\text{ Hz}$), 2.94 (1H, s), 2.96 (1H, d, $J = 2.5\text{ Hz}$), 3.53 (1H, d, $^3J = 2.8\text{ Hz}$), 3.82 (3H, s), 5.13–5.18 (1H, m), 6.11 (1H, dt, $^3J = 15.9, 1.8\text{ Hz}$), 6.88–6.91 (2H, m), 6.94 (1H, dt, $^3J = 15.9, 7.1\text{ Hz}$), 7.31–7.34 (2H, m); δ_{C} (CDCl_3) δ 12.1, 25.6, 48.0, 55.3, 69.7, 113.8, 127.0, 130.6, 138.0, 150.6, 159.0, 200.7; ν_{max} (neat) 3451, 2968, 2837, 1614, 1514, 1462, 1303, 1249, 1176, 1110, 1034; m/z (HRMS, FI) found 234.1244 ($[\text{M}]^+$), $\text{C}_{14}\text{H}_{18}\text{O}_3$ requires 234.1256.

(E)-1-Hydroxy-1-(4-methoxyphenyl)-oct-4-en-3-one 1c

Prepared from anisaldehyde (0.45 ml, 3.73 mmol) and 3-hepten-2-one (0.73 ml, 5.6 mmol) according to the general procedure. The crude product was purified by column chromatography on silica (hexane:ethyl acetate 3:1) to yield **1c** (0.65 g, 2.62 mmol, 71%) as a colourless oil. R_f (hexane:ethyl acetate, 1:1) = 0.43; δ_{H} (CDCl_3) 0.92 (3H, t, $^3J = 7.6$ Hz), 1.50 (2H, h, $^3J = 7.6$ Hz), 2.20 (2H, q, $^3J = 7.1$ Hz), 2.92 (1H, s), 2.96 (1H, d, $^3J = 3.0$ Hz), 3.54 (1H, bs), 3.81 (3H, s), 5.13-5.18 (1H, m), 6.11 (1H, dt, $^3J = 15.9$, 1.5 Hz), 6.87 (1H, dt, $^3J = 15.9$, 7.1 Hz), 6.89 (2H, d, $^3J = 8.4$ Hz), 7.34 (2H, d, $^3J = 8.4$ Hz); δ_{C} (CDCl_3) 13.7, 21.2, 34.5, 48.1, 55.3, 69.7, 113.8, 127.0, 130.6, 135.1, 149.1, 159.0, 200.6; ν_{max} (neat) 3456, 2961, 2934, 1662, 1615, 1514, 1464, 1303, 1249, 1176, 1036; m/z (HRMS, FI) found 248.1412 ($[\text{M}]^+$), $\text{C}_{15}\text{H}_{20}\text{O}_3$ 248.1412.

(E)-1-Hydroxy-1-(4-methoxyphenyl)-pentadec-4-en-3-one 1d

To a Schlenk tube containing a solution of **1a** (200 mg, 0.91 mmol) and 1-dodecene (600 μl , 2.72 mmol) in anhydrous dichloromethane (3 ml, EtOH free) was added Hoveyda-Grubbs catalyst (30 mg, 0.048 mmol) at room temperature. The reaction was stirred under an argon atmosphere for 16 h and then concentrated under reduced pressure to afford a dark brown oil. The reaction mixture was purified by column chromatography (hexane:ethyl acetate, 2:1) to yield **1d** (240 mg, 77%) as a brown oil; R_f (hexane:ethyl acetate, 1:1) = 0.59; δ_{H} (CDCl_3) 0.89 (3H, dd, $J = 7.1$, 6.5 Hz), 1.23–1.35 (14H, m), 1.38–1.51 (2H, m), 2.18–2.26 (2H, m), 2.90–3.01 (2H, m), 3.54 (1H, d, $J = 2.8$), 3.81 (3H, s), 5.12–5.18 (1H, m), 6.10 (1 H, dt, $J = 16.0$, 1.4 Hz), 6.85 (1H, dt, $J = 16.0$, 7.0 Hz), 6.90 (2H, d, $J = 8.6$), 7.32 (2H, d, $J = 8.6$); δ_{C} (CDCl_3) 14.1, 22.7, 28.0, 29.2, 29.3, 29.3, 29.5, 29.5, 31.9, 32.6, 48.0, 55.3, 69.7, 113.8 (2C), 126.9 (2C), 130.5, 135.1, 149.5, 159.0; ν_{max} (neat) 3454, 2926, 2854, 1660, 1514, 1465, 1248, 1175, 1037.

(E)-8-Furan-2-yl-6-hydroxy-2-methyl-octa-2,7-dien-4-one 1e

Synthesized from 3-furan-2-yl-propionaldehyde (1.22 g, 10 mmol) and mesityl oxide (1.75 ml, 15 mmol) according to the general procedure. Purification by column chromatography (hexane:ethyl acetate, 5:1) afforded **1e** (1.62 g, 74%) as an unstable oil; R_f (hexane:ethyl acetate, 1:1) = 0.39; δ_{H} (CDCl_3) 1.85 (3H, d, $J = 1.2$ Hz), 2.12 (3H, d, $J = 1.2$ Hz), 2.63 (1H, dd, $J = 17.1$, 8.0 Hz), 2.67 (1H, dd, $J = 17.1$, 4.4 Hz), 3.69 (1H, br s), 4.66–4.73 (1H, m), 6.02 (1H, m), 6.11 (1H, dd, $J = 15.8$, 5.8 Hz), 6.17 (1H, d, $J = 3.2$ Hz), 6.30 (1H, dd, $J = 3.4$, 2.0 Hz), 6.43 (1H, d, $J = 15.6$ Hz), 7.28 (1H, d, $J = 2.0$ Hz); δ_{C} (CDCl_3) 21.0, 27.7, 50.1, 68.2, 108.0, 111.2, 118.1, 123.8, 129.3, 141.8, 152.3, 157.3, 200.2; ν_{max} (CHCl_3) 3428.4, 1681.8, 1614.0; m/z (HRMS, GCT, FI) found 220.1099 (M^+), $\text{C}_{13}\text{H}_{16}\text{O}_3$ requires 220.1099.

6-Hydroxy-7-(4-methoxyphenyl)-2-methyl-hept-2-en-4-one 1f

Synthesized from mesityl oxide (0.35 ml, 3 mmol) and 4-methoxyphenyl-acetaldehyde[†] (300 mg, 2 mmol) using the procedure described above. Purification by column chromatography (hexane:ethyl acetate, 4:1) yielded the product (298 mg, 60%) as an oil; R_f (hexane:ethyl acetate, 4:1) = 0.28; δ_{1H} (CDCl₃) 1.89 (3H, s), 2.15 (3H, s), 2.51 (1H, dd, J = 17.3, 8.8 Hz), 2.60 (1H, dd, J = 17.3, 2.8 Hz), 2.68 (1H, dd, J = 13.7, 6.8 Hz), 2.82 (1H, dd, J = 13.7 Hz), 3.34 (1H, br s), 3.80 (3H, s), 4.22–4.31 (1H, m), 6.02 (1H, s), 6.85 (2H, d, J = 8.6 Hz), 7.14 (2H, d, J = 8.6 Hz); δ_{13C} (CDCl₃) 20.9, 27.7, 42.09, 49.1, 55.1, 69.2, 113.8 (2C), 123.8, 130.1, 130.4 (2C), 156.7, 158.2, 200.9; ν_{max} (neat) 3465, 1681, 1613; m/z (HRMS, GCT, FI) found 248.1405 ([M⁺]), C₁₅H₂₀O₃ requires 248.1412.

6-Hydroxy-2-methyl-8-phenyl-oct-2-en-4-one 1g

Synthesized from mesityl oxide (4.4 ml, 37.5 mmol) and 3-phenylpropionaldehyde (3.3 ml, 25 mmol) using the procedure described above. Purification by column chromatography (hexane:ethyl acetate, 4:1) yielded the product (5.07 g, 87%) as a colorless oil; R_f (hexane:ethyl acetate, 1:1) = 0.48; δ_{1H} (CDCl₃) 1.65–1.90 (2H, m), 1.91 (3H, d, J = 0.8 Hz), 2.17 (3H, s), 2.55 (1H, d, J = 12.4, 8.8 Hz), 2.62 (1H, d, J = 12.4, 2.8 Hz), 2.71 (1H, ddd, J = 6.8, 13.8, 9.6 Hz), 2.83 (1H, ddd, J = 4.8, 13.8, 9.4 Hz), 3.50 (1H, br s), 4.04–4.13 (1H, m), 6.03–6.06 (1H, m), 7.16–7.32 (5H, m); δ_{13C} (CDCl₃) 20.9, 27.8, 31.8, 38.1, 50.0, 67.2, 123.8, 125.8, 128.4 (2C), 128.5 (2C), 142.0, 157.1, 201.4; ν_{max} (neat) 3344, 1674, 1614; m/z (HRMS, GCT, FI) found 232.1463 ([M⁺]), C₁₅H₂₀O₂ requires 232.1463.

6-Hydroxy-8-(4-methoxyphenyl)-2-methyl-octa-2,7-dien-4-one 1h

Synthesized from mesityl oxide (1.32 ml, 11.3 mmol) and 4-methoxycinnamaldehyde (1.22 g, 7.5 mmol) using the procedure described above. Purification by column chromatography (hexane:ethyl acetate, 4:1) yielded the product (1.24 g, 64%) as a yellow oil; R_f (hexane:ethyl acetate, 1:1) = 0.49; δ_{1H} (CDCl₃) 1.92 (3H, d, J = 1.2 Hz), 2.19 (3H, d, J = 0.8 Hz), 2.71 (1H, dd, J = 17.2, 8.4 Hz), 2.76 (1H, dd, J = 17.2, 4.0 Hz), 3.48 (1H, br s), 3.80 (3H, s), 4.72–4.78 (1H, m), 6.06–6.09 (1H, m), 6.09 (1H, dd, J = 6.8, 16.4 Hz), 6.58 (1H, d, J = 16 Hz), 6.85 (2H, d, J = 8.8 Hz), 7.32 (2H, d, J = 8.8 Hz); δ_{13C} (CDCl₃) 21.0, 27.9, 50.1, 55.3, 69.0, 113.9 (2C), 123.8, 127.6 (2C), 128.2, 129.4, 129.7, 157.4, 159.2, 200.0; ν_{max} (neat) 3432, 1682, 1614; m/z (HRMS, FI) found 260.1417 ([M⁺]), C₁₆H₂₀O₃ requires 260.1412.

(E)-1-Hydroxy-1-(6-methoxynaphthalen-2-yl)-hex-4-en-3-one 1i

[†] For the preparation of (4-methoxyphenyl)-acetaldehyde, see A. Harris, *Chem. Ber.* **1916**, 1032.

Prepared from 3-penten-2-one (1.1 g, 11.2 mmol) and 6-methoxy-2-naphthaldehyde (1.4 g, 7.5 mmol) according to the general procedure. The crude product was purified by column chromatography on silica (hexane:ethyl acetate, 5:1 to 2:1) to yield **1i** (1.32 g, 65%) as a colorless solid (mp 66.5–67.5 °C); R_f (hexane:ethyl acetate, 1:1) = 0.35; δ_{H} (CDCl_3) 1.88 (3H, dd, $J = 6.9, 1.6$ Hz), 2.98 (1H, dd, $J = 16.4, 4.0$ Hz), 3.02 (1H, dd, $J = 16.4, 8.4$), 3.81 (1H, br s), 3.90 (3H, s), 5.28–5.35 (1H, m), 6.13 (1H, dq, $J = 15.8, 1.6$), 6.87 (1H, dq, $J = 15.8, 6.9$), 7.12 (1H, br d, $J = 2.5$), 7.15 (1H, dd, $J = 8.8, 2.5$), 7.44 (1H, dd, $J = 8.5, 1.7$), 7.71 (1H, d, $J = 8.8$), 7.72 (1H, d, $J = 8.5$), 7.75 (1H, br s); δ_{C} (CDCl_3) 18.4, 48.0, 55.3, 70.1, 105.6, 118.9, 124.3, 124.5, 127.1, 128.7, 129.5, 132.1, 134.0, 138.2, 144.6, 157.6, 200.2; m/z (HRMS, ESI^+) found 293.1162 ($[\text{M}+\text{Na}]^+$), $\text{C}_{17}\text{H}_{18}\text{O}_3$ requires 293.1154.

(E,E)-6-Hydroxy-8-(4-methoxyphenyl)-octa-2,7-dien-4-one 1j

Synthesized from pent-3-en-2-one (0.29 ml, 3 mmol) and 4-methoxycinnamaldehyde (325 mg, 1.5 mmol) using the procedure described above. Purification by column chromatography (hexane:ethyl acetate, 1:1) yielded the product (334 mg, 68%) as a yellow solid (mp 43–44 °C); R_f (hexane:ethyl acetate, 1:1) = 0.27; δ_{H} (CDCl_3) 1.93 (3H, dd, $J = 1.5, 6.5$ Hz), 2.84 (1H, dd, $J = 17.2, 8.0$ Hz), 2.87 (1H, dd, $J = 17.2, 4.0$ Hz), 3.36 (1H, d, $J = 3.5$ Hz), 3.81 (3H, s), 4.74–4.81 (1H, m), 6.10 (1H, dd, $J = 6.2, 16.0$ Hz), 6.15 (1H, dq, $J = 1.5, 16.0$ Hz), 6.59 (1H, d, $J = 16.0$ Hz), 6.85 (2H, d, $J = 9.0$ Hz), 6.92 (1H, dq, $J = 6.5, 16.0$ Hz), 7.32 (2H, d, $J = 9.0$ Hz); δ_{C} (CDCl_3) 18.4, 46.9, 55.2, 68.8, 113.9 (2C), 127.6 (2C), 128.0, 129.3, 129.8, 132.2, 144.3, 159.3, 200.2; ν_{max} (neat) 3435, 1659, 1607; m/z (HRMS, FI) found 246.1254 ($[\text{M}]^+$), $\text{C}_{15}\text{H}_{18}\text{O}_3$ requires 246.1256.

