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Organocatalytic Asymmetric Michael Reaction of Cyclic 1,3-Dicarbonyl Compounds and α,β-Unsaturated Ketones - A Highly Atom Efficient Catalytic One-Step Formation of Optically Active Warfarin Anticoagulant

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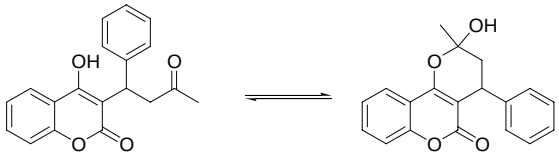
General methods. The 1H NMR and ^{13}C NMR[i] spectra were recorded at 400 MHz and 100 MHz, respectively, using $CDCl_3$ or $(CD_3)_2SO$ as solvents and were reported in ppm relative to $CHCl_3$ (δ = 7.26) for ^{1}H NMR and relative to the central $CDCl_3$ (δ=77.00) or $(CD_3)_2SO$ (δ=39.52) resonance for ^{13}C NMR. Coupling constants in ^{1}H NMR are in Hz. Flash chromatography (FC) was carried out using silica gel 60 (230-400 mesh). The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC using a Daicel Chiralpack AD column and hexane/2-propanol 70/30 containing 0.1% TFA as the eluent or using a Daicel Chiralpack AS column and hexane/EtOH 70/30 containing 0.1% TFA as the eluent (compounds **1h**,**i**). Retention times are indicated in the respective entries.

Materials. Commercially available compounds **2a-c**,**e**,**g** **3a**,**b**,**f**,**h**,**i**, and solvents were used without further purification or drying. Commercially available 5-methyl-hex-3-en-2-one **3g** was purified by FC using Et_2O/pentane before use. 4-Nitro-benzylideneacetone[ii] **3c**, 4-methoxy-benzylideneacetone[iii] **3d**, 2-naphthylideneacetone[iv] **3e**, 1-phenyl-pent-1-en-3-one[v] **3j**, 4-methyl-1-phenyl-pent-1-en-3-one[vi] **3k**, 7-fluoro-4-hydroxycoumarin[vii] **2d** and 4-hydroxy-thiochromen-2-one[viii] **2f** was prepared according to literature procedures. Catalysts **4a**,**b** was also prepared according to literature procedures.[ix]

General procedure for the organocatalytic Michael reaction of α,β-unsaturated enones with cyclic 1,3-dicarbonyl compounds. To a stirred solution of α,β-unsaturated enone (0.5 mmol) and Michael donor (0.525 mmol, 1.05 equiv.) in 1.0 mL solvent at ambient temperature was added 13.4 mg (0.05 mmol) (4*S*,5*S*)-4,5-diphenyl-imidazolidine-2-carboxylic acid **4c** and the mixture was stirred for the time indicated in the table. The crude reaction mixture was purified by FC to yield the pure products. The enantiomeric excess of the products was determined by HPLC using a chiral stationary phase.



4-Hydroxy-3-(3-oxo-1-phenyl-butyl)-chromen-2-one (warfarin) (1a).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The hemiketal was crystallized and characterised by single crystal X-ray analysis (see below). The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.3 and 8.0 min). ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 1.35H, CH_3 ketal), 1.70 (s, 1.35H, CH_3 ketal), 1.99 (m, 0.4H, CH_2 ketal), 2.28 (s, 0.3H, CH_3 keto), 2.39-2.55 (m, 1.4H, CH_2 ketal), 3.17 (br s, 0.9H, OH ketal, position is concentration dependent), 3.30 (dd, *J* = 0.6, 19.4 Hz, 0.1H, CH_2 keto), 3.85 (dd, *J* = 10.3, 19.4 Hz, 0.1H, CH_2 keto), 4.14 (dd, *J* = 6.6, 11.1 Hz, 0.45H, CH ketal) 4.28 (dd, *J* = 3.3, 6.5 Hz, 0.45H, CH ketal), 4.67 (dd, 1.8, 10.2 Hz, 0.1H, CH keto), 7.19-35 (m, 7H, ArH), 7.49 (br t, *J* = 8.1 Hz, 0.55H, ArH), 7.55 (dt, *J* = 1.6, 8.7 Hz, 0.45H, ArH), 7.80 (d, *J* = 7.9 Hz, 0.45H, ArH), 7.88 (dd, *J* = 1.5, 7.9 Hz, 0.45H, ArH), 7.93 (d, *J* = 7.6 Hz, 0.1H, ArH) 9,19 (br s, 0.1H, OH keto, position is concentration dependent); ^{13}C NMR ($CDCl_3$) δ 27.8, 28.3, 30.3, 34.4, 35.0 35.5, 40.2, 42.8, 45.3 99.2, 100.7, 101.3, 104.3, 115.7, 116.1, 116.6, 116.8, 122.9, 123.2, 123.8, 124.1, 126.7, 127.2, 127.2, 127.4, 128.1, 128.4, 128.8, 129.4, 131.7, 132.2, 141.7, 143.4, 153.0, 153.1, 159.1, 159.9, 161.6, 162.4; HRMS (TOF ES$^+$) m/z 331.0945 (M+Na$^+$), calc. for $C_{19}H_{16}O_4Na^+$ 331.0946.

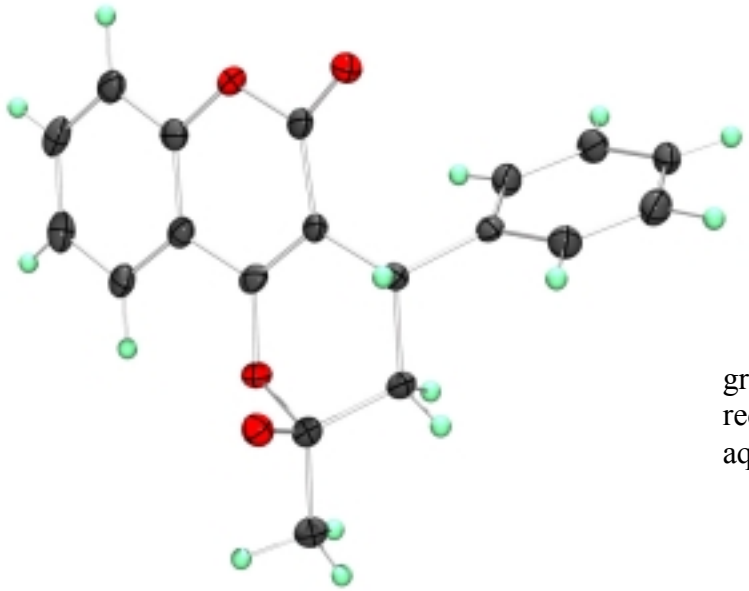
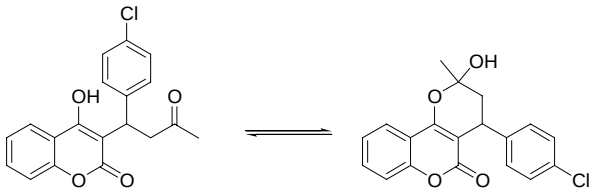


Figure 1. X-ray crystal structure of warfarin **1a** on hemiketal form.



3-[1-(4-Chloro-phenyl)-3-oxo-butyl]-4-hydroxy-chromen-2-one (coumachlor) (1b).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The hemiketal was crystallized and characterised by single crystal X-ray analysis (see below). The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.6 and 9.9 min). ^{1}H NMR ($CDCl_3$) δ 1.70 (s, 1.13H, CH_3 ketal), 1.75 (s, 1.53H, CH_3 ketal), 1.95 (m, 0.47H, CH_2 ketal), 2.30 (s, 0.33H, CH_3 keto), 2.37-2.50 (m, 1.33H, CH_2 ketal), 2.97 (s, 0.33 H, OH ketal, position is concentration dependent), 3.09 (s, 0.36 H, OH ketal, position is concentration dependent), 3.28 (dd, *J* = 2.4, 19.8 Hz, 0.1H, CH_2 keto), 3.86 (dd, *J* = 10.8, 19.8 Hz, 0.1H, CH_2 keto), 4.14 (dd, *J* = 6.4, 11.3 Hz, 0.5H, CH ketal), 4.21 (dd, *J* = 3.6, 7.1 Hz, 0.36H, CH ketal), 4.64 (dd, *J* = 2.5, 10.9 Hz, 0.13H, CH keto), 7.15-7.36 (m, 6H, ArH), 7.52 (dt, *J* = 1.6, 6.6 Hz, 0.66H, ArH) 7.57 (dt, *J* = 1.8, 6.9 Hz, 0.33H, ArH), 7.81 (dd, *J* = 1.6, 6.6 Hz, 0.5H, ArH), 7.88 (dd, *J* = 1.6, 7.6 Hz, 0.4H, ArH), 7.95 (dd, *J* = 1.4, 7.5 Hz, 0.1H, ArH), 9.56 (s, 0.1H, OH keto); ^{13}C NMR (CD_2Cl_2) δ 28.1, 35.2, 40.2, 42.6, 99.4, 100.6, 101.7, 103.8, 115.9, 116.2, 116.4, 116.7, 123.0, 123.2, 124.0, 124.2, 128.7, 128.8, 128.9, 129.2, 132.0, 132.3, 141.8, 142.7, 153.1, 159.6, 160.1, 161.6, 162.3; HRMS (TOF ES$^+$) m/z 365.0558 (M+Na$^+$), calc. for $C_{19}H_{15}O_4ClNa^+$ 365.0557.

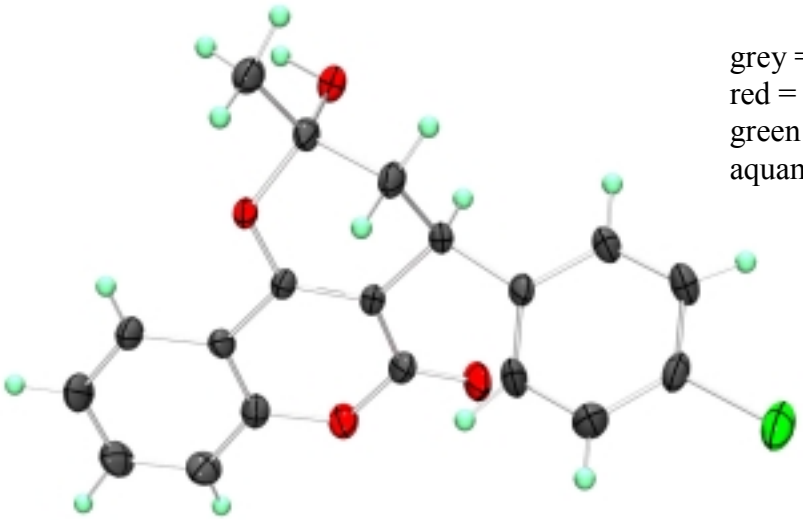
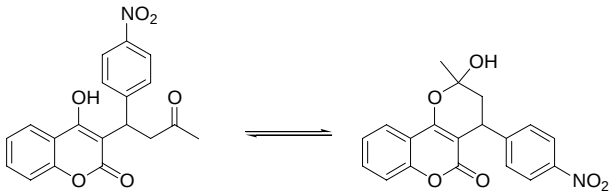
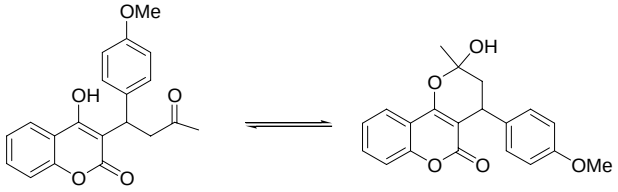


Figure 2. X-ray crystal structure of (*S*)-coumachlor **1b** on hemiketal form.