(E,E)-5-Hydroxy-1-methoxy-7-(4-methoxyphenyl)-hepta-1,6-dien-3-one 1k

To di-isopropylamine (0.95 ml, 6.75 mmol) in dry THF (15 ml) in an ice bath was added n-butyllithium (3.2 ml, 6.75 mmol) under argon. The mixture was allowed to stir in the ice bath for 30 min. The reaction was then cooled to –78 °C and HMPA (1.5 ml) followed by 4-methoxy-but-3-en-2-one (0.87 ml, 8.53 mmol) were then added. The reaction was allowed to stir at –78 °C for 2 h. To this was added *para*-methoxycinnamaldehyde (811 mg, 5 mmol) in dry THF (15 ml) *via* cannula, and the mixture allowed to stir for 1 h at –78 °C. The reaction was then quenched with buffer (25 ml of buffer containing 2.5 g of NaH_2PO_4 and the pH adjusted to pH 7 with NaOH) and allowed to warm to room temperature. The aqueous layer was extracted with ethyl acetate (3×25 ml). The organic fractions were combined, dried (MgSO_4), filtered under suction and the solvent removed *in vacuo*. Purification by column

chromatography (hexane:ethyl acetate, 1:1) to yield the product (807 mg, 63%) as a yellow solid (mp 72–73 °C); R_f (hexane:ethyl acetate, 1:1) = 0.22; δ_{1H} (CDCl₃) 2.76 (1H, dd, J = 17.3, 8.0 Hz), 2.80 (1H, dd, J = 17.3, 3.6 Hz), 3.51 (1H, d, J = 2.8 Hz), 3.74 (3H, s), 3.82 (3H, s), 4.73–4.81 (1H, m), 5.62 (1H, d, J = 12.8 Hz), 6.10 (1H, dd, J = 6.2, 16 Hz), 6.60 (1H, d, J = 16.0 Hz), 6.86 (2H, d, J = 8.6 Hz), 7.32 (2H, d, J = 8.6 Hz), 7.66 (1H, d, J = 12.8 Hz); δ_{13C} (CDCl₃) 47.0, 55.2, 57.7, 105.9, 113.9 (2C), 127.6 (2C), 128.2, 129.4, 129.8, 159.3, 163.6, 199.7; ν_{max} (neat) 3480, 1621, 1589; m/z (HRMS, GCT, FI) 262.1168 ($[M]^+$), C₁₅H₁₈O₄ requires 262.1205.

(*E*)-5-Hydroxy-7-(4-methoxyphenyl)-hepta-1,6-dien-3-one 11

Synthesized from methyl vinyl ketone (0.62 ml, 7.5 mmol) and 4-methoxycinnamaldehyde (811 mg, 5 mmol) according to the general procedure. Purification by column chromatography (hexane:ethyl acetate, 4:1) yielded the product (314 mg, 27%) as a yellow oil; R_f (hexane:ethyl acetate, 1:1) = 0.27; δ_{1H} (CDCl₃) 2.92 (2H, d, J = 6.4 Hz), 3.14 (1H, br s), 3.81 (3H, s), 4.80 (1H, dt, J = 6.4, 6.0 Hz), 5.93 (1H, dd, J = 0.8, 10.0 Hz), 6.11 (1H, dd, J = 15.8, 6.0 Hz), 6.27 (1H, dd, J = 0.8, 17.4 Hz), 6.39 (1H, dd, J = 17.4, 10.2 Hz), 6.60 (1H, d, J = 15.6 Hz), 6.85 (2H, d, J = 6.4 Hz), 7.32 (2H, d, J = 6.4 Hz); δ_{13C} (CDCl₃) 45.9, 55.2, 68.7, 114.5 (2C), 127.7 (2C), 127.9, 129.2, 129.4, 130.0, 136.7, 159.3, 200.5; ν_{max} (neat) 3438, 1676, 1607; m/z (HRMS, FI) found 232.1098 ($[M]^+$), C₁₄H₁₆O₃ requires 232.1099.

Preparation of (±)-2f–h (racemic standards for chiral HPLC studies)

6-(4-Methoxybenzyl)-2,2-dimethyltetrahydropyran-4-one (±)-2f

To aldol (±)-**1f** (200 mg, 0.81 mmol) in dichloromethane (4 ml) at $-78\text{ }^{\circ}\text{C}$ was added DIPEA (0.02 ml, 0.16 mmol) and TMSOTf (0.04 ml, 0.22 mmol). The reaction was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 2 h and then warmed to $-15\text{ }^{\circ}\text{C}$. The reaction was allowed to stir at $-15\text{ }^{\circ}\text{C}$ for 40 h and then quenched with $\text{NaHCO}_{3(\text{aq})}$ (5 ml). The mixture was extracted with dichloromethane (3×5 ml), the combined organic fractions dried over MgSO_4 , filtered under suction and the solvent removed *in vacuo*. Purification by column chromatography (hexane:ethyl acetate, 4:1) yielded the product (133 mg, 67%) as an oil; R_f (hexane:ethyl acetate, 1:1) = 0.55; δ_{H} (CDCl_3) 1.16 (3H, s), 1.38 (3H, s), 2.14–2.42 (4H, m), 2.73 (1H, dd, $J = 13.9, 6.0\text{ Hz}$), 2.95 (1H, dd, $J = 13.9, 6.0\text{ Hz}$), 3.80 (3H, s), 3.96–4.06 (1H, m), 6.83 (2H, d, $J = 8.6\text{ Hz}$), 7.13 (2H, d, $J = 8.6\text{ Hz}$); δ_{C} (CDCl_3) 24.0, 30.9, 41.9, 46.7, 53.1, 55.1, 71.8, 75.1, 113.7 (2C), 129.4, 130.4 (2C), 161.2, 208.2; ν_{max} (neat) 1717; m/z (GCT, CI^+) 231 ($[\text{M}-\text{OH}]^+$, 29%), 249 ($[\text{M}+\text{H}]^+$, 61%), 266 ($[\text{M}+\text{NH}_4]^+$, 100%); m/z (HRMS, GCT, CI^+) found 266.1760 ($[\text{M}+\text{NH}_4]^+$), $\text{C}_{15}\text{H}_{24}\text{NO}_3$ requires 266.1756.

2,2-Dimethyl-6-phenethyltetrahydropyran-4-one (±)-2g

To aldol (±)-**1g** (200 mg, 0.86 mmol) in dichloromethane (4 ml) at $-78\text{ }^{\circ}\text{C}$ was added DIPEA (0.02 ml, 0.16 mmol) and TMSOTf (0.04 ml, 0.22 mmol).[†] The reaction was allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 2 h and then warmed to $-20\text{ }^{\circ}\text{C}$. The reaction was allowed to stir at $-20\text{ }^{\circ}\text{C}$ for 24 h and then quenched with saturated aqueous NaHCO_3 (5 ml). The mixture was extracted with dichloromethane (3×5 ml), the combined organic fractions dried over MgSO_4 , filtered under suction and the solvent removed *in vacuo*. Purification by column chromatography (hexane:ethyl acetate, 4:1) yielded the product (140 mg, 70%) as an oil; R_f (hexane:ethyl acetate, 1:1) = 0.54; δ_{H} (CDCl_3) 1.20 (3H, s), 1.44 (3H, s), 1.80–2.06 (2H, m), 2.20–2.48 (4H, m), 2.74 (1H, ddd, $J = 7.6, 14.1, 8.2\text{ Hz}$), 2.86 (1H, ddd, $J = 5.2, 14.1, 9.0\text{ Hz}$), 3.81–3.89 (1H, m), 7.21–7.36 (5H, m); δ_{C} (CDCl_3) 24.0, 31.0, 31.5, 38.2, 47.5, 53.2, 69.6, 75.0, 125.9, 128.4 (2C), 128.5 (2C), 141.66, 208.1; ν_{max} (CHCl_3) 1721; m/z (CGT, CI^+) 233 ($[\text{M}+\text{H}]^+$, 100%), 250 ($[\text{M}+\text{NH}_4]^+$, 100%); m/z (HRMS, GCT, CI^+) found 250.1809 ($[\text{M}+\text{NH}_4]^+$), $\text{C}_{15}\text{H}_{24}\text{NO}_2$ requires 250.1807.

[†] Addition of trimethylsilyl triflate imparts a red color to the reaction. The reaction did not proceed when this red color was not observed and additional TMSOTf was added as necessary.

6-[2-(4-Methoxyphenyl)-ethyl]-2,2-dimethyltetrahydropyran-4-one (±)-2h

Aldol (±)-**1h** (100 mg, 0.35 mmol) in toluene (10 ml) was added to $\text{RhCl}(\text{PPh}_3)_3$ (100 mg, 1 mass eq). The mixture was degassed and placed under H_2 (3-layer balloon) and allowed to stir for 18 h. The solvent was removed *in vacuo* and the residue taken up in dichloromethane (2 ml) and filtered through a plug of silica which was washed with dichloromethane. The solvent was removed *in vacuo* to yield a yellow oil. The residue was dissolved in dichloromethane (2 ml) and cooled to -78°C . To this was added diisopropylethylamine (0.01 ml, 0.08 mmol) and TMSOTf (0.02 ml, 0.11 mmol) and the mixture allowed to stir for 1 h. The mixture was then allowed to warm to -20°C , stirred for 3 h and then placed in the freezer overnight. The reaction was quenched by addition of saturated $\text{NaHCO}_3(\text{aq})$ (5 ml). The mixture was extracted with dichloromethane (3×5 ml), the combined organic fractions dried over MgSO_4 , filtered under suction and the solvent removed *in vacuo*. The residue was purified by column chromatography (cyclohexane:diethyl ether, 2:1) to yield the desired product (56 mg, 56% over 2 steps) as an oil; R_f (cyclohexane:diethyl ether, 1:1) = 0.36; δ_{H} (CDCl_3) 1.15 (3H, s), 1.39 (3H, s), 1.72–1.98 (2H, m), 2.17–2.43 (4H, m), 2.64 (1H, ddd, J = 7.6, 14.1, 7.8 Hz), 2.75 (1H, ddd, J = 5.2, 14.1, 9.2 Hz), 3.75–3.83 (1H, m), 3.79 (3H, s), 6.83 (2H, d, J = 8.6 Hz), 7.11 (2H, d, J = 8.6 Hz); $\delta_{13\text{C}}$ (CDCl_3) 24.16, 30.6, 30.9, 38.5, 47.5, 53.2, 55.2, 69.6, 74.9, 113.8 (2C), 129.3 (2C), 141.7, 157.8, 208.2; ν_{max} (neat) 1718; m/z (GCT, CI^+) 263 ($[\text{M}+\text{H}]^+$, 100%), 280 ($[\text{M}+\text{NH}_4]^+$, 87%); m/z (HRMS, GCT, CI^+) found 280.1905 ($[\text{M}+\text{NH}_4]^+$), $\text{C}_{16}\text{H}_{26}\text{NO}_3$ requires 280.1913.

2-(4-Methoxyphenyl)-6-methyl-2,3-dihydro-4H-pyran-4-one (±)-**3a**

A 25 ml Schlenk tube was charged with palladium(II) chloride (55 mg, 0.31 mmol) and copper(I) chloride (31 mg, 0.31 mmol) before evacuating and back-filling with oxygen (balloon). To this was added a solution of aldol (±)-**1a** (345 mg, 1.57 mmol) in toluene (2.5 ml). The reaction was heated to 50 °C before adding phosphate-buffered saline (2.5 ml, pH 7.4). The addition was accompanied by a gradual darkening of colour and the appearance of Pd black. The resulting biphasic mixture was stirred vigorously at 50 °C for 87 h. The reaction was then cooled to room temperature and the toluene layer separated. The aqueous phase was extracted with ethyl acetate (3×10 ml) and the combined organic phases were filtered through a plug of silica gel and dried over anhydrous magnesium sulphate. The solvent was evaporated under reduced pressure to afford **3a** (342 mg, quant.) as a yellow solid (mp 56–58 °C); R_f (hexane:ethyl acetate, 1:1) = 0.32; δ_{H} (CDCl_3) 2.07 (3H, s), 2.56 (1H, ddd, J = 16.8, 3.4, 1.0 Hz), 2.84 (1H, dd, J = 16.8, 14.3 Hz), 3.84 (3H, s), 5.34 (1H, dd, J = 14.3, 3.4 Hz), 5.43 (1H, s), 6.95 (2H, d, J = 8.7 Hz), 7.35 (2H, d, J = 8.7 Hz); δ_{C} (CDCl_3) 21.1, 42.1, 55.3, 80.6, 105.1, 114.1(2C), 127.8, 130.2 (2C), 160.0, 174.4, 192.3; ν_{max} (CHCl_3) 3019, 2400, 1659, 1609, 1517; m/z (GCT, Cl^-) found 219.1014 ($[\text{M}+\text{H}]^+$), $\text{C}_{13}\text{H}_{15}\text{O}_3$ requires 219.1021.

Antibody-Catalyzed Reactions

General: High performance liquid chromatography (HPLC): Analytical HPLC and semi-preparative HPLC were performed on a Waters HPLC system (626 Pump, 600S Controller, 996 Photodiode Array Detector, Millenium³² Software). Phosphate-buffered saline (PBS) was made up as 10 mM phosphate, 16 mM NaCl, pH 7.4. All antibody-catalyzed reactions were carried out using stock solutions of the antibodies. Abzyme 84G3 (RMM~150000) was available as a 32 μ M or a 66.7 μ M solution in PBS, abzyme 93F3 (RMM~150000) was available as an 82 μ M solution in PBS, abzyme 33F12 (RMM~150000) was available as a 66.7 μ M in PBS and abzyme 38C2 (RMM~150000) was available as an 83.3 μ M solution in PBS. All reactions were carried out in PBS at pH 7.4 with MeCN as a co-solvent.

Supplementary Material for the data reported in Table 1

Aldol reactions were followed by analytical RP-HPLC on a Nova-pak Waters column, C-18, 60 Å pore size, 4 μ m particle size, 3.9×150 mm, flow rate 1 ml min⁻¹. Aldols were isolated by semi-preparative reverse-phase HPLC, Hypersil ODS column, 5 μ m particle size, 7×250 mm, flow rate 2.0 ml min⁻¹ or Phenomenex Luna C18 column, 8.8 μ m particle size, 15×250 mm, flow rate 8.0 ml min⁻¹. Enantioselectivities were determined by normal phase HPLC using a Chiracel OD, Chiracel OJ, Chiracel OJ-H or a Chiracel AD column, 10 μ m particle size, 46×250 mm, flow rate 1 ml min⁻¹.

General procedure for screening of antibody-catalyzed retro-aldol reactions:

Antibody (6.4 nmol) was added to a stock solution of the racemic aldol (80 μ l of 800 μ M in 10% acetonitrile, 90% PBS, 64 nmol). The reactions were monitored by RP-HPLC using a Nova-pak Waters column, C18, 60 Å pore size, 4 μ m particle size, 3.9×150mm, flow rate 1.0 ml min⁻¹, solvent A: water, solvent B: acetonitrile:water (1:1), solvent C: acetonitrile. A blank was made up as for the antibody-catalyzed reaction with the antibody replaced by PBS and was monitored using the same procedure.

Reference dehydrated product: 8-(4-Methoxyphenyl)-2-methylocta-2,5,7-trien-4-one

To aldol ($\pm$)-**1g** (100 mg, 0.38 mmol) in dichloromethane (2 ml) at 0 °C was added two drops of trifluoroacetic acid. The mixture was allowed to stir for 5 min and the solvent removed *in vacuo* to yield essentially pure alkene (92 mg, quant.) as a yellow solid (mp 82–83°C); R_f (hexane:ethyl acetate, 1:1) = 0.63; δ_{1H} (CDCl₃) 1.94 (3H, s), 2.20 (3H, s), 3.84 (3H, s), 6.26–6.28 (1H, m), 6.30 (1H, d, J = 15.2 Hz), 6.79 (1H, dd, J = 10.8, 15.4 Hz), 6.90 (1H, d, J = 15.2 Hz), 6.90 (2H, d, J = 8.8 Hz), 7.36 (1H, dd, J = 15.2, 10.8 Hz), 7.43 (2H, d, J = 8.6 Hz); δ_{13C} (CDCl₃) 20.9, 27.8, 55.3, 114.3 (2C), 123.6, 125.0, 128.6 (2C), 129.1, 130.8, 140.4, 142.5, 155.3, 160.4, 190.3; ν_{max} (neat) 1623.7, 1602.0, 1577.1; m/z (GCT, Cl⁺) 243 ([M+H]⁺, 100%); m/z (HRMS, GCT, Cl⁺) found 243.1379 ([M+H]⁺), C₁₆H₁₉O₂ requires 243.1385.

Screening results for selected antibody-catalyzed retro-aldolizations

Aldol	Conditions	Results
(±)- 1a	10% Ab84G3, 0.5 h	51% loss of aldol; 41% formation of aldehyde
	10% Ab93F3, 0.5 h	58% loss of aldol; 36% formation of aldehyde
	PBS, 0.5 h	No reaction
(±)- 1b	10% Ab84G3, 6 h	58 % loss of aldol; 20 % formation of aldehyde
	10% Ab93F3, 9 h	55 % loss of aldol; 22 % formation of aldehyde
	PBS, 12 h	No reaction
(±)- 1f	10% Ab84G3, 44 h	47% loss of aldol
	10% Ab93F3, 44 h	49% loss of aldol
	PBS, 44 h	No reaction
(±)- 1g	10% Ab84G3, 42 h	34% loss of aldol
	10% Ab93F3, 42 h	46% loss of aldol
	PBS, 42 h	No reaction
(±)- 1h	10% Ab84G3, 1 h	55% loss of aldol; 39% formation of aldehyde [†]
	10% Ab93F3, 1 h	51% loss of aldol; 39% formation of aldehyde [†]
	PBS, 1 h	No reaction
(±)- 1i	10% Ab84G3, 2 h	58% loss of aldol; 21% formation of aldehyde
	10% Ab93F3, 2 h	55% loss of aldol; 22% formation of aldehyde
	PBS, 2 h	No reaction
(±)- 1j	10% Ab84G3, 40 m	49% loss of aldol; 43% formation of aldehyde
	10% Ab93F3, 40 m	55% loss of aldol; 42% formation of aldehyde
	PBS, 40 m	No reaction
(±)- 1k	10% Ab84G3, 48 h	74% loss of aldol; 5% formation of aldehyde
	PBS, 48 h	54% loss of aldol; No aldehyde observed
(±)- 1l	10% Ab84G3, 12 h	97% loss of aldol; No aldehyde observed
	10% Ab93F3, 12 h	98% loss of aldol; No aldehyde observed
	PBS, 12 h	11% loss of aldol; No aldehyde observed

[†] Dehydrated product also observed (see above)

Reverse-phase retention times for the products in Figure 1:

Reaction of **1a**: Isocratic 65% A: 35% B, t_R ketone = 3.4 min,
 t_R anisaldehyde = 15.2 min, t_R aldol **1a** = 22.7 min.

Reaction of **1b**: Isocratic 40% A: 60% B, t_R ketone = 3.8 min,
 t_R anisaldehyde = 5.6 min, t_R aldol **1b** = 10.1 min.

Reaction of **1c**: Isocratic 40% A: 60% B, t_R ketone = 3.8 min,
 t_R anisaldehyde = 5.6 min, t_R aldol **1c** = 18.6 min.

Reaction of **1d**: Isocratic 30% A: 70% C, t_R aldol **1d** = 9.9 min.

Reaction of **1e**: Isocratic 50% A: 50% B, t_R anisaldehyde = 3.7 min,
 t_R aldol **1e** = 12.8 min.

Reaction of **1f**: Isocratic 50% A: 50% B, t_R mesityl oxide = 4.0 min,
 t_R (4-methoxyphenyl)-acetaldehyde = 11.3 min, t_R aldol **1f** = 14.9 min.

Reaction of **1g**: Isocratic 30% A: 70% B, t_R mesityl oxide = 2.8 min,
 t_R 3-phenylpropionaldehyde = 4.7 min, t_R aldol **1g** = 9.5 min.

Reaction of **1h**: Isocratic 50% A: 50% B, t_R mesityl oxide = 4.0 min,
 t_R 4-methoxycinnamaldehyde = 9.9 min, t_R aldol **1h** = 20.8 min,
 t_R dehydrated product = 62.7 min.

Reaction of **1i**: Isocratic 20% A: 80% B, t_R anisaldehyde = 8.4 min,
 t_R aldol **1i** = 5.4 min.

Reaction of **1j**: Isocratic 50% A: 50% B, t_R pent-3-en-2-one = 2.3 min,
 t_R 4-methoxycinnamaldehyde = 9.9 min, t_R aldol **1j** = 14.1 min.

Reaction of **1k**: Isocratic 60% A: 40% B, t_R 4-methoxy-but-3-en-2-one = 4.3 min,
 t_R 4-methoxycinnamaldehyde = 16.0 min, t_R aldol **1k** = 19.0 min.

Reaction of **1l**: Isocratic 62% A: 38% B, t_R methyl vinyl ketone = 2.1 min,
 t_R 4-methoxycinnamaldehyde = 19.5 min, t_R aldol **1l** = 22.9 min.

General procedure for *ee* determination of antibody-catalyzed retro-aldol reactions:

Antibody (32 nmol) was added to a stock solution of racemic aldol (10 μ l of 80 mM in acetonitrile, 800 nmol). The reactions were monitored by RP-HPLC using a Waters Nova-pak column, C18, 60 Å pore size, 4 μ m particle size, 3.9×150mm, flow rate 1.0 ml min⁻¹, solvent A: water, solvent B: acetonitrile:water (1:1) as above. After reaching 50% conversion, the unreacted aldol was isolated by semi-preparative reversed-phase HPLC (Hypersil ODS column, 5 μ m particle size, 7×250 mm, flow rate 2.0 ml min⁻¹ or Phenomenex Luna C18 column, 8.8 μ m particle size, 15×250 mm, flow rate 8.0 ml min⁻¹). The fractions were freeze-dried, the residue was redissolved in 200 μ l of dichloromethane:hexane (50:50) and the *ee* was determined by normal-phase HPLC using a Chiracel OD, Chiracel OJ, Chiracel OJ-H or a Chiracel AD column, 10 μ m particle size, 4.6×250mm, flow rate 1 ml min⁻¹. Solvent C: hexane, solvent D: *iso*-propanol, solvent E: ethanol.

Chiral HPLC retention times for the aldol products in Table 1:

Aldol **1a**: on OJ-H column (1 ml min^{-1}), Isocratic 97% C: 3% E, t_R (R)-**1a** = 56.6 min, t_R (S)-**1a** = 62.2 min.

Aldol **1b**: on OD column (1 ml min^{-1}), Isocratic 99% C: 1% E, t_R (R)-**1b** = 37.0 min, t_R (S)-**1b** = 39.0 min.

Aldol **1c**: on OD column (1 ml min^{-1}), Isocratic 99% C: 1% E, t_R (R)-**1c** = 30.4 min, t_R (S)-**1c** = 33.6 min.

Aldol **1d**: on OD column (1 ml min^{-1}), Isocratic 99% C: 1% E, t_R (R)-**1c** = 25.4 min, t_R (S)-**1c** = 27.5 min.

Aldol **1f**: on AD column (1 ml min^{-1}), Isocratic 95% C: 5% D, t_R (R)-**1f** = 19.8 min, t_R (S)-**1f** = 28.4 min.

Aldol **1g**: on OJ column (1 ml min^{-1}), Isocratic 99% C: 1% E, t_R (S)-**1g** = 18.4 min, t_R (R)-**1g** = 20.5 min.

Aldol **1h**: on OJ column (1 ml min^{-1}), Isocratic 75% C: 25% D, t_R (S)-**1h** = 13.9 min, t_R (R)-**1h** = 17.2 min.

Aldol **1i**: on OJ-H column (1 ml min^{-1}), Isocratic 80% C: 20% E, t_R (S)-**1i** = 37.0 min, t_R (R)-**1i** = 41.8 min.

Aldol **1j**: on AD column (1 ml min^{-1}), Isocratic 80% C: 20% E, t_R (R)-**1j** = 18.3 min, t_R (S)-**1j** = 21.8 min.

Aldol **1k**: on AD column (1 ml min^{-1}), Isocratic 70% C: 30% E, t_R **1k** = 15.8 and 19.3 min.

Aldol **1l**: on OJ-H column (1 ml min^{-1}), Isocratic 80% C: 20% E, t_R **1l** = 18.3 and 19.3 min.

Chiral HPLC retention times for the HDA adducts

2f: on OJ column (1 ml min^{-1}), Isocratic 93% C: 7% E, t_R (R)-**2f** = 10.2 min, t_R (S)-**2f** = 11.8 min.

2g: on OD column (1 ml min^{-1}), Isocratic 96% C: 4% E, t_R (R)-**2g** = 8.4 min, t_R (S)-**2g** = 9.6 min.

2h: on OJ-H column (1 ml min^{-1}), Isocratic 91% C: 9% E, t_R (S)-**2h** = 12.7 min, t_R (R)-**2h** = 13.7 min.

3a: on OJ-H column (1 ml min^{-1}), Isocratic 97% C: 3% E, t_R (R)-**3a** = 59.4 min, t_R (S)-**3a** = 66.2 min.

Antibody-Catalyzed Kinetic Measurements

Kinetic measurements were carried out using a constant concentration of antibody and varying the substrate concentration. Aliquots were periodically removed from the reactions and quenched with acetic acid.

Figure 3. Demonstration of adherence to the Michaelis–Menten equation for the retro-aldol reaction of **1a** to give anisaldehyde and pent-3-en-2-one, catalyzed by Ab84G3.

All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing less than 3% of acetonitrile as the organic solvent. All catalyzed reactions were performed in the presence of 0.65 μM of Ab84G3. The concentration of the aldol product was varied from 20 to 120 μM . Initial velocities were determined by following the formation of anisaldehyde by RP-HPLC within <5% reaction completion. The points were determined experimentally and the best fit value of V_{max} and K_{m} were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression using SigmaPlot 5.0 (from SPSS Inc). The data are reported per antibody active site. An IgG antibody possesses two active sites per MW of $\sim 150000 \text{ g mol}^{-1}$.

Concentration of 1a (μM)	v_i ($\mu\text{M min}^{-1}$)	Calculated
20	0.1891	0.1777
30	0.2260	0.2313
40	0.2832	0.2724
50	0.2873	0.3049
60	0.3258	0.3331
100	0.4112	0.4006
120	0.4209	0.4227

Variable	Value	Std. Error
V_{max} ($\mu\text{M min}^{-1}$)	0.5838	0.0263
k_{cat} (min^{-1})	0.452	
K_{m} (μM)	45.718	4.844

Figure 3. Demonstration of adherence to the Michaelis–Menten equation for the retro-aldol reaction of **1a** to give anisaldehyde and pent-3-en-2-one, catalyzed by Ab93F3.

All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing less than 3% of acetonitrile as the organic solvent. All catalyzed reactions were performed in the presence of 0.8 μM of Ab93F3. The concentration of the aldol product was varied from 20 to 140 μM . Initial velocities were determined by following the formation of anisaldehyde by RP-HPLC within <5% reaction completion. The points were determined experimentally and the best fit value of V_{max} and K_{m} were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression using SigmaPlot 5.0 (from SPSS Inc). The data are reported per antibody active site. An IgG antibody possesses two active sites per MW of $\sim 150000 \text{ g mol}^{-1}$.