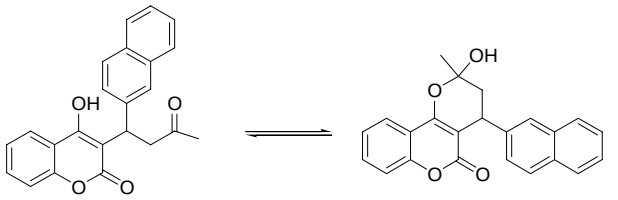
4-Hydroxy-3-[1-(4-nitro-phenyl)-3-oxo-butyl]-chromen-2-one (acenocoumarin) (1c).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 6.3 and 16.5 min). ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 1.13H, CH_3 ketal), 1.79 (s, 1.75H, CH_3 ketal), 1.93 (m, 0.53 H, CH_2 ketal), 2.34 (s, 0.12H, CH_3 keto), 2.39-2.52 (m, 1.40H, CH_2 ketal), 2.96 (s, 0.28H, OH ketal), 3.24 (s, 0.5H, OH ketal), 3.34 (dd, *J* = 2.9, 20.3 Hz, 0.04H, CH_2 keto), 3.90 (dd, *J* = 11.1, 20.5 Hz, 0.04H, CH_2 keto), 4.27 (m, 0.96H, CH ketal), 4.73 (dd, 1.7, 12.6 Hz, 0.04H), 7.25-7.44 (m, 4H, ArH), 7.54 (dt, *J* = 1.3, 7.7 Hz, 0.69H, ArH), 7.59 (dt, *J* = 1.3, 7.7 Hz, 0.31H, ArH), 7.82 (dd, *J* = 1.3, 8.4 Hz, 0.69H, ArH) 7.87 (dd, *J* = 1.3, 8.4 Hz, 0.31H, ArH), 8.12-8.18 (m, 2H, ArH); ^{13}C NMR ($(CD_3)_2SO$) δ 26.5, 27.2, 35.2, 35.3, 41.9, 99.7, 100.9, 101.0, 102.5, 115.4, 115.6, 116.4, 116.5, 122.8, 122.9, 123.1, 123.6, 124.2, 124.3, 128.6, 129.0, 132.3, 132.4, 145.7, 146.0, 152.4, 152.5, 152.6, 159.4, 159.8, 160.5, 161.1; HRMS (TOF ES$^+$) m/z 376.0798 (M+Na$^+$), calc. for $C_{19}H_{15}O_6NNa^+$ 376.0797.



4-Hydroxy-3-[1-(4-methoxy-phenyl)-3-oxo-butyl]-chromen-2-one (1d).

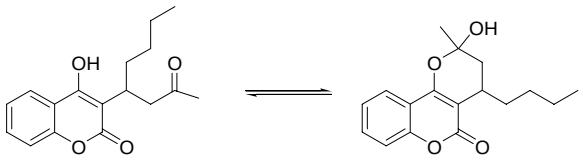
The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 5.2 and 11.1 min). ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 1.34H, CH_3 ketal), 1.71 (s, 1.34H, CH_3 ketal), 1.99 (dd, *J* = 11.6, 14.0 Hz, 0.44H, CH_2 ketal), 2.29 (s, 0.33H, CH_3 keto), 2.38 (dd, *J* = 6.8, 14.4 Hz, 0.44H, CH_2 ketal), 2.46 (dd, *J* = 7.2, 14.0 Hz, 0.44H, CH_2 ketal), 2.53 (dd, *J* = 2.8, 14.0 Hz, 0.44H, CH_2 ketal), 3.26 (br s, 0.44H, OH ketal, position is concentration dependent), 3.29 (s, 0.44H, OH ketal, position is concentration dependent), 3.76 (s, 0.44H, OMe ketal), 3.77 (s, 0.44H, OMe ketal), 3.81-3.90 (m, 0.22H, CH_2 keto), 4.12 (dd, *J* = 6.8, 11.6 Hz, 0.44H, CH ketal), 4.25 (dd, *J* = 2.8, 6.8 Hz, 0.44H, CH ketal), 4.64 (br d, *J* = 6 Hz, 0.11H, CH keto), 6.80-6.87 (m, 1.78H, ArH), 7.13-7.36 (m, 4.29H, ArH), 7.49 (br t, *J* = 7.8 Hz, 0.44H, ArH), 7.57 (dt, *J* = 1.6, 7.8 Hz, 0.44H ArH), 7.80 (dd, *J* = 1.6, 8.0 Hz, 0.44H, ArH), 7.89 (dd, *J* = 1.6, 8.0 Hz, 0.44H, ArH), 7.93 (br d, *J* = 8.0 Hz, 0.11H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.5, 27.8, 33.3, 34.4, 55.1, 55.2, 99.1, 100.5, 101.3, 104.1, 113.9, 114.5, 115.5, 115.8, 116.2, 116.5, 122.6, 123.0, 123.5, 123.9, 127.9, 128.0, 131.3, 131.9, 133.1, 135.2, 152.6, 152.8, 157.9, 158.4, 158.8, 159.6, 161.5, 162.3; HRMS (TOF ES$^+$) m/z 360.1050 (M+Na$^+$), calc. for $C_{20}H_{18}O_5Na^+$ 360.1052.



4-Hydroxy-3-(1-naphthalen-2-yl-3-oxo-butyl)-chromen-2-one (1e).

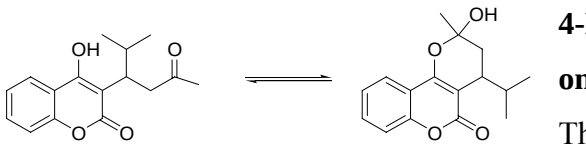
The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 5.2 and 12.0 min). ^{1}H NMR ($CDCl_3$) δ 1.68 (s, 1.35H, CH_3 ketal), 1.71 (s, 1.35H, CH_3 ketal), 2.08 (m, 0.45H, CH_2 ketal), 2.34 (s, 0.30H, CH_3 keto), 2.43-2.54 (m, 0.90H, CH_2 ketal), 2.64 (dd, *J* = 3.2, 14.4 Hz, 0.45H, CH_2 ketal), 3.31 (s, 0.65H, OH ketal, position is concentration dependent), 4.34 (dd, *J* = 6.8, 11.2 Hz, 0.45H, CH ketal), 4.45 (dd, *J* = 2.8, 6.8 Hz, 0.45H, CH ketal), 4.85 (br d, 0.10H, CH keto), 7.27-7.95 (m, 11H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.2, 27.6, 34.6, 35.3, 39.6, 42.3, 99.2, 100.6, 101.0, 103.7, 115.5, 115.8, 116.2, 116.5, 122.7, 123.1, 123.5, 123.9, 125.0, 125.2,

125.3, 125.5, 125.6, 125.7, 125.8, 126.1, 127.5, 127.7, 128.2, 128.9, 131.4, 132.0, 132.3, 132.4, 133.4, 133.5, 139.1, 140.7, 152.6, 152.8, 159.3, 160.0, 161.8, 162.4; HRMS (TOF ES^+) m/z 381.1103 ($M+Na^+$), calc. for $C_{23}H_{18}O_4Na^+$ 381.1103.



4-Hydroxy-3-[1-(2-oxo-propyl)-pentyl]-chromen-2-one (1f).

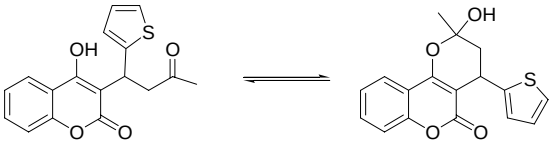
The compound was isolated as a colorless oil after FC in Et_2O/CH_2Cl_2, but solidified upon standing. The product was found to exist predominantly on the keto form but in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 6.9 and 8.8 min). ^{1}H NMR ($CDCl_3$) δ 0.77 (t, *J* = 6.8 Hz, 2.01H, CH_3 ketal), 0.84 (q, *J* = 8.0 Hz, 1.34H), 1.07-1.61 (m, 5.12H), 1.65 (s, 0.45H, CH_3 ketal), 1.71 (s, 0.45H, CH_3 ketal), 1.70-2.30 (m, 1.61H), 2.13 (s, 2.01H, $COCH_3$ keto), 2.70 (br d, *J* = 20.0 Hz, 0.67H, CH_2 keto), 2.70-3.18 (m, 0.83H, CH_2 ketal and CH ketal), 3.12 (br q, *J* = 12.8 Hz, 0.67H, CH_2 keto), 3.31 (dd, *J* = 10.4, 20.0 Hz, 0.67H, CH keto), 3.84-3.92 (m, 0.17H, CH ketal), 7.16-7.24 (m, 2H, ArH), 7.39-7.44 (m, 1H, ArH), 7.70 (br t, *J* = 7.6 Hz, 0.33H, ArH), 7.85 (dd, *J* = 1.2, 8.0 Hz, 0.67H, ArH); ^{13}C NMR ($CDCl_3$) δ 13.9, 14.0, 14.1, 22.2, 22.3, 22.6, 22.7, 23.8, 27.7, 28.0, 28.1, 28.3, 29.0, 29.2, 29.6, 29.7, 30.2, 30.3, 30.7, 30.8, 31.1, 34.1, 38.0, 47.8, 98.9, 100.1, 104.9, 105.2, 106.9, 107.8, 115.8, 115.9, 116.0, 116.2, 116.5, 122.5, 123.4, 123.5, 123.7, 131.0, 131.1, 131.5, 152.3, 152.5, 157.6, 158.2, 161.7, 162.3, 162.4, 162.7, 213.9; HRMS (TOF ES^+) m/z 311.1261 ($M+Na^+$), calc. for $C_{17}H_{20}O_4Na^+$ 311.1259.



4-Hydroxy-3-(1-isopropyl-3-oxo-butyl)-chromen-2-one (1g).

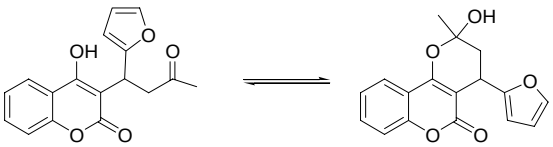
The compound was isolated as a colorless oil after FC in Et_2O/CH_2Cl_2, but solidified upon standing. The product was found to exist predominantly on the keto form but in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.5 and 10.9 min). ^{1}H NMR ($CDCl_3$) δ 0.66 (d, *J* = 6.4 Hz, 0.72H, $CH(C\mathbf{H}_3)_2$ ketal), 0.75 (d, *J* = 6.6 Hz, 2.28H, $CH(C\mathbf{H}_3)_2$ keto), 0.98 (d, *J* = 6.0 Hz, 2.28H, $CH(C\mathbf{H}_3)_2$ keto), 1.00 (d, *J* = 7.2 Hz, 0.72H, $CH(C\mathbf{H}_3)_2$ ketal), 1.80 (s, 0.72H, $COCH_3$ ketal), 1.98-2.08 (m, 0.24H, $C\mathbf{H}(CH_3)_2$ ketal), 2.15 (dd, *J* = 7.1, 13.6 Hz, CH_2 ketal), 2.20 (s, 2.28H, $COCH_3$ keto), 2.51-2.62 (m, 0.76H $C\mathbf{H}(CH_3)_2$

keto), 2.74 (br t, 10.4 Hz, 0.76H, CH_2 keto), 2.95 (br d, *J* = 20.0 Hz, 0.76H, CH_2 keto), 3.01-3.07 (m, 0.24H, CH_2 ketal), 3.19-3.28 (m, 0.24H, C*H ketal), 3.30 (dd, *J* = 10.4, 20.0 Hz, C*H keto), 7.21-7.29 (m, 2.0H, ArH), 7.44-7.51 (m, 1H, ArH), 7.72-7.80 (m, 0.24H, ArH), 7.91 (dd, *J* = 1.6, 8.4 Hz, 0.76H, ArH); ^{13}C NMR ($CDCl_3$) δ 15.7, 16.7, 20.3, 20.5, 21.5, 21.6, 25.1, 25.2, 26.7, 27.1, 28.6, 29.9, 31.2, 33.1, 36.2, 38.3, 45.5, 99.0, 101.7, 103.4, 104.9, 107.5, 115.7, 116.0, 116.1, 116.2, 116.5, 122.6, 122.8, 123.5, 123.6, 123.8, 131.1, 131.4, 131.5, 152.4, 152.5, 152.6, 158.8, 159.5, 161.7, 162.0, 162.4, 162.5, 214.2; HRMS (TOF ES^+) m/z 297.1104 ($M+Na^+$), calc. for $C_{16}H_{18}O_4Na^+$ 297.1103.



4-Hydroxy-3-(3-oxo-1-thiophen-2-yl-butyl)-chromen-2-one (1h).