Concentration of 1a (μM)	v_i ($\mu\text{M min}^{-1}$)	Calculated
20	0.1539	0.1812
30	0.2409	0.2382
40	0.3083	0.2827
50	0.3113	0.3184
80	0.3968	0.3928
100	0.4310	0.4259
120	0.4567	0.4513
140	0.4570	0.4714

Variable	Value	Std. Error
V_{max} ($\mu\text{M min}^{-1}$)	0.6431	0.0323
k_{cat} (min^{-1})	0.40	
K_{m} (μM)	50.984	6.351

Figure 3. Demonstration of adherence to the Michaelis–Menten equation for the retro-aldol reaction of **1b** to give anisaldehyde and hex-3-en-2-one, catalyzed by Ab84G3.

All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing less than 3% of acetonitrile as the organic solvent. All catalyzed reactions were performed in the presence of 10.34 μM of Ab84G3. The concentration of the aldol product was varied from 20 to 140 μM . Initial velocities were determined by following the formation of anisaldehyde by RP-HPLC within <5% reaction completion. The points were determined experimentally and the best fit value of V_{max} and K_{m} were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression using SigmaPlot 5.0 (from SPSS Inc). The data are reported per antibody active site. An IgG antibody possesses two active sites per MW of $\sim 150000 \text{ g mol}^{-1}$.

Concentration of 1b (μM)	v_i ($\mu\text{M min}^{-1}$)	Calculated
20	0.0615	0.740
30	0.1026	0.1035
40	0.1300	0.1291
60	0.1851	0.1718
80	0.2068	0.2058
100	0.2267	0.2335
140	0.2759	0.2759

Variable	Value	Std. Error
V_{max} ($\mu\text{M min}^{-1}$)	0.5016	0.044
k_{cat} (min^{-1})	0.025	
K_{m} (μM)	116.76	17.51

Figure 2. Demonstration of adherence to the Michaelis–Menten equation for the retro-aldol reaction of **1g** to give 3-phenylpropionaldehyde and mesityl oxide, catalyzed by Ab84G3.

All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing less than 3% of acetonitrile as the organic solvent. All catalyzed reactions were performed in the presence of 9.9 μM of Ab84G3. The concentration of the aldol product was varied from 100 to 800 μM. Initial velocities were determined by following the formation of mesityl oxide by RP-HPLC within <5% reaction completion. The points were determined experimentally and the best fit value of $V_{\max}$ and K_m were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression using SigmaPlot 5.0 (from SPSS Inc). The data are reported per antibody active site. An IgG antibody possesses two active sites per MW of ~ 150000 g mol⁻¹.

Concentration of 1g (μM)	v_i (μM min ⁻¹)	Calculated
100	0.0262	0.0272
150	0.0369	0.0367
200	0.0436	0.0445
300	0.0571	0.0566
400	0.0670	0.0654
500	0.0720	0.0721
600	0.0780	0.0774
800	0.0843	0.0854

Variable	Value	Std. Error
$V_{\max}$ (μM min ⁻¹)	0.123	0.003
k_{cat} (min ⁻¹)	0.006	0.00015
K_m (μM)	352	16.8

Figure 3. Demonstration of adherence to the Michaelis–Menten equation for the retro-aldol reaction of **1h** to give 4-methoxycinnamaldehyde and mesityl oxide, catalyzed by Ab84G3.

All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing less than 3% of acetonitrile as the organic solvent. All catalyzed reactions were performed in the presence of 0.078 μM of Ab84G3. The concentration of the aldol product was varied from 20 to 140 μM . Initial velocities were determined by following the formation of 4-methoxycinnamaldehyde by RP-HPLC within <5% reaction completion. The points were determined experimentally and the best fit value of V_{max} and K_{m} were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression using SigmaPlot 5.0 (from SPSS Inc). The data are reported per antibody active site. An IgG antibody possesses two active sites per MW of $\sim 150000 \text{ g mol}^{-1}$.

Concentration of 1h (μM)	v_i ($\mu\text{M min}^{-1}$)	Calculated
20	0.1010	0.1059
30	0.1392	0.1409
40	0.1702	0.1688
50	0.1901	0.1915
60	0.2148	0.2104
80	0.2379	0.2401
100	0.2594	0.2622
120	0.2807	0.2794
140	0.2905	0.2931

Variable	Value	Std. Error
V_{max} ($\mu\text{M min}^{-1}$)	0.416	0.007
k_{cat} (min^{-1})	2.68	0.045
K_{m} (μM)	59.0	2.28

Figure 4. Demonstration of adherence to the Michaelis–Menten equation for the retro-aldol reaction of **1h** to give 4-methoxycinnamaldehyde and mesityl oxide, catalyzed by Ab93F3.

All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing less than 3% of acetonitrile as the organic solvent. All catalyzed reactions were performed in the presence of 0.064 μM of Ab93F3. The concentration of the aldol product was varied from 20 to 140 μM . Initial velocities were determined by following the formation of 4-methoxycinnamaldehyde by RP-HPLC within <5% reaction completion. The points were determined experimentally and the best fit value of V_{max} and K_{m} were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression using SigmaPlot 5.0 (from SPSS Inc). The data are reported per antibody active site. An IgG antibody possesses two active sites per MW of $\sim 150000 \text{ g mol}^{-1}$.

Concentration of 1h (μM)	v_i ($\mu\text{M min}^{-1}$)	Calculated
20	0.1155	0.1228
30	0.1682	0.1650
40	0.1986	0.1993
50	0.2247	0.2277
60	0.2583	0.2515
80	0.2919	0.2894
100	0.3160	0.3182
120	0.3426	0.3409
140	0.3557	0.3591

Variable	Value	Std. Error
V_{max} ($\mu\text{M min}^{-1}$)	0.529	0.012
k_{cat} (min^{-1})	4.13	0.094
K_{m} (μM)	66.1	3.19

Figure 5. Demonstration of adherence to the Michaelis–Menten equation for the retro-aldol reaction of **1j** to give 4-methoxycinnamaldehyde and pent-3-en-2-one, catalyzed by Ab84G3.

All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing less than 3% of acetonitrile as the organic solvent. All catalyzed reactions were performed in the presence of 0.078 μM of Ab84G3. The concentration of the aldol product was varied from 20 to 140 μM . Initial velocities were determined by following the formation of 4-methoxycinnamaldehyde by RP-HPLC within <5% reaction completion. The points were determined experimentally and the best fit value of V_{max} and K_{m} were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression using SigmaPlot 5.0 (from SPSS Inc). The data are reported per antibody active site. An IgG antibody possesses two active sites per MW of $\sim 150000 \text{ g mol}^{-1}$.

Concentration of 1j (μM)	v_i ($\mu\text{M min}^{-1}$)	Calculated
20	0.1144	0.1151
30	0.1509	0.1480
40	0.1702	0.1726
50	0.1909	0.1918
60	0.2094	0.2071
80	0.2300	0.2301
100	0.2439	0.2465
120	0.2581	0.2588
140	0.2707	0.2684

Variable	Value	Std. Error
V_{max} ($\mu\text{M min}^{-1}$)	0.345	0.004
k_{cat} (min^{-1})	2.22	0.025
K_{m} (μM)	40.0	1.17

Figure 6. Demonstration of adherence to the Michaelis–Menten equation for the retro-aldol reaction of **1j** to give 4-methoxycinnamaldehyde and pent-3-en-2-one, catalyzed by Ab93F3.

All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing less than 3% of acetonitrile as the organic solvent. All catalyzed reactions were performed in the presence of 0.064 μM of Ab93F3. The concentration of the aldol product was varied from 20 to 140 μM. Initial velocities were determined by following the formation of *para*-methoxycinnamaldehyde by RP-HPLC within <5% reaction completion. The points were determined experimentally and the best fit value of $V_{\max}$ and K_m were obtained by fitting the v_i versus $[S]_0$ data to hyperbolic saturation curves by weighted non-linear regression using SigmaPlot 5.0 (from SPSS Inc). The data are reported per antibody active site. An IgG antibody possesses two active sites per MW of $\sim 150000 \text{ g mol}^{-1}$.

Concentration of 1j (μM)	v_i (μM min ⁻¹)	Calculated	Variable	Value	Std. Error
20	0.1422	0.1466	$V_{\max}$ (μM min ⁻¹)	0.415	0.006
30	0.1836	0.1869	k_{cat} (min ⁻¹)	3.24	0.047
40	0.2180	0.2167	K_m (μM)	36.6	1.42
50	0.2443	0.2396			
60	0.2605	0.2578			
80	0.2851	0.2848			
100	0.3080	0.3039			
120	0.3150	0.3181			
140	0.3255	0.3291			

Uncatalyzed kinetics: All reactions were carried out at room temperature in PBS (10 mM phosphate, 16 mM NaCl, pH 7.4) containing 2.5% of acetonitrile as the organic solvent. The reactions were followed by RP-HPLC, and at a concentration of 4 mM no formation of aldehyde or ketone was observed after 5 days.

Antibody-catalyzed route to enantioenriched HDA adducts

(*R*)-6-(4-Methoxybenzyl)-2,2-dimethyltetrahydropyran-4-one (*R*)-2f

Antibody 84G3 (1 ml, 32 nmol) was added to a stock solution of aldol ($\pm$)-**1f** (10 μ l of 80 mM in acetonitrile, 800 nmol). The reaction was monitored by RP-HPLC. After 216 h the reaction was observed to have reached 68% conversion and the unreacted aldol was isolated by semi-preparative reversed-phase HPLC. The fractions were freeze-dried, the residue was redissolved in dichloromethane (3 $\times$ 20 ml), filtered and the solvent removed *in vacuo*. The recovered aldol has an *ee* of 83%. The residue was dissolved in dichloromethane (2.5 ml) and cooled to -78 $^{\circ}$ C. To this was added diisopropylethylamine (2 $\times$ 7.3 μ l of a solution made up as 0.1 ml in 10 ml dichloromethane, 0.85 μ mol) and TMSOTf (2 $\times$ 8.3 μ l of a solution made up as 0.1 ml in 10 ml dichloromethane, 0.92 μ mol). The mixture was stirred at -78 $^{\circ}$ C for 1 h then warmed to -20 $^{\circ}$ C and stirred overnight. The mixture was then allowed to warm to 10 $^{\circ}$ C for 6 h. The crude mixture contained (*R*)-**2f** with an *ee* of 83%.

(*R*)-2,2-Dimethyl-6-phenylethyltetrahydropyran-4-one (*R*)-2g

Antibody 84G3 (1 ml, 32 nmol) was added to a stock solution of aldol ($\pm$)-**1g** (10 μ l of 80 mM in acetonitrile, 800 nmol). The reaction was monitored by RP-HPLC. After 216 h the reaction had reached 51% conversion and the unreacted aldol was isolated by semi-preparative reverse-phase HPLC. The fractions were freeze-dried, the residue was redissolved in dichloromethane (3 $\times$ 20 ml), filtered and the solvent removed *in vacuo*. The recovered aldol has an *ee* of 72%. The residue was dissolved in dichloromethane (2.5 ml) and cooled to -78 $^{\circ}$ C. To this was added DIPEA (2 $\times$ 7.3 μ l of a solution made up as 0.1 ml in 10 ml dichloromethane, 0.85 μ mol) and TMSOTf (2 $\times$ 8.3 μ l of a solution made up as 0.1 ml in 10 ml dichloromethane, 0.92 μ mol). The mixture was stirred at -78 $^{\circ}$ C for 1 h then allowed to warm to -20 $^{\circ}$ C and stirred overnight. The mixture was then warmed to 10 $^{\circ}$ C for 6 h. The crude mixture contained (*R*)-**2g** with an *ee* of 72%.

(R)-6-[2-(4-Methoxyphenyl)-ethyl]-2,2-dimethyltetrahydropyran-4-one (R)-2h

Aldol ($\pm$)-**1h** (2.5 mg, 0.019 mmol) was dissolved in MeCN (200 μ l). To this was added PBS (1.8 ml) and Ab93F3 (1 ml, 164 nmol). The reaction was monitored by RP-HPLC. After 44 h the reaction had reached 52% conversion and the unreacted aldol was isolated by semi-preparative reverse-phase HPLC. The fractions were freeze-dried, the residue was redissolved in dichloromethane (3 $\times$ 20 ml), filtered and the solvent removed *in vacuo* to yield the product (1.1 mg, 40%). The recovered aldol has an *ee* of >99%. The residue was dissolved in toluene (0.2 ml) and added to RhCl(PPh₃)₃ (0.83 mg, ~0.75 mass eq). The mixture was degassed and placed under H₂ (3-layer balloon) and stirred for 24 h. The solvent was removed *in vacuo* and the residue was taken up in dichloromethane (1 ml), filtered through a silica plug and concentrated. The residue was redissolved in dichloromethane (0.5 ml) and cooled to –78 °C. To this was added DIPEA (0.01 ml of a 1% solution in dichloromethane, 0.8 μ mol) and TMSOTf (0.02 ml of a 1% solution in dichloromethane, 0.0011 mmol) and the mixture was stirred for 1 h. The mixture was then allowed to warm to –20 °C and stirred for 3 h before standing in the freezer overnight. The reaction was quenched by addition of saturated NaHCO_{3(aq)} (0.5 ml) and extracted with dichloromethane (3 $\times$ 0.5 ml). The combined organic fractions were dried over MgSO₄, filtered under suction and the solvent removed *in vacuo*. The crude mixture contained (*R*)-**2h** with an *ee* of >99%.

(S)-2-(4-Methoxyphenyl)-6-methyl-2,3-dihydro-4H-pyran-4-one (S)-3a

The racemic β -hydroxyenone ($\pm$)-**1a** (5 mg, 23 μ mol) was added to a Teflon[®] tube and dissolved in either toluene or chlorobenzene (275 μ l). To this was added a 66.7 μ M solution of Ab84G3 (34 mg, 0.23 μ mol) in PBS (3.4 ml, pH 7.4) and the tube sealed. The mixture was placed in a shaking bath (250 strokes/minute) at room temperature. The *ee* of the unreacted **1a** was monitored periodically by HPLC on chiral stationary phase (10 μ l aliquots were removed from the organic layer and diluted to 100 μ l with mobile phase before analysis). Once the desired substrate *ee* was attained, the mixture was placed in a freezer for several hours, after which time the organic layer was decanted and the aqueous layer was allowed to thaw. The aqueous layer was then extracted with 1:1 toluene–ethyl acetate (2 $\times$ 5 ml) and the combined organic phases were dried over sodium sulfate, filtered through a plug of silica gel and the solvent was removed under reduced pressure. The crude mixture contained (*S*)-**1a** in 97% *ee*.

The crude reaction product was redissolved in toluene (100 μ l) and added to a Schlenk tube containing palladium(II) chloride (1 mg, 6 μ mol) and copper(I) chloride (0.5 mg, 5 μ mol). The vessel was purged with oxygen and the reaction was heated to 50 °C before adding PBS (100 μ l). The addition is accompanied by a gradual change

in colour from amber to black. The biphasic mixture was stirred vigorously at 50 °C for a further 4 h. After cooling to room temperature, toluene (5 ml) and ethyl acetate (5 ml) were added and the organic layer separated. The aqueous layer was further extracted with ethyl acetate (3×5 ml) and the organic layers were combined and evaporated under reduced pressure. The crude mixture was purified by passing through a short silica plug (0.15×150 cm) using hexane–ethyl acetate (2:1) as eluent. Analysis by chiral phase HPLC revealed complete consumption of (*S*)-**1a** and cyclised product (*S*)-**3a** with 97% ee.

(*S*)-1-Hydroxy-1-(4-methoxyphenyl)-pentadec-4-en-3-one (*S*)-1d****

The racemic β -hydroxyenone ($\pm$)-**1a** (25 mg, 0.11 mmol) was added to a Teflon[®] tube and dissolved in chlorobenzene (1.3 ml). To this was added a 66.7 μ M solution of Ab84G3 (100 mg, 0.67 μ mol) in PBS (10.0 ml, pH 7.4) and the tube sealed. The mixture was placed in a shaking bath (250 strokes/minute) at room temperature. The ee of the unreacted **1a** was monitored periodically by HPLC on chiral stationary phase (10 μ l aliquots were removed from the organic layer and diluted to 100 μ l with mobile phase before analysis). After 7 d and 11 d, further Ab84G3 solution was added (4.7 ml and 1 ml of 66.7 μ M solution respectively) to the reaction. Once the desired substrate ee was attained, the mixture was placed in a freezer for several hours, after which time the organic layer was decanted and the aqueous layer was allowed to thaw. The aqueous layer was then extracted with ethyl acetate (3×10 ml) and the combined organic phases were dried over sodium sulfate, filtered through a plug of silica gel and the solvent was removed under reduced pressure. The crude mixture contained (*S*)-**1a** in 91% ee.

To a Schlenk tube containing a solution of (*S*)-1-hydroxy-1-(4-methoxyphenyl)-hex-4-en-3-one (*S*)-**1a** (6 mg, 0.0272 mmol) and dodecene (18 μ l, 0.0817 mmol) in anhydrous dichloromethane (1.5 ml) was added Hoveyda-Grubbs catalyst (1.5 mg, 0.002 mmol, 10 mol%). The reaction was stirred under an argon atmosphere for 24 h and then concentrated under reduced pressure to afford a dark brown oil. The reaction mixture was purified by column chromatography (eluent 4:1 cyclohexane–ethyl acetate) to yield (*S*)-1-hydroxy-1-(4-methoxyphenyl)-pentadec-4-en-3-one (*S*)-**1d** (8 mg, 0.023 mmol) a pale brown oil in 85 % yield.

Analysis by chiral phase HPLC revealed complete consumption of (*S*)-**1a** and cross-metathesis product (*S*)-**1d** with 90% ee.

Assignment of absolute configurations: Independent asymmetric syntheses of 1f–h, 1j and 2f–h

(4S)-Benzyl-3-((3S)-hydroxy-5-(4-methoxyphenyl)-pent-4-enoyl)-oxazolidin-2-one (4a)

(4S)-Benzyl-3-((3R)-hydroxy-5-(4-methoxyphenyl)-pent-4-enoyl)-oxazolidin-2-one (4b)

Di-n-butylboron triflate (5 ml, 1 M in dichloromethane, 5 mmol) and Et₃N (0.77 ml, 5.5 mmol) were added to a solution of oxazolidinone (1 g, 4.56 mmol) in dichloromethane (7 ml). The reaction mixture was stirred at –78 °C for 30 min and at 0 °C for 1 h. After cooling the mixture to –78 °C, a solution of 4-methoxycinnamaldehyde (740 mg, 4.56 mmol) in dichloromethane (10 ml) was added dropwise. The reaction was stirred for 30 min at –78 °C and then at 0 °C for 1 h. The reaction was then quenched by addition of sat. NH₄Cl (25 ml) and extracted with ethyl acetate (3×25 ml). The combined organic fractions were dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (dichloromethane:hexane:ethyl acetate, 7:2:1) afforded **4a** and **4b** (*de* = 54%) as colorless solids (971 mg, 56%). Analytical data for **4a** (major diastereomer): mp 135–136 °C; R_f (dichloromethane:hexane:ethyl acetate, 7:2:1) = 0.23; [α]_D²⁵ +40.4° (c = 0.1, CHCl₃); δ_{1H} (CDCl₃) 2.81 (1H, dd, *J* = 13.6, 9.6 Hz), 3.18–3.39 (4H, m), 4.18 (1H, dd, *J* = 8.2, 3.2 Hz), 4.21 (1H, dd, *J* = 8.2, 9.2 Hz), 4.68–4.75 (1H, m), 4.79–4.87 (1H, m), 6.18 (1H, dd, *J* = 16.0, 6.4 Hz), 6.64 (1H, d, *J* = 16.0 Hz), 6.86 (2H, d, *J* = 8.6 Hz), 7.22 (2H, d, *J* = 8.4 Hz), 7.20–7.37 (5H, m); δ_{13C} (CDCl₃) 37.7, 42.8, 55.1, 55.3, 66.3, 68.9, 114.0 (2C), 127.4, 127.8 (3C), 129.0 (2C), 129.1, 129.4 (2C), 130.3, 135.0, 153.4, 159.3, 172.0; ν_{max} (CHCl₃) 3553, 1784, 1692; *m/z* (HRMS, FI) found 404.1485 ([M⁺]) [C₂₂H₂₃NO₅+Na]⁺ requires 404.1474; Anal. Calcd for C₂₂H₂₃NO₅: C, 69.28; H, 6.08; N, 3.67. Found: C, 69.26; H, 6.10; N, 3.71; Analytical data for **4b** (minor diastereomer): mp 146 °C; R_f (dichloromethane:hexane:ethyl acetate, 7:2:1) = 0.15; [α]_D²⁵ +62.1° (c = 1, CHCl₃); δ_{1H} (CDCl₃) 2.80 (1H, dd, *J* = 12.6, 9.6 Hz), 3.02 (1H, d, *J* = 4.4 Hz), 3.27 (1H, dd, *J* = 17.2, 8.4 Hz), 3.33 (1H, dd, *J* = 17.2, 4.0 Hz), 3.33 (1H, dd, *J* = 12.6, 3.2 Hz), 6.18 (1H, dd, *J* = 15.8, 6.4 Hz), 6.65 (1H, d, *J* = 15.6 Hz), 6.87 (2H, d, *J* = 8.6 Hz), 7.31 (2H, d, *J* = 8.4 Hz), 7.21–7.38 (5H, m); δ_{13C} (CDCl₃) 37.9, 42.7, 55.1, 55.3, 66.4, 68.9, 114.0 (2C), 127.4, 127.6, 127.8 (2C), 129.0 (2C), 129.1, 129.4 (2C), 130.4, 135.1, 153.4, 159.4, 171.9; ν_{max} (CHCl₃) 3607, 1784, 1692; *m/z* (HRMS, FI) found 404.1469 ([M⁺]) [C₂₂H₂₃NO₅+Na]⁺ requires 404.1474; Anal. Calcd for C₂₂H₂₃NO₅: C, 69.28; H, 6.08; N, 3.67. Found: C, 68.95; H, 6.08; N, 3.75.

(S)-3-Hydroxy-5-(4-methoxyphenyl)-pent-4-enoic acid methoxymethylamide (S)-5

Trimethylaluminium (2 ml, 2 M in dichloromethane, 4 mmol) in toluene was added to a solution of N,O-dimethylhydroxylamine hydrochloride (397 mg, 4 mmol) in THF (13 ml) at 0 °C. After stirring 30 min at 0 °C and 20 min at RT, the reaction mixture was cooled to -15 °C and a solution of aldol **4a** (500 mg, 1.3 mmol) in THF (10 ml) was added dropwise. The cloudy mixture was warmed to 0 °C and stirred for further 4 h. The reaction was then quenched with 0.5 M HCl and the aqueous layer was extracted with ethyl acetate (3×25 ml). The organic layer was washed with water, dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (100% ethyl acetate) afforded (S)-**5** (258 mg, 75%) as a colorless oil; R_f (ethyl acetate) = 0.35; ee > 99%; [α]_D²⁵ -27.3° (c = 0.6, CHCl₃); δ_{1H} (CDCl₃) 2.69 (1H, dd, *J* = 16.6, 9.1 Hz), 2.80 (1H, d, *J* = 16.6 Hz), 3.22 (3H, s), 3.70 (3H, s), 3.81 (3H, s), 4.00 (1H, br s), 4.70-4.78 (1H, m), 6.12 (1H, dd, *J* = 6.2, 15.9 Hz), 6.62 (1H, d, *J* = 15.9 Hz), 6.85 (2H, d, *J* = 8.6 Hz), 7.33 (2H, d, *J* = 8.6 Hz); δ_{13C} (CDCl₃) 31.8, 38.6, 55.2, 61.2, 68.8, 113.9 (2C), 127.6 (2C), 128.5, 129.4, 129.6, 159.1, 172.9; ν_{max} (neat) 3427.5, 1644.9; *m/z* (HRMS, GCT, FI) 265.1314 ([M⁺]), C₁₄H₁₉NO₄ requires 265.1314.

(S)-6-Hydroxy-8-(4-methoxy-phenyl)-2-methyl-octa-2,7-dien-4-one (S)-1h

2-Methyl-1-prop-1-enyl-magnesium bromide (9.6 ml, 4.8 mmol) was added to a solution of Weinreb amide (S)-**5** (240 mg, 0.85 mmol) in THF (8 ml) at -40 °C. The mixture was allowed to warm to 0 °C over 30 min and stirred for further 48 h. Sat. NH₄Cl was added (30 ml) and the mixture allowed to warm up to RT. The reaction was extracted with dichloromethane (3×30 ml), dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (hexane:ethyl acetate, 7:3) afforded (S)-**1h** (70 mg, 32%, ee = 40%) as a yellow oil; R_f (hexane:ethyl acetate, 7:3) = 0.66; [α]_D²⁵ -5.8° (c = 1, CHCl₃)

(R)-6-[2-(4-Methoxyphenyl)-ethyl]-2,2-dimethyltetrahydropyran-4-one (R)-2h

Aldol (*S*)-**1h** (6 mg, 0.023 mmol) in toluene (1 ml) was added to $\text{RhCl}(\text{PPh}_3)_3$ (4.5 mg, 0.75 mass eq). The mixture was degassed and placed under H_2 . The mixture was allowed to stir for 24 h. The solvent was removed *in vacuo*. The residue was taken up in dichloromethane (1 ml) and filtered through a plug of silica which was washed with dichloromethane. The solvent was removed *in vacuo* to yield a yellow oil. The residue was dissolved in dichloromethane (0.5 ml) and cooled to -78°C . To this was added diisopropylethylamine (0.01 ml of a 10% solution in dichloromethane, 0.008 mmol) and TMSOTf (0.02 ml of a 10% solution in dichloromethane, 0.011 mmol) and the mixture allowed to stir for 1 h. The mixture was then allowed to warm to -20°C and allowed to stir for 3 h. The mixture was then placed in the freezer overnight. The mixture was quenched by addition of saturated $\text{NaHCO}_3(\text{aq})$ (2.5 ml). The mixture was extracted with dichloromethane (3×2.5 ml), the combined organic fractions dried over MgSO_4 , filtered under suction and the solvent removed *in vacuo*. The residue was purified by column chromatography (cyclohexane:diethyl ether, 2:1) to yield the (*R*)-**2h** (3.5 mg, 58% over 2 steps) as an oil; $[\alpha]_{\text{D}}^{25} +16.4^\circ$ ($c = 0.25$, CHCl_3).

(S)-6-Hydroxy-8-(4-methoxyphenyl)-2-methyl-octa-2,7-dien-4-one (S)-1j

1-Prop-1-enyl magnesium bromide (12 ml, 6 mmol) was added to a solution of Weinreb amide (*S*)-**5** (280 mg, 0.99 mmol) in THF (6 ml) at -40°C . The mixture was allowed to warm to 0°C over 30 min and stirred for further 6 h. Sat. NH_4Cl was added (20 ml) and the mixture allowed to warm up to RT. The reaction was extracted with dichloromethane (3×30 ml), dried over MgSO_4 and concentrated *in vacuo*. Purification by column chromatography (hexane:ethyl acetate, 6:4) afforded (*S*)-**1j** (140 mg, 58%, $ee > 99\%$) as a yellow oil; R_f (hexane:ethyl acetate, 6:4) = 0.34; $[\alpha]_{\text{D}}^{25} -16.5^\circ$ ($c = 0.6$, CHCl_3).