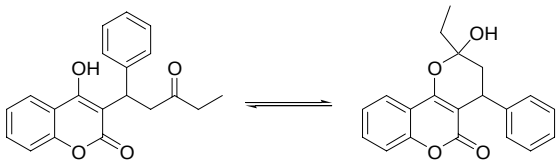
The compound was isolated as a slightly yellow solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.8 and 6.4 min). ^{1}H NMR ($CDCl_3$) δ 1.71 (s, 2.4H, CH_3 ketal), 2.21 (dd, *J* = 10.4, 14.0 Hz, 0.27H, CH_2 ketal), 2.29 (s, 0.6H, CH_3 keto), 2.40 (dd, *J* = 6.8, 14.4 Hz, 0.54H, CH_2 ketal), 2.55 (dd, *J* = 6.8, 14.0 Hz, 0.27H, CH_2 ketal), 2.69 (dd, *J* = 2.4, 14.4 Hz, 0.54H, CH_2 ketal), 3.33-3.38 (br m, 0.4H), 3.64 (br s, 0.4H), 3.83 (dd, *J* = 9.2, 20.0 Hz, 0.20H, CH_2 keto), 3.92-3.98 (m, 0.2H, CH_2 keto), 4.50-4.55 (m, 0.80H, CH ketal), 4.92 (dd, *J* = 1.6, 9.0 Hz, 0.20H, CH keto), 6.89-6.95 (m, 1.87H, ArH), 7.13 (dd, *J* = 1.2, 5.2 Hz, 0.32H, ArH), 7.16 (dd, *J* = 1.2, 4.8 Hz, 0.18H, ArH), 7.23-7.37 (m, 2.73H, ArH), 7.48-7.60 (m, 1H, ArH), 7.80 (dd, *J* = 1.6, 8.4 Hz, 0.28H, ArH), 7.90 (dd, *J* = 1.6, 8.0 Hz, 0.44H, ArH), 7.93 (dd, *J* = 1.6, 8.0 Hz, 0.18H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.6, 27.8, 29.6, 30.7, 39.7, 42.8, 99.4, 100.3, 101.0, 103.6, 115.3, 115.7, 116.3, 116.5, 122.8, 123.0, 123.2, 123.6, 124.0, 124.6, 125.2, 126.6, 127.0, 128.1, 129.1, 131.6, 131.9, 132.2, 141.2, 145.4, 146.5, 152.6, 152.8, 158.6, 159.3, 161.5, 162.2; HRMS (TOF ES^+) m/z 337.0514 ($M+Na^+$), calc. for $C_{17}H_{14}O_4SNa^+$ 337.0510.



3-(1-Furan-2-yl-3-oxo-butyl)-4-hydroxy-chromen-2-one (1i).

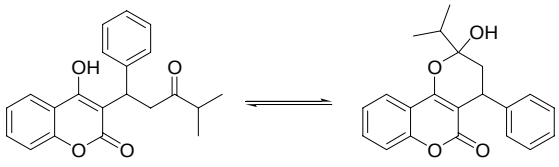
The compound was isolated as a slightly brown solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-

diastereomers are observed during HPLC analysis (τ = 4.8 and 5.7 min). ^{1}H NMR ($CDCl_3$) δ 1.63 (s, 0.71H, CH_3 ketal), 1.71 (s, 1.66H, CH_3 ketal), 2.22-2.26 (m, 0.47H, CH_2 ketal), 2.28 (s, 0.63H, CH_3 keto), 2.30-2.37 (m, 0.55H, CH_2 ketal), 2.66-2.70 (m, 0.55H, CH_2 ketal), 3.31 (dd, *J* = 2.8, 19.3 Hz, 0.21H, CH_2 keto), 3.64 (dd, *J* = 8.1, 19.3 Hz, 0.21H, CH_2 keto), 4.15 (br, 0.23H, OH), 4.28-4.33 (m, 1.34H, CH ketal and OH), 4.74 (dd, *J* = 2.8, 8.1 Hz, 0.21H, CH keto), 6.11 (d, *J* = 3.1 Hz, 0.21H, ArH), 6.14 (d, *J* = 3.1 Hz, 0.21H, ArH), 6.17 (d, *J* = 3.3 Hz, 0.58H, ArH), 6.30 (dd, *J* = 2.0, 3.3 Hz, 1H, ArH), 7.17-7.57 (m, 4H, ArH), 7.77 (dd, *J* = 1.0, 7.8 Hz, 0.23H, ArH), 7.87 (dd, *J* = 1.2, 7.8 Hz, 0.55H, ArH), 7.92 (dd, *J* = 1.2, 7.8 Hz, 0.55H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.6, 28.1, 28.2, 29.4, 30.0, 30.5, 36.0, 38.3, 45.2, 99.2, 99.6, 99.8, 106.3, 106.5, 106.9, 110.6, 111.0, 115.6, 115.9, 116.4, 116.6, 116.7, 116.8, 122.9, 123.4, 123.8, 124.0, 124.1, 124.2, 131.8, 132.2, 132.4, 141.1, 141.5, 142.5, 152.8, 153.0, 154.1, 154.5, 159.5, 162.2, 162.9, 212.3; HRMS (TOF ES$^+$) m/z 321.0742 (M+Na$^+$), calc. for $C_{17}H_{14}O_5Na^+$ 321.0739.



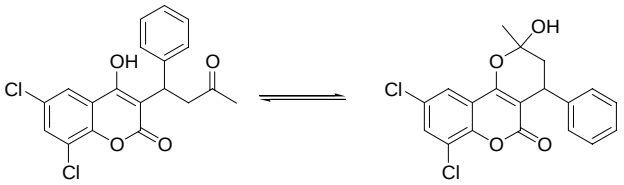
4-Hydroxy-3-(3-oxo-1-phenyl-pentyl)-chromen-2-one (**1j**).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.5 and 9.3 min). ^{1}H NMR ($CDCl_3$) δ 1.06-1.11 (m, 3H, CH_3 keto and ketal), 1.88-2.01 (m, 2.28H, CH_2 keto and ketal), 2.36-2.64 (m, 1.58H, CH_2 keto and ketal), 3.18 (br, 0.43H, OH ketal), 3.31 (br, 0.43H, OH ketal), 3.84 (dd, *J* = 9.6, 19.6 Hz, 0.14H, C**H**$_2$CH keto), 4.17 (dd, *J* = 6.4, 11.2 Hz, 0.43H, CH ketal), 4.30 (dd, *J* = 2.8, 6.4 Hz, 0.43H, CH ketal), 4.72 (dd, *J* = 1.2, 9.6 Hz, 0.14H, CH keto), 7.19-7.36 (m, 7H, ArH), 7.46-7.58 (m, 1H, ArH), 7.79 (dd, *J* = 1.6, 8.4 Hz, 0.43H, ArH), 7.88 (dd, *J* = 1.6, 8.0 Hz, 0.43H, ArH), 7.94 (br d, *J* = 7.6 Hz, 0.14H, ArH); ^{13}C NMR ($CDCl_3$) δ 7.3, 7.4, 7.6, 33.3, 33.6, 33.7, 34.7, 35.1, 36.0, 37.7, 40.2, 43.8, 100.7, 101.2, 102.0, 104.2, 108.0, 115.5, 115.9, 116.1, 116.3, 116.6, 122.6, 122.9, 123.5, 123.9, 126.4, 126.6, 126.9, 127.0, 127.1, 127.9, 128.1, 128.5, 129.1, 131.4, 131.7, 131.9, 139.8, 141.5, 143.4, 152.7, 152.9, 159.0, 159.7, 161.4, 162.2; HRMS (TOF ES$^+$) m/z 345.1094 (M+Na$^+$), calc. for $C_{20}H_{18}O_4Na^+$ 345.1103.



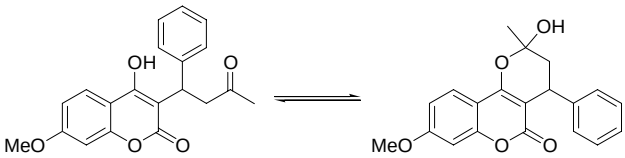
4-Hydroxy-3-(4-methyl-3-oxo-1-phenyl-pentyl)-chromen-2-one (1k).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.5 and 10.9 min). ^{1}H NMR ($CDCl_3$) δ 1.06-1.18 (m, 6H, CH_3 keto and ketal), 1.88 (dd, *J* = 11.6, 14.0 Hz, 0.41H, CH_2 ketal), 2.11 (septet, *J* = 6.8 Hz, 0.4H, $CH(Me)_2$ ketal), 2.18 (septet, *J* = 7.2 Hz, 0.4H, $CH(Me)_2$ ketal), 2.41 (dt, *J* = 6.4, 14.4 Hz, 0.81H, CH_2 ketal), 2.50 (dd, *J* = 2.8, 14.8 Hz, 0.41H, CH_2 ketal), 2.76 (septet, *J* = 6.8 Hz, 0.19H, $CH(Me)_2$ keto), 2.93 (br s, 0.41H, OH ketal), 3.06 (br s, 0.41H, OH ketal), 3.30 (br d, *J* = 18.8 Hz, 0.19H, CH_2 keto), 3.92 (dd, *J* = 10.4, 18.8 Hz, 0.19H, CH_2 keto), 7.21-7.38 (m, 7H, ArH), 7.48-7.59 (m, 1H, ArH), 7.79 (d, *J* = 7.6 Hz, 0.40H, ArH), 7.88 (dd, *J* = 1.6, 8.0 Hz, 0.40H, ArH), 7.96 (d, *J* = 8.0 Hz, 0.19H, ArH); ^{13}C NMR ($CDCl_3$) δ 16.1, 16.2, 16.7, 16.9, 18.2, 26.3, 33.3, 35.0, 35.3, 37.2, 37.3, 37.8, 40.9, 42.1, 101.1, 102.4, 103.6, 104.3, 115.6, 116.0, 116.3, 116.6, 122.5, 122.8, 123.5, 123.9, 126.4, 127.0, 127.1, 128.1, 128.5, 128.9, 129.1, 131.0, 131.4, 131.9, 141.4, 143.6, 152.7, 152.8, 159.0, 159.8, 161.3.162.3; HRMS (TOF ES$^+$) m/z 359.1254 (M+Na$^+$), calc. for $C_{21}H_{20}O_4Cl_2Na^+$ 359.1259.



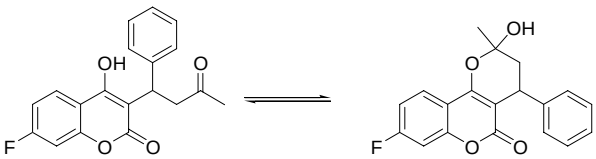
6,8-Dichloro-4-hydroxy-3-(3-oxo-1-phenyl-butyl)-chromen-2-one (1l).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.1 and 4.7 min). ^{1}H NMR ($CDCl_3$) δ 1.69 (s, 1.16H, CH_3 ketal), 1.73 (s, 1.45H, CH_3 ketal), 1.95-2.04 (m, 0.48H, CH_2 ketal), 2.31 (s, 0.39H, CH_3 keto), 2.39-2.59 (m, 1.26H, CH_2 ketal), 3.20 (s, 0.34H, OH ketal), 3.31 (s, 0.48H, OH ketal), 3.34 (m, 0.13H, CH_2 keto), 3.86 (dd, *J* = 9.1, 19.3 Hz, 0.13 H, CH_2 keto), 4.16 (dd, *J* = 6.9, 12.0 Hz, 0.48H, CH ketal), 4.29 (dd, *J* = 2.8, 6.9 Hz, 0.39H, CH ketal), 4.67 (dd, *J* = 1.9, 10.3 Hz, 0.13H, CH keto), 7.20-7.37 (m, 5H, ArH), 7.53 (d, *J* = 2.3 Hz, 0.48H, ArH) 7.61 (d, *J* = 2.3 Hz, 0.39H, ArH), 7.68 (d, *J* = 2.3 Hz, 0.48H, ArH) 7.77 (d, *J* = 2.3 Hz, 0.39H, ArH), 7.85 (d, *J* = 2.3 Hz, 0.13H, ArH), 9.72 (br, OH keto); ^{13}C NMR δ ($(CD_3)_2SO$) 25.8, 27.0, 35.3, 36.0, 41.2, 42.6, 100.5, 102.2, 103.5, 104.9, 118.1, 118.2, 120.9, 121.0, 121.1, 121.2, 125.8, 126.1, 127.2, 127.4, 127.9, 128.0, 128.3, 131.2, 143.3, 146.9, 157.6, 158.1, 158.8, 159.3; HRMS (TOF ES$^+$) m/z 399.0163 (M+Na$^+$), calc. for $C_{19}H_{14}O_4Cl_2Na^+$ 399.0167.