(S)-3-Hydroxy-5-phenyl-pentanoic acid ethyl ester (S)-6[†]

In a 1 L round bottom flask was placed 3-oxo-5-phenyl-pentanoic acid ethyl ester (2.4 g, 10.8 mmol), 376 ml of petroleum ether (boiling range $40-60^\circ\text{C}$), 112 g of yeast (10 g/mmol of substrate), 90 ml of water (0.8 ml/g of yeast), and the reaction stirred at room temperature. After 24 h the reaction mixture was filtered through cotton wool and the yeast washed with ethyl acetate (4×50 ml), filtered and the solvent removed

[†] Reference: N. Athanasiou, A.J. Smallridge; M.A. Trehwella *Journal of Molecular Catalysis B. Enzymatic* **2001**, *11* (4-6), 2003.

under reduced pressure. Purification by column chromatography on silica (hexane:ethyl acetate, 8:2) afforded (*S*)-**6** (1.4 g, 56%) as a colorless oil; R_f (hexane:ethyl acetate, 7:3) = 0.27; ee>99%; $[\alpha]_D^{25}$ -2.6° (c = 0.5, CHCl₃).

(*S*)-3-Hydroxy-5-phenyl-pentanoic acid methoxymethylamide (*S*)-7

Trimethylaluminium (1.4 ml, 2 M in dichloromethane, 2.8 mmol) in toluene was added to a solution of N,O-dimethylhydroxylamine hydrochloride (266 mg, 2.7 mmol) in THF (8 ml) at 0 °C. After stirring 30 min at 0 °C and 20 min at RT, the reaction mixture was cooled to -15 °C and a solution of aldol (*S*)-**6** (200 mg, 0.9 mmol) in THF (5 ml) was added dropwise. The cloudy mixture was warmed to 0 °C and stirred for further 4 h. The reaction was then quenched with 0.5 M HCl (2 ml) and the aqueous layer was extracted with ethyl acetate (3×10 ml). The organic layer was washed with water, dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (hexane:ethyl acetate, 4:6) afforded (*S*)-**7** (180 mg, 85%) as a colorless oil; R_f (c-hexane:ethyl acetate, 4:6) = 0.20; ee>99%; $[\alpha]_D^{25}$ +28.6° (c = 1.08, CHCl₃); δ_{1H} (CDCl₃) 1.73–1.82 (1H, m), 1.85–1.95 (1H, m), 2.54 (1H, dd, J = 16.4, 9.2 Hz), 2.65 (1H, app. d, J = 16.4 Hz), 2.74 (1H, ddd, J = 14.1, 6.8, 9.6 Hz), 2.88 (1H, ddd, J = 14.1, 5.2, 9.4 Hz), 3.18 (3H, s), 3.65 (3H, s), 4.04–4.15 (2H, m), 7.16–7.32 (5H, m); δ_{13C} (CDCl₃): 32.2, 32.3, 38.8 (2C), 61.6, 67.6, 126.2, 128.8 (2C), 128.9 (2C), 142.5, 174.1; ν_{max} (neat) 3437, 1647; m/z (HRMS, FI) found 237.1366 ([M⁺]) C₁₃H₁₉NO₃ requires 237.1365.

(*S*)-6-Hydroxy-2-methyl-8-phenyl-oct-2-en-4-one (*S*)-1g

2-Methyl-1-prop-1-enyl-magnesium bromide (17 ml, 8.5 mmol) was added to a solution of Weinreb amide (*S*)-**7** (380 mg, 1.6 mmol) in THF (15 ml) at -40 °C. The mixture was allowed to warm to 0 °C over 30 min and stirred for further 48 h. Sat. NH₄Cl was added (30 ml) and the mixture allowed to warm up to RT. The reaction was extracted with dichloromethane, dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (hexane:ethyl acetate, 7:3) afforded (*S*)-**1g** (120 mg, 32%, ee>99%) as a yellow oil; R_f (c-hexane:ethyl acetate, 4:6) = 0.75; $[\alpha]_D^{25}$ +15° (c = 0.21, CHCl₃).

2,2-Dimethyl-(6*S*)-phenylethyl-tetrahydro-pyran-4-one (*S*)-2g

Diisopropylethylamine (12.8 μ l, 0.075 mmol) and TMSOTf (24.5 μ l, 0.13 mmol) were added to a solution of aldol (*S*)-**1g** (116 mg, 0.5 mmol) in dichloromethane (2.5 ml) at -78 °C. The reaction was stirred 1 h at -78 °C and then at -20 °C overnight. After 24 h the reaction mixture was quenched with NaHCO₃ and the aqueous layer was extracted with ethyl acetate. The organic layer was washed with water, dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography

(hexane:ethyl acetate, 8:2) afforded (*S*)-**2g** (80 mg, 69%, ee>99%) as a colorless oil; R_f (c-hexane:ethyl acetate, 8:2) = 0.34 ; $[\alpha]_D^{25}$ -44.8° (c = 0.62, CHCl₃).

(4*R*)-Benzyl-3-((3*R*)-hydroxy-4-(4-methoxy-phenyl)-butyryl)-oxazolidin-2-one 8

(4*R*)-Benzyl-3-((3*S*)-hydroxy-4-(4-methoxy-phenyl)-butyryl)-oxazolidin-2-one 9

Di-*n*-butylboron triflate (5 ml, 1M in dichloromethane, 5 mmol) and triethylamine (0.77 ml, 5.5 mmol) were added to a solution of oxazolidinone (1 g, 4.56 mmol) in dichloromethane (7 ml). The reaction mixture was stirred at -78 °C for 30 min and at 0 °C for 1 h. After cooling the mixture to -78 °C, a solution of (4-methoxyphenyl)-acetaldehyde (684 mg, 4.56 mmol) in dichloromethane (10 ml) was added dropwise. The reaction was allowed to stir at -78 °C for 30 min and then 0 °C for 1 h. The reaction was then quenched by addition of sat. NH₄Cl (25 ml) and extracted with ethyl acetate (3×25 ml). The combined organic fractions were dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (dichloromethane:ethyl acetate, 9:1) afforded the two diastereomers **8** and **9** (*de* = 19%) as white solids (897 mg, 53%); Analysis for **8**: mp 88 °C; R_f (dichloromethane:ethyl acetate, 9:1) = 0.36; $[\alpha]_D^{25}$ +22.9 (c = 0.95, CHCl₃); δ_{1H} (CDCl₃) 2.79 (1H, app. d, *J* = 13.4 Hz), 2.82 (1H, dd, *J* = 13.8, 4.8 Hz), 2.88 (1H, dd, *J* = 13.8, 7.2 Hz), 3.12 (1H, dd, *J* = 17.4, 8.0 Hz), 3.14 (1H, dd, *J* = 17.4, 4.4 Hz), 3.29 (1H, dd, *J* = 13.4, 3.6 Hz), 3.81 (3H, s), 4.19 (1H, dd, *J* = 8.8, 4.0 Hz), 4.21 (1H, dd, *J* = 8.8, 9.2 Hz), 4.30–5.38 (1H, m), 4.65–4.72 (1H, m), 6.88 (2H, d, *J* = 8.4 Hz), 7.19 (2H, d, *J* = 8.4 Hz), 7.17–7.38 (5H, m); ν_{max} (CHCl₃) 3567, 1784, 1692; *m/z* (HRMS, ESI⁺) found 392.1479 ([M+Na]⁺) C₂₁H₂₄NO₅ requires 392.1474; Analysis for **9**: R_f (dichloromethane:ethyl acetate, 9:1) = 0.30; $[\alpha]_D^{25}$ 74.8 (c = 1, CHCl₃); δ_{1H} (CDCl₃) 2.76 (1H, dd, *J* = 13.5, 9.6 Hz), 2.82 (1H, dd, *J* = 13.6, 6.0 Hz), 2.86 (1H, dd, *J* = 13.6, 6.8 Hz), 2.91 (1H, br s), 3.07 (1H, dd, *J* = 17.4, 8.8 Hz), 3.19 (1H, dd, *J* = 17.4, 2.4 Hz), 3.30 (1H, dd, *J* = 13.5, 3.2 Hz), 3.81 (3H, s), 4.17 (1H, dd, *J* = 8.7, 3.2 Hz), 4.20 (1H, dd, *J* = 8.7, 9.2 Hz), 4.35–4.43 (1H, m), 4.64–4.72 (1H, m), 6.89 (2H, d, *J* = 8.6 Hz), 7.21 (2H, d, *J* = 8.4 Hz), 7.18–7.37 (5H, m); δ_{13C} (CDCl₃) 37.9, 42.0, 42.1, 55.1, 55.2, 66.3, 69.0, 114.0 (2C), 127.4, 129.0 (2C), 129.4 (2C), 129.8, 130.5 (2C), 135.1, 153.4, 158.4, 172.4; ν_{max} (CHCl₃) 3572, 1784, 1693; *m/z* (HRMS, ESI⁺) found 392.1471 ([M+Na]⁺) C₂₁H₂₄NO₅ requires 392.1474.

(*R*)-3-Hydroxy-*N*-methoxy-4-(4-methoxyphenyl)-*N*-methylbutyramide (*R*)-10

Trimethylaluminium (1.4 ml, 2 M in dichloromethane, 2.8 mmol) in toluene was added to a solution of *N*,*O*-dimethylhydroxylamine hydrochloride (278 mg, 2.8 mmol) in THF (5 ml) at 0 °C. After stirring 30 min at 0 °C and 20 min at RT, the reaction mixture was cooled to -15 °C and a solution of aldol **8** (349 mg, 0.94 mmol) in THF (5 ml) was added dropwise. The mixture was warmed to 0 °C and stirred for further 4

h. The reaction was then quenched with 0.5 M HCl (2 ml) and the aqueous layer was extracted with ethyl acetate (3×10 ml). The organic layer was washed with water, dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (hexane:ethyl acetate, 4:6) afforded (*R*)-**10** (200 mg, 88%) as a colorless oil; R_f (c-hexane:ethyl acetate, 8:2) = 0.13; ee>99%; [α]_D²⁵−46.96° (c = 1.08, CHCl₃); δ_{1H} (CDCl₃) 2.49 (1H, dd, *J* = 16.3, 9.2 Hz), 2.67 (1H, app. d, *J* = 16.3 Hz), 2.73 (1H, dd, *J* = 13.6, 6.4 Hz), 2.87 (1H, dd, *J* = 13.6, 7.2 Hz), 3.19 (3H, s), 3.64 (3H, s), 3.80 (3H, s), 4.22–4.29 (1H, m), 6.86 (2H, d, *J* = 8.8 Hz), 7.17 (2H, d, *J* = 8.8 Hz); δ_{13C} (CDCl₃) 31.8, 37.3, 42.0 55.2, 61.2, 69.2, 113.8 (2C), 130.2, 130.3 (2C), 158.2; ν_{max} (neat) 3434, 1759; *m/z* (HRMS, CI⁺) found 254.1391 ([M+H⁺]) C₁₃H₂₀NO₄ requires 254.1392.

(*R*)-6-Hydroxy-7-(4-methoxyphenyl)-2-methylhept-2-en-4-one (*R*)-1f

2-Methyl-1-prop-1-enyl magnesium bromide (6.4 ml, 3.2 mmol) was added to a solution of Weinreb amide (*R*)-**10** (134 mg, 0.53 mmol) in THF (5 ml) at −40 °C. The mixture was allowed to warm to 0 °C over 30 min and stirred for further 48 h. Sat. NH₄Cl was added (10 ml) and the mixture allowed to warm up to RT. The reaction was extracted with dichloromethane (3×15 ml), dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (c-hexane:ethyl acetate, 8:2) afforded (*R*)-**1f** (40 mg, 30%, ee>99%) as a yellow oil; [α]_D²⁵−15.3° (c = 1, CHCl₃).

(6*R*)-4-Methoxybenzyl-2,2-dimethyltetrahydropyran-4-one (*R*)-2f

Diisopropylethylamine (6 μl, 0.023 mmol) and trimethylsilyl triflate (12 μl, 0.063 mmol) were added to a solution of aldol (*R*)-**1f** (39 mg, 0.16 mmol) in dichloromethane (2 ml) at −78 °C. The reaction was stirred 1 h at −78 °C, 4 h at −10 °C and then overnight at 0 °C. After 24 h the reaction mixture was quenched with NaHCO₃ (2 ml) and the aqueous layer was extracted with ethyl acetate (3×10 ml). The organic layer was washed with water, dried over MgSO₄ and concentrated *in vacuo*. Purification by column chromatography (c-hexane:ethyl acetate, 9:1) afforded (*R*)-**2f** as a colorless oil (80 mg, 70%, ee >99%). R_f (c-hexane:ethyl acetate, 8:2) = 0.34; [α]_D²⁵+22.17° (c = 0.62, CHCl₃).

Inhibition Experiments

Control experiment 1: Racemization of β -hydroxyenone **1b**

Entry	Time (days)	Conversion (%)	ee (%)
1	8 ½	52	40
2	10	52	26

Control experiment 2: Inhibition by β -hydroxyenones **1l** and **1k**.

Entry	Time (min)	0 mol% 1k / Conv. (%)	50 mol% 1k / Conv. (%)	100 mol% 1k / Conv. (%)	200 mol% 1k / Conv. (%)
1	40	33	56	51	47
2	80	50	53	48	44
3	200	50	50	33	28

Entry	Time (min)	0 mol% 1l / Conv. (%)	50 mol% 1l / Conv. (%)	100 mol% 1l / Conv. (%)
1	40	33	22	22
2	80	50	18	16
3	200	50	11	4

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for **4a** C₂₂H₂₃NO₅ (ARC331)
Andrew R. Cowley

Crystals of **ARC331** were grown by recrystallisation from methylene chloride. A large single crystal was cut to give a fragment having dimensions approximately 0.12 x 0.32 x 0.34 mm. This was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package¹.

Examination of the systematic absences of the intensity data showed the space group to be either

$P 2_1$ or $P 2_1/m$. The structure was solved in the space group $P 2_1$ using the direct-methods program SIR92², which located all non-hydrogen atoms. Examination of the resulting model clearly showed no mirror plane to be present, confirming the assignment of symmetry. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The hydroxyl H atom was located in a difference Fourier map and its coordinates and isotropic thermal parameter subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebyshev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0278$, $wR = 0.0363$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning H atoms.