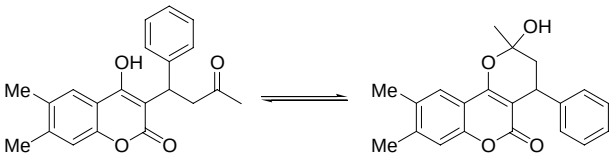
4-Hydroxy-7-methoxy-3-(3-oxo-1-phenyl-butyl)-chromen-2-one (1m).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.8 and 8.3 min). ^{1}H NMR ($CDCl_3$) δ 1.66 (s, 1.36H, CH_3 ketal), 1.71 (s, 1.36H, CH_3 ketal), 1.95-2.04 (m, 0.42H, CH_2 ketal), 2.30 (s, 0.28H, CH_3 keto) 2.39-2.56 (m, 1.36H, CH_2 ketal), 3.14 (s, 0.73H, OH ketal), 3.84 (s, 0.42H, OCH_3 keto), 3.85 (s, 1.36H, OCH_3 ketal), 3.88 (s, 1.36H, OCH_3 ketal), 4.13 (dd, *J* = 6.8, 11.4 Hz, 0.43H, CH ketal), 4.26 (dd, *J* = 2.9, 7.1 Hz, 0.43H, CH ketal), 4.66 (dd, *J* = 1.8, 10.3 Hz, 0.14H, CH keto), 6.75-6.89 (m, 2H, ArH) 7.21-7.35 (m, 5H, ArH), 7.70 (d, *J* = 9.3 Hz, 0.43H, ArH), 7.78 (d, *J* = 9.8 Hz, 0.43H, ArH), 7.83 (d, *J* = 8.8 Hz, 0.14H, ArH), 9.40 (s, 0.12H, OH keto); ^{13}C NMR ($CDCl_3$) δ 27.3, 27.8, 27.9, 34.6, 35.2, 40.3, 42.8, 42.9, 55.6, 55.7, 55.8, 98.6, 99.2, 99.3, 99.8, 99.9, 100.2, 100.6, 101.2, 108.8, 109.2, 112.1, 112.3, 112.4, 123.7, 123.8, 124.2, 126.4, 127.0, 127.1, 127.2, 128.0, 128.2, 128.6, 129.0, 142.1, 143.8, 154.4, 154.6, 160.0, 160.5, 162.4, 162.5, 162.9, 163.0; HRMS (TOF ES$^+$) m/z 361.1052 (M+Na$^+$), calc. for $C_{20}H_{18}O_5Na^+$ 361.1052.



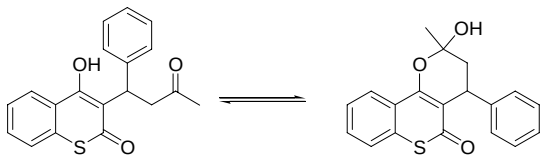
7-Fluoro-4-hydroxy-3-(3-oxo-1-phenyl-butyl)-chromen-2-one (1n).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.3 and 5.9 min). ^{1}H NMR ($CDCl_3$) δ 1.65 (s, 1.13H, CH_3 ketal), 1.70 (s, 1.5H, CH_3 ketal), 1.97 (dd, *J* = 11.2, 13.5 Hz, 0.48H, CH_2 ketal) 2.28 (s, 0.37H, CH_3 keto), 2.37-2.55 (m, 1.41H, CH_2 ketal), 3.22-3.35 (br, 0.95H, OH ketal), 3.82 (dd, *J* = 10.5, 19.9 Hz, 0.12H, CH_2 keto), 4.11 (dd, *J* = 6.8, 11.4 Hz, 0.49H, CH ketal), 4.24 (dd, *J* = 2.9, 6.5 Hz, 0.44H, CH ketal), 4.65 (dd, *J* = 2.6, 9.9, Hz, 0.07H, CH keto), 6.90-7.05 (m, 2H, ArH), 7.18-7.33 (m, 6H, ArH), 7.76-7.94 (m, 1H, ArH); ^{13}C NMR ($(CD_3)_2SO$) δ 25.8, 27.2, 35.1, 36.0, 99.9, 101.1, 101.7, 102.5, 103.7, 103.9, 111.8, 112.0, 112.5, 112.6, 124.9, 125.0, 125.7, 126.0, 127.1, 127.3, 127.9, 128.3, 143.7, 143.8, 153.4, 153.6, 158.6, 159.2, 160.1, 160.6, 162,5, 165.0; HRMS (TOF ES$^+$) m/z 349.0854 (M+Na$^+$), calc. for $C_{19}H_{15}O_4FNa^+$ 349.0852.



4-Hydroxy-6,7-dimethyl-3-(3-oxo-1-phenyl-butyl)-chromen-2-one (1o).

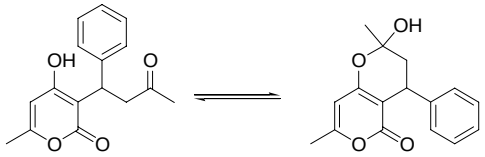
The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.3 and 6.3 min). hemiketalized form which gives rise to diastereomers. ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 1.36H, CH_3 ketal), 1.68 (s, 1.36H, CH_3 ketal), 1.98 (m, 0.45H, CH_2 ketal), 2.28 (s, 1.5H, $ArCH_3$), 2.29 (s, 1.5H, $ArCH_3$), 2.32 (s, 0.28H CH_3 keto), 2.33 (s, 1.5H, $ArCH_3$), 2.36 (s, 1.5H, $ArCH_3$), 2.38-2.55 (m, 1.36H, CH_2 ketal), 3.22 (br s, 0.36H, OH ketal), 3.33-3.38 (m, 0.09H, CH_2 keto), 3.56 (br s, 0.45H OH ketal), 3.85 (dd, *J* = 9.8, 19.6 Hz, 0.09H, CH_2 keto), 4.15 (dd, *J* = 6.6, 11.3 Hz, 0.45H, CH ketal), 4.26 (dd, *J* = 3.3, 6.8 Hz, 0.45H, CH ketal), 4.68 (dd, *J* = 1.9, 9.8 Hz, 0.09H, CH keto), 6.98 (s, 0.45H, ArH ketal), 7.03 (s, 0.09H, ArH keto), 7.10 (s, 0.45H, ArH ketal), 7.18-7.34 (m, 5H, ArH), 7.51 (s, 0.45H, ArH ketal), 7.61 (s, 0.45H, ArH ketal), 7.65 (s, 0.09H, ArH keto), 9.40 (br, 0.09H, OH keto); ^{13}C NMR ($CDCl_3$) δ 19.3, 19.4, 20.2, 20.3, 27.3, 27.8, 34.7, 35.4, 40.4, 42.9, 99.3, 100.3, 100.7, 102.9, 113.1, 113.5, 116.6, 117.0, 122.5, 123.0, 126.4, 127.0, 127.1, 127.2, 128.6, 129.0, 132.3, 132.9, 141.3, 142.0, 142.1, 143.9, 151.1, 151.3, 159.8, 160.3, 162.5, 163.0; HRMS (TOF ES$^+$) m/z 359.1250 (M+Na$^+$), calc. for $C_{21}H_{20}O_4Na^+$ 359.1259.