Comment:

The hydroxyl hydrogen atom forms a bifurcated hydrogen bond with the amide O atom of the same molecule (O(2)···O(1) 2.9319(17) Å) and with the carbamate carbonyl O atom of a second molecule related by a translation along the *b* axis (O(1)···O(4)' 2.8874(18) Å). The corresponding O–H···O angles are 127(3) and 136(3)° respectively.

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC331
Chemical formula	C ₂₂ H ₂₃ NO ₅
Formula weight	381.43
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	<i>P</i> 2 ₁
<i>a</i> (Å)	6.9822(1)
<i>b</i> (Å)	6.4712(1)
<i>c</i> (Å)	20.9553(4)
α (°)	90
β (°)	94.6879(8)
γ (°)	90
Cell volume (Å ³)	943.7
<i>Z</i>	2
Calculated density (Mg/m ³)	1.342
Absorption coefficient (mm ⁻¹)	0.095
<i>F</i> ₀₀₀	404.122
Crystal size (mm)	0.12 x 0.32 x 0.34
Description of crystal	Colourless fragment
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.97, 0.99
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	-9 ≤ <i>h</i> ≤ 9, 0 ≤ <i>k</i> ≤ 8, 0 ≤ <i>l</i> ≤ 27
Reflections measured	10862
Unique reflections	2311
<i>R</i> _{int}	0.028
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	1998
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	257
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	0.9632
<i>R</i>	0.0278
<i>wR</i>	0.0363
Residual electron density (min,max) (eÅ ⁻³)	-0.13, 0.16

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
N(1)	0.39243(19)	0.0912(2)	0.21000(6)	0.0211
C(1)	0.5030(2)	0.2360(3)	0.24622(7)	0.0200
O(1)	0.43238(16)	0.4025(2)	0.25742(6)	0.0268
C(2)	0.7052(2)	0.1742(3)	0.26953(8)	0.0225
C(3)	0.8059(2)	0.3405(3)	0.31106(7)	0.0220
O(2)	0.83698(18)	0.5264(2)	0.27620(6)	0.0277
C(4)	1.0014(2)	0.2758(3)	0.33984(8)	0.0233
C(5)	1.0735(2)	0.0854(3)	0.34366(7)	0.0220
C(6)	1.2653(2)	0.0311(3)	0.37375(7)	0.0220
C(7)	1.3459(2)	-0.1598(3)	0.36223(8)	0.0241
C(8)	1.5276(2)	-0.2165(3)	0.38971(8)	0.0252
C(9)	1.6293(2)	-0.0794(3)	0.43046(7)	0.0222
C(10)	1.5507(2)	0.1130(3)	0.44304(8)	0.0256
C(11)	1.3719(2)	0.1678(3)	0.41491(8)	0.0250
O(3)	1.80689(16)	-0.1168(2)	0.46128(6)	0.0282
C(12)	1.8939(3)	-0.3112(3)	0.4491(1)	0.0353
C(13)	0.4484(2)	-0.1047(3)	0.19230(7)	0.0250
O(4)	0.60527(18)	-0.1833(2)	0.19898(6)	0.0325
O(5)	0.29478(18)	-0.2032(2)	0.16346(6)	0.0301
C(14)	0.1225(3)	-0.0820(3)	0.17009(8)	0.0267
C(15)	0.1967(2)	0.1376(3)	0.18240(7)	0.0207
C(16)	0.2033(2)	0.2680(3)	0.12150(7)	0.0218
C(17)	0.0054(2)	0.3018(3)	0.08831(7)	0.0188
C(18)	-0.0480(2)	0.2034(3)	0.03037(7)	0.0220
C(19)	-0.2307(2)	0.2317(3)	-0.00010(8)	0.0246
C(20)	-0.3623(2)	0.3589(3)	0.02670(8)	0.0268
C(21)	-0.3102(2)	0.4585(3)	0.08421(8)	0.0273
C(22)	-0.1279(2)	0.4303(3)	0.11502(7)	0.0235

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(1)	0.712(5)	0.578(6)	0.2617(16)	0.077(11)
H(21)	0.7001	0.0442	0.2952	0.0267
H(22)	0.7803	0.1489	0.2316	0.0267
H(31)	0.7164	0.3644	0.3452	0.0261
H(41)	1.0868	0.3888	0.3582	0.0276
H(51)	0.9916	-0.0294	0.3247	0.0262
H(71)	1.2719	-0.2599	0.3334	0.0286
H(81)	1.5835	-0.3542	0.3801	0.0300
H(101)	1.6239	0.2118	0.4725	0.0302
H(111)	1.3176	0.3067	0.4240	0.0297
H(121)	2.0219	-0.3202	0.4741	0.0419
H(122)	1.8094	-0.4256	0.4624	0.0419
H(123)	1.9113	-0.3237	0.4024	0.0419
H(141)	0.0531	-0.1327	0.2069	0.0316
H(142)	0.0347	-0.0880	0.1300	0.0316
H(151)	0.1141	0.2216	0.2094	0.0245
H(161)	0.2615	0.4053	0.1333	0.0259
H(162)	0.2846	0.1953	0.0914	0.0259
H(181)	0.0459	0.1115	0.0106	0.0264
H(191)	-0.2673	0.1599	-0.0416	0.0291
H(201)	-0.4937	0.3788	0.0048	0.0319
H(211)	-0.4043	0.5511	0.1036	0.0329
H(221)	-0.0919	0.5023	0.1565	0.0281

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	0.0200(6)	0.0202(6)	0.0222(6)	0.0003(5)	-0.0050(5)	0.0025(5)
C(1)	0.0196(7)	0.0204(7)	0.0199(6)	-0.0002(6)	0.0006(5)	-0.0000(6)
O(1)	0.0220(5)	0.0235(6)	0.0339(6)	-0.0059(5)	-0.0035(4)	0.0036(5)
C(2)	0.0204(7)	0.0239(8)	0.0225(7)	-0.0009(6)	-0.0038(6)	0.0023(6)
C(3)	0.0205(7)	0.0215(8)	0.0232(7)	-0.0004(6)	-0.0027(5)	0.0023(6)
O(2)	0.0244(6)	0.0222(6)	0.0354(6)	0.0039(5)	-0.0049(5)	0.0002(5)
C(4)	0.0198(7)	0.0242(8)	0.0251(7)	-0.0007(7)	-0.0027(6)	0.0004(6)
C(5)	0.0201(7)	0.0253(8)	0.0202(7)	-0.0007(6)	-0.0014(5)	0.0007(6)
C(6)	0.0215(7)	0.0248(8)	0.0193(7)	0.0013(7)	-0.0009(6)	0.0006(7)
C(7)	0.0246(7)	0.0228(8)	0.0240(7)	-0.0023(6)	-0.0031(6)	0.0018(7)
C(8)	0.0241(7)	0.0223(8)	0.0288(7)	-0.0002(7)	-0.0008(6)	0.0028(7)
C(9)	0.0189(7)	0.0251(8)	0.0221(7)	0.0034(7)	-0.0005(5)	0.0015(7)
C(10)	0.0244(7)	0.0264(8)	0.0249(7)	-0.0018(7)	-0.0048(6)	0.0001(7)
C(11)	0.0251(8)	0.0260(8)	0.0232(7)	-0.0025(7)	-0.0017(6)	0.0042(7)
O(3)	0.0201(5)	0.0295(7)	0.0337(6)	0.0001(5)	-0.0068(4)	0.0041(5)
C(12)	0.0250(8)	0.033(1)	0.047(1)	0.0017(9)	-0.0041(7)	0.0108(8)
C(13)	0.0311(8)	0.0209(8)	0.0220(7)	0.0009(6)	-0.0037(6)	0.0021(7)
O(4)	0.0329(6)	0.0244(6)	0.0386(6)	-0.0051(6)	-0.0074(5)	0.0100(6)
O(5)	0.0341(6)	0.0199(6)	0.0341(6)	-0.0035(5)	-0.0097(5)	0.0009(5)
C(14)	0.0276(8)	0.0224(8)	0.0292(8)	0.0038(7)	-0.0031(6)	-0.0023(7)
C(15)	0.0169(7)	0.0216(8)	0.0228(7)	-0.0002(6)	-0.0033(5)	0.0007(6)
C(16)	0.0184(7)	0.0223(8)	0.0241(7)	0.0023(6)	-0.0020(5)	-0.0004(6)
C(17)	0.0179(6)	0.0171(7)	0.0212(6)	0.0027(6)	0.0003(5)	-0.0013(6)
C(18)	0.0227(7)	0.0193(8)	0.0240(7)	-0.0013(6)	0.0013(6)	0.0010(6)
C(19)	0.0242(7)	0.0253(8)	0.0235(7)	-0.0014(6)	-0.0032(6)	-0.0022(7)
C(20)	0.0202(7)	0.0295(9)	0.0301(8)	0.0023(7)	-0.0026(6)	-0.0007(7)
C(21)	0.0203(7)	0.0280(9)	0.0340(9)	-0.0029(7)	0.0050(6)	0.0029(7)
C(22)	0.0261(8)	0.0221(8)	0.0221(7)	-0.0014(6)	0.0011(6)	0.0003(7)

Table 5: Bond lengths (Å)

N(1) - C(1)	1.398(2)
N(1) - C(13)	1.386(2)
N(1) - C(15)	1.4708(18)
C(1) - O(1)	1.216(2)
C(1) - C(2)	1.510(2)
C(2) - C(3)	1.520(2)
C(3) - O(2)	1.433(2)
C(3) - C(4)	1.506(2)
O(2) - H(1)	0.96(4)
C(4) - C(5)	1.331(2)
C(5) - C(6)	1.475(2)
C(6) - C(7)	1.387(2)
C(6) - C(11)	1.405(2)
C(7) - C(8)	1.399(2)
C(8) - C(9)	1.386(2)
C(9) - C(10)	1.395(2)
C(9) - O(3)	1.3723(18)
C(10) - C(11)	1.382(2)
O(3) - C(12)	1.429(2)
C(13) - O(4)	1.205(2)
C(13) - O(5)	1.347(2)
O(5) - C(14)	1.452(2)
C(14) - C(15)	1.527(2)
C(15) - C(16)	1.534(2)
C(16) - C(17)	1.5110(19)
C(17) - C(18)	1.395(2)
C(17) - C(22)	1.398(2)
C(18) - C(19)	1.391(2)
C(19) - C(20)	1.386(2)
C(20) - C(21)	1.389(2)
C(21) - C(22)	1.392(2)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

C(1) - N(1) - C(13)	127.09(14)
C(1) - N(1) - C(15)	122.06(14)
C(13) - N(1) - C(15)	110.77(13)
N(1) - C(1) - O(1)	118.96(14)
N(1) - C(1) - C(2)	117.28(14)
O(1) - C(1) - C(2)	123.76(15)
C(1) - C(2) - C(3)	111.96(14)
C(2) - C(3) - O(2)	112.63(12)
C(2) - C(3) - C(4)	113.20(14)
O(2) - C(3) - C(4)	105.53(13)
C(3) - O(2) - H(1)	106.3(23)
C(3) - C(4) - C(5)	127.42(15)
C(4) - C(5) - C(6)	124.88(15)
C(5) - C(6) - C(7)	120.31(15)
C(5) - C(6) - C(11)	121.94(16)
C(7) - C(6) - C(11)	117.74(14)
C(6) - C(7) - C(8)	121.95(16)
C(7) - C(8) - C(9)	119.17(16)
C(8) - C(9) - C(10)	119.91(14)
C(8) - C(9) - O(3)	125.07(15)
C(10) - C(9) - O(3)	115.02(14)
C(9) - C(10) - C(11)	120.25(16)
C(6) - C(11) - C(10)	120.98(17)
C(9) - O(3) - C(12)	116.92(13)
N(1) - C(13) - O(4)	128.89(17)
N(1) - C(13) - O(5)	108.72(14)
O(4) - C(13) - O(5)	122.38(17)
C(13) - O(5) - C(14)	109.69(13)
O(5) - C(14) - C(15)	104.29(13)
N(1) - C(15) - C(14)	99.65(13)
N(1) - C(15) - C(16)	110.45(13)
C(14) - C(15) - C(16)	113.84(13)
C(15) - C(16) - C(17)	111.98(12)
C(16) - C(17) - C(18)	120.26(13)
C(16) - C(17) - C(22)	121.02(13)
C(18) - C(17) - C(22)	118.72(13)
C(17) - C(18) - C(19)	120.62(14)
C(18) - C(19) - C(20)	120.36(15)
C(19) - C(20) - C(21)	119.46(14)
C(20) - C(21) - C(22)	120.43(15)
C(17) - C(22) - C(21)	120.39(14)

Note – geometrically-positioned H atoms have been excluded

Inorganic Chemistry Crystallography Service

Single-crystal X-ray diffraction report for C₂₁H₂₃NO₅ **8** (ARC667)

Andrew R. Cowley

Crystals of **ARC667** were grown by were grown by recrystallisation from methylene chloride/hexane. A single crystal having dimensions approximately 0.08 x 0.10 x 0.32 mm was mounted on a glass fibre using perfluoropolyether oil and cooled rapidly to 150K in a stream of cold N₂ using an Oxford Cryosystems CRYOSTREAM unit. Diffraction data were measured using an Enraf-Nonius KappaCCD diffractometer (graphite-monochromated MoK_α radiation, $\lambda = 0.71073$ Å). Intensity data were processed using the DENZO-SMN package¹. Examination of the systematic absences of the intensity data showed the space group to be

$P 2_1 2_1 2_1$. The structure was solved using the direct-methods program SIR92², which located all non-hydrogen atoms. Subsequent full-matrix least-squares refinement was carried out using the CRYSTALS program suite³. Coordinates and anisotropic thermal parameters of all non-hydrogen atoms were refined. The hydroxyl hydrogen atom was located in a difference Fourier map and its coordinates and isotropic thermal parameter subsequently refined. Other hydrogen atoms were positioned geometrically after each cycle of refinement. A 3-term Chebychev polynomial weighting scheme was applied. Refinement converged satisfactorily to give $R = 0.0302$, $wR = 0.0334$.