4-Hydroxy-3-(3-oxo-1-phenyl-butyl)-thiochromen-2-one (1p).

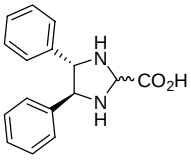
The compound was isolated as a yellow oil after FC in Et_2O/CH_2Cl_2, but solidified upon standing. The product was found to exist predominantly a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.4 and 6.8 min). ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 1.50H, CH_3 ketal), 1.69 (s, 1.50H, CH_3 ketal), 1.96-2.06 (m, 0.50H, CH_2 ketal), 2.32-2.57 (m, 1.50H, CH_2 ketal), 3.23 (br s, 0.50H, OH position is concentration dependent), 3.48 (br s, 0.50H, OH position is concentration dependent), 4.28 (dd, *J* = 7.2, 10.8 Hz, 0.50H, CH ketal), 4.47 (dd, *J* = 3.6, 6.4 Hz, 0.50H, CH ketal), 7.13-7.55 (m, 8H, ArH), 8.18 (d, *J* = 8.1 Hz, 0.50H, ArH), 8.26 (d, *J* = 8.1 Hz, 0.50H, ArH); ^{13}C NMR ($CDCl_3$) δ 27.6, 28.0, 34.3, 36.2, 39.6, 42.5, 98.4, 99.9, 112.5, 115.6, 123.5, 123.9, 125.0, 125.1, 125.3, 125.8, 125.9, 126.1, 126.2, 126.3, 126.8, 127.0, 128.5,

129.1, 129.5, 129.6, 130.0, 135.6, 145.7 141.9, 144.3 159.4, 160.2, 183.2, 183.6; HRMS (TOF ES^+) m/z 347.0719 ($M+Na^+$), calc. for $C_{19}H_{16}O_3SNa^+$ 347.0718.



4-Hydroxy-6-methyl-3-(3-oxo-1-phenyl-butyl)-pyran-2-one (1q).

The compound was isolated as a colorless solid after FC in Et_2O/CH_2Cl_2. The product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no pseudo-diastereomers are observed during HPLC analysis (τ = 4.2 and 5.3 min). ^1H NMR ($CDCl_3$) δ 1.53 (s, 1.20H, CH_3 ketal), 1.55 (s, 1.20H, CH_3 ketal), 1.87 (dd, *J* = 11.6, 14.0 Hz, 0.52H, CH_2 ketal), 2.07 (s, 0.60H, CH_3 keto), 2.19 (s, 1.20H, CH_3 ketal), 2.20 (s, 0.60H, CH_3 keto), 2.25 (s, 1.20H, CH_3 ketal), 2.27-2.45 (m, 1.28H, CH_2 ketal), 3.10-3.30 (br, 0.8H, OH ketal), 3.69 (dd, *J* = 9.6, 18.0 Hz, 0.20H, CH_2 keto), 4.00 (dd, *J* = 8.0, 11.6 Hz, 0.40H, CH ketal), 4.11 (dd, *J* = 3.2, 6.8 Hz, 0.40H, CH ketal), 4.61 (br d, *J* = 5.6 Hz, 0.20H, CH keto), 5.69 (s, 0.20H, C=CH keto), 5.78 (s, 0.40H, C=CH ketal), 5.86 (s, 0.40H, C=CH ketal), 7.14-7.35 (m, 5H, ArH); ^{13}C NMR ($CDCl_3$) δ 19.7, 19.8, 27.4, 27.9, 30.1, 33.6, 34.5, 34.7, 40.0, 42.5, 45.6, 98.3, 98.6, 100.1, 100.6, 100.7, 101.0, 104.1, 126.3, 126.8, 126.9, 127.0, 127.8, 128.1, 128.4, 129.0, 141.4, 142.1, 143.1, 160.5, 161.0, 161.5, 163.6, 164.2, 164.6, 166.1, 210.2; HRMS (TOF ES^+) m/z 295.0945 ($M+Na^+$), calc. for $C_{16}H_{16}O_4Na^+$ 295.0946.



(4*S*,5*S*)-diphenyl-imidazolidine-2-carboxylic acid (4c).

To a solution of commercially available (*S*,*S*)-diphenylethanediamine (636.9 mg, 3.0 mmol) in 50 ml CH_2Cl_2 was added commercially available glyoxylic acid monohydrate (276.2 mg, 3.0 mmol) and the reaction mixture was stirred for 15 hours in a closed vessel. The solvent was removed by rotary evaporation affording a quantitative yield of (4*S*,5*S*)-diphenyl-imidazolidine-2-carboxylic acid **4c** as a 1:1 mixture of diastereomers obtained as a colorless bench-stable powder which was dried further under vacuum. The catalyst was found to retain undiminished catalytic activity even after more than a year of storage.

^1H NMR ($(CD_3)_2CO$) δ 4.01 (d, J = 9.0 Hz, 1H, PhCH), 4.30 (d, J = 9.0 Hz, 1H, PhCH), 5.29 (s, 1H, aminal-H), 7.09-7.11 (m, 3H, NH and OH), 7.21-7.28 (m, 10H, ArH); ^{13}C NMR ($(CD_3)_2SO$) δ 55.0, 56.0, 68.1, 69.2, 74.6, 127.5, 127.7, 127.9, 128.4, 128.5, 137.9, 138.5, 171.4.

[i] It should be noted that since most of the compounds exist in only about 10% keto form, the signals arising from quarternary carbons of the keto form are not observed in all cases.

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