Attached is a thermal ellipsoid plot (ORTEP-3⁴) at 40% probability. A summary of crystallographic data is given below, as are full lists of atomic coordinates, anisotropic thermal parameters and those bond lengths and angles not concerning geometrically-positioned H atoms.

Comment:

The OH group forms a hydrogen bond to the ether O atom of a neighbouring molecule (O(4)···O(5)ⁱ 2.821(2) Å, symmetry operator 1/2+x, 3/2-y, 1-z). The hydrogen bonds link the molecules to form helical chains running parallel to the crystallographic *a* axis.

References:

- 1 Z. Otwinowski and W. Minor, *Processing of X-ray Diffraction Data Collected in Oscillation Mode, Methods Enzymol.*, 1997, **276**, Eds C. W. Carter and R. M. Sweet, Academic Press.
- 2 A. Altomare, G. Cascarano, G. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori and M. Camalli, *J. Appl. Cryst.* 1994, **27**, 435.
- 3 D. J. Watkin, C. K. Prout, J. R. Carruthers, P. W. Betteridge and R. I. Cooper, CRYSTALS issue 11, Chemical Crystallography Laboratory, Oxford, UK, 2001.
- 4 ORTEP-3 v. 1.0.2, C. K. Johnson and M. K. Burnett, 1998.

Table 1: Crystal data and refinement details

Crystal identification	ARC667
Chemical formula	C ₂₁ H ₂₃ NO ₅
Formula weight	369.42
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Orthorhombic
Space group	<i>P</i> 2 ₁ 2 ₁ 2 ₁
<i>a</i> (Å)	6.1113(2)
<i>b</i> (Å)	10.0071(2)
<i>c</i> (Å)	30.1100(5)
α (°)	90
β (°)	90
γ (°)	90
Cell volume (Å ³)	1841.42(8)
Z	4
Calculated density (Mg/m ³)	1.332
Absorption coefficient (mm ⁻¹)	0.095
<i>F</i> ₀₀₀	784
Crystal size (mm)	0.08 x 0.10 x 0.32
Description of crystal	Colourless prism
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min,max)	0.97, 0.99
θ range for data collection (°)	5.0 ≤ θ ≤ 27.5
Index ranges	0 ≤ <i>h</i> ≤ 7, 0 ≤ <i>k</i> ≤ 12, 0 ≤ <i>l</i> ≤ 38
Reflections measured	12925
Unique reflections	2408
<i>R</i> _{int}	0.035
Observed reflections (<i>I</i> > 3 σ (<i>I</i>))	1839
Refinement method	Full-matrix least-squares on <i>F</i>
Parameters refined	248
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	1.0680
<i>R</i>	0.0302
<i>wR</i>	0.0334
Residual electron density (min,max) (eÅ ⁻³)	-0.15, 0.16

Table 2: Atomic coordinates and equivalent isotropic thermal parameters ($\text{\AA}^2$) of non-hydrogen atoms

Atom	x	y	z	U_{equiv}
N(1)	0.3068(3)	0.11734(16)	0.63745(5)	0.0230
C(1)	0.1744(3)	0.0074(2)	0.64418(7)	0.0272
O(1)	-0.0131(2)	-0.00808(15)	0.63326(5)	0.0372
O(2)	0.2875(2)	-0.08719(14)	0.66628(5)	0.0338
C(2)	0.5128(3)	-0.0455(2)	0.67259(7)	0.0279
C(3)	0.5224(3)	0.10103(19)	0.65832(7)	0.0268
C(4)	0.2681(3)	0.22546(19)	0.60896(6)	0.0250
C(5)	0.0492(3)	0.23623(18)	0.58654(6)	0.0255
C(6)	0.0273(3)	0.36555(18)	0.56016(6)	0.0247
C(7)	-0.1509(3)	0.3533(2)	0.52461(6)	0.0286
C(8)	-0.1670(3)	0.4759(2)	0.49525(6)	0.0254
C(9)	-0.3523(3)	0.5568(2)	0.49558(6)	0.0282
C(10)	-0.3650(3)	0.6713(2)	0.46949(6)	0.0291
C(11)	-0.1896(3)	0.7070(2)	0.44295(6)	0.0265
C(12)	-0.0042(3)	0.6277(2)	0.44124(6)	0.0271
C(13)	0.0046(3)	0.5123(2)	0.46747(6)	0.0276
C(14)	0.5622(4)	0.1983(2)	0.69667(7)	0.0337
C(15)	0.3862(4)	0.1977(2)	0.73178(7)	0.0327
C(16)	0.3952(4)	0.1100(2)	0.76777(7)	0.0381
C(17)	0.2263(5)	0.1062(3)	0.79885(7)	0.0429
C(18)	0.0507(4)	0.1935(3)	0.79521(8)	0.0447
C(19)	0.0440(4)	0.2834(3)	0.76017(8)	0.0438
C(20)	0.2084(4)	0.2844(2)	0.72846(7)	0.0383
O(3)	0.4162(3)	0.30451(15)	0.60299(5)	0.0352
O(4)	-0.0257(3)	0.46969(15)	0.59087(5)	0.0291
O(5)	-0.2126(3)	0.82583(14)	0.42006(4)	0.0338
C(21)	-0.0390(4)	0.8667(2)	0.39126(7)	0.0377

Table 3: Atomic coordinates and isotropic thermal parameters ($\text{\AA}^2$) of hydrogen atoms

Atom	x	y	z	U_{iso}
H(1)	0.042(6)	0.537(3)	0.5839(9)	0.06(1)
H(21)	0.5556	-0.0547	0.7045	0.0335
H(22)	0.6130	-0.1008	0.6538	0.0335
H(31)	0.6484	0.1220	0.6383	0.0321
H(51)	-0.0681	0.2335	0.6097	0.0307
H(52)	0.0311	0.1588	0.5659	0.0307
H(61)	0.1676	0.3857	0.5444	0.0296
H(71)	-0.2949	0.3396	0.5397	0.0343
H(72)	-0.1173	0.2742	0.5055	0.0343
H(91)	-0.4789	0.5321	0.5150	0.0338
H(101)	-0.5003	0.7275	0.4699	0.0349
H(121)	0.1214	0.6523	0.4216	0.0325
H(131)	0.1379	0.4545	0.4662	0.0331
H(141)	0.7041	0.1743	0.7111	0.0405
H(142)	0.5723	0.2907	0.6841	0.0405
H(161)	0.5241	0.0494	0.7713	0.0457
H(171)	0.2316	0.0404	0.8238	0.0514
H(181)	-0.0698	0.1917	0.8177	0.0537
H(191)	-0.0804	0.3479	0.7578	0.0525
H(201)	0.1993	0.3480	0.7029	0.0459
H(211)	-0.0778	0.9538	0.3770	0.0453
H(212)	0.0986	0.8774	0.4089	0.0453
H(213)	-0.0164	0.7974	0.3678	0.0453

Table 4: Anisotropic thermal parameters ($\text{\AA}^2$)

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
N(1)	0.0173(8)	0.0215(7)	0.0303(8)	0.0015(6)	0.0022(7)	0.0000(7)
C(1)	0.021(1)	0.025(1)	0.035(1)	0.0062(8)	0.0062(8)	0.0023(9)
O(1)	0.0214(8)	0.0303(8)	0.0599(9)	0.0113(7)	0.0032(7)	-0.0021(7)
O(2)	0.0236(7)	0.0270(7)	0.0507(8)	0.0141(7)	0.0057(7)	0.0015(6)
C(2)	0.022(1)	0.0263(9)	0.035(1)	0.0013(8)	0.0002(8)	0.0023(9)
C(3)	0.0183(9)	0.0238(9)	0.038(1)	0.0024(8)	0.0011(8)	-0.0002(8)
C(4)	0.024(1)	0.0211(9)	0.0299(9)	0.0011(8)	0.0079(8)	-0.0014(9)
C(5)	0.0256(11)	0.0217(9)	0.029(1)	0.0027(8)	-0.0001(8)	-0.0027(8)
C(6)	0.025(1)	0.0224(9)	0.0263(8)	0.0001(7)	0.0018(8)	-0.0015(9)
C(7)	0.029(1)	0.028(1)	0.0288(9)	0.0009(8)	-0.0014(8)	-0.0009(9)
C(8)	0.028(1)	0.0253(9)	0.0235(8)	-0.0027(8)	-0.0030(8)	-0.0007(9)
C(9)	0.024(1)	0.0346(11)	0.0258(9)	-0.0016(8)	0.0012(8)	-0.0014(9)
C(10)	0.027(1)	0.0325(11)	0.0282(9)	-0.0048(8)	-0.0018(8)	0.0062(9)
C(11)	0.031(1)	0.0247(9)	0.0239(8)	-0.0017(8)	-0.0039(8)	0.0026(9)
C(12)	0.028(1)	0.0294(9)	0.0234(8)	0.0001(8)	0.0016(8)	0.003(1)
C(13)	0.027(1)	0.030(1)	0.0256(8)	0.0001(8)	-0.0011(8)	0.0027(9)
C(14)	0.026(1)	0.030(1)	0.0452(11)	-0.0020(9)	-0.0078(9)	-0.003(1)
C(15)	0.0305(11)	0.032(1)	0.035(1)	-0.0122(9)	-0.0097(9)	-0.000(1)
C(16)	0.0380(12)	0.0374(12)	0.0388(11)	-0.011(1)	-0.007(1)	0.0087(11)
C(17)	0.0489(14)	0.0451(13)	0.035(1)	-0.012(1)	-0.0022(11)	0.0041(13)
C(18)	0.0365(13)	0.0545(14)	0.0432(12)	-0.0215(12)	-0.0014(11)	0.0013(13)
C(19)	0.0351(13)	0.0487(13)	0.0475(12)	-0.0238(11)	-0.0103(11)	0.0125(12)
C(20)	0.0363(12)	0.0347(11)	0.0437(11)	-0.014(1)	-0.0147(11)	0.0064(11)
O(3)	0.0256(7)	0.0290(7)	0.0510(8)	0.0093(7)	-0.0000(7)	-0.0055(7)
O(4)	0.0319(8)	0.0239(7)	0.0315(7)	-0.0028(6)	0.0012(6)	-0.0013(7)
O(5)	0.0391(9)	0.0264(7)	0.0360(7)	0.0045(6)	0.0022(7)	0.0078(7)
C(21)	0.0490(14)	0.028(1)	0.036(1)	0.0021(9)	0.0074(11)	0.0007(11)

Table 5: Bond lengths (Å)

N(1) - C(1)	1.381(3)	C(8) - C(13)	1.390(3)
N(1) - C(3)	1.469(2)	C(9) - C(10)	1.391(3)
N(1) - C(4)	1.401(2)	C(10) - C(11)	1.384(3)
C(1) - O(1)	1.202(3)	C(11) - C(12)	1.384(3)
C(1) - O(2)	1.348(2)	C(11) - O(5)	1.381(2)
O(2) - C(2)	1.451(3)	C(12) - C(13)	1.400(3)
C(2) - C(3)	1.529(3)	C(14) - C(15)	1.508(3)
C(3) - C(14)	1.530(3)	C(15) - C(16)	1.395(3)
C(4) - C(5)	1.502(3)	C(15) - C(20)	1.394(3)
C(4) - O(3)	1.215(2)	C(16) - C(17)	1.394(3)
C(5) - C(6)	1.524(3)	C(17) - C(18)	1.388(4)
C(6) - C(7)	1.532(3)	C(18) - C(19)	1.387(4)
C(6) - O(4)	1.430(2)	C(19) - C(20)	1.386(3)
C(7) - C(8)	1.516(3)	O(4) - H(1)	0.82(3)
C(8) - C(9)	1.391(3)	O(5) - C(21)	1.430(3)

Note – geometrically-positioned H atoms have been excluded

Table 6: Bond angles (°)

C(1) - N(1) - C(3)	111.97(15)	C(7) - C(8) - C(13)	120.92(18)
C(1) - N(1) - C(4)	127.35(16)	C(9) - C(8) - C(13)	117.77(17)
C(3) - N(1) - C(4)	119.94(16)	C(8) - C(9) - C(10)	121.34(18)
N(1) - C(1) - O(1)	128.38(19)	C(9) - C(10) - C(11)	119.71(18)
N(1) - C(1) - O(2)	109.37(16)	C(10) - C(11) - C(12)	120.46(18)
O(1) - C(1) - O(2)	122.25(19)	C(10) - C(11) - O(5)	115.56(18)
C(1) - O(2) - C(2)	110.47(15)	C(12) - C(11) - O(5)	123.96(18)
O(2) - C(2) - C(3)	105.96(16)	C(11) - C(12) - C(13)	118.92(18)
N(1) - C(3) - C(2)	101.09(16)	C(8) - C(13) - C(12)	121.78(19)
N(1) - C(3) - C(14)	113.24(17)	C(3) - C(14) - C(15)	114.41(17)
C(2) - C(3) - C(14)	113.85(17)	C(14) - C(15) - C(16)	121.3(2)
N(1) - C(4) - C(5)	118.74(16)	C(14) - C(15) - C(20)	120.2(2)
N(1) - C(4) - O(3)	117.89(18)	C(16) - C(15) - C(20)	118.5(2)
C(5) - C(4) - O(3)	123.36(17)	C(15) - C(16) - C(17)	120.6(2)
C(4) - C(5) - C(6)	111.92(16)	C(16) - C(17) - C(18)	120.1(2)
C(5) - C(6) - C(7)	111.02(16)	C(17) - C(18) - C(19)	119.4(2)
C(5) - C(6) - O(4)	107.55(14)	C(18) - C(19) - C(20)	120.5(2)
C(7) - C(6) - O(4)	110.41(16)	C(15) - C(20) - C(19)	120.7(2)
C(6) - C(7) - C(8)	112.90(16)	C(6) - O(4) - H(1)	109.(2)
C(7) - C(8) - C(9)	121.30(18)	C(11) - O(5) - C(21)	118.22(17)

Note – geometrically-positioned H atoms have been excluded