Supplementary Information

Synthesis of a-hydroxycinnamic acids (5)

α-hydroxycinnamic acids **5a,b** were commercially available and **5g** was prepared by a literature procedure.[1]

Ethyl 3-(4-chlorophenyl)- 3-cyano-2-oxopropanoate (4c). A solution of NaOEt (1.98 g, 29 mmol) in absolute EtOH (25 cm^3) was treated with diethyl oxalate (3.86 g, 26.4 mmol) and then a solution of aryl acetonitrile **3c** (4g, 26.4 mmol) was added dropwise. After 19 h (TLC monitoring) the mixture was acidified (HCl, 1M). The precipitated yellow solid (5.07 g, 76%) was filtered, washed with water and dried, mp 140 °C (from toluene); ν_{max}(KBr)/cm^{-1} 3200, 2200 and 1735; d_H(300 MHz; $CDCl_3$; Me_4Si) 7.82 (2 H, d, *J* 8.79, ArH), 7.40 (2 H, d, *J* 8.79, ArH), 4.55 (2 H, q, *J* 7.14, CH_2) and 1.50 (3 H, t, *J* 7.14, CH_3); δ_C (300 MHz; $CDCl_3$; Me_4Si) 163.07, 148.67, 135.24, 130.32, 129.25, 128.76, 116.70, 95.87, 64.98, and 13.90.

Ethyl 3-(4-trifluoromethylphenyl)- 3-cyano-2-oxopropanoate (4f). By the same procedure, **3f** (0.5 g, 2.7 mmol), NaOEt (0.238 g, 3.513 mmol) and diethyl oxalate (0.524 g, 2.702 mmol) yielded **4f** (0.6 g, 78%) as a yellow solid, mp 162-164 °C ; ν_{max}(KBr)/cm^{-1} 3200, 2200, 1735 and 1330; d_H(300 MHz; $CDCl_3$; Me_4Si) 7.98 (2 H, d, *J* 9.52, ArH), 7.69 (2 H, d, *J* 9.52, ArH), 4.57 (2 H, q, *J* 7.14, CH_2) and 1.51 (3 H, t, *J* 7.14, CH_3).

Ethyl 3-cyano-3-(4-methylphenyl)-2-oxopropanoate (4h). By the same procedure, **3h** (8 g, 60.98 mmol), NaOEt (4.57g, 67 mmol) and diethyl oxalate (8.91 g, 60.98 mmol) yielded **4h** (10.3 g, 73%) as a yellow solid, mp 94 °C (from hexane); ν_{max}(KBr)/cm^{-1} 3350, 2230 and 1700; d_H(300 MHz; $CDCl_3$; Me_4Si) 7.75 (2 H, d, *J* 8.25, ArH), 7.21 (2 H, d, *J* 8.25, ArH), 4.50 (2 H, q, *J* 7.14, CH_2), 2.36 (3 H, s, CH_3) and 1.46 (3 H, t, *J*

7.14, CH_3); δ_C (300 MHz; $CDCl_3$; Me_4Si) 163.11, 148.14, 139.38, 129.11, 128.79, 127.85, 117.06, 96.76, 64.49, 21.16 and 13.77.

3-(4-chlorophenyl)-2-oxo-propanoic acid (5c). Cold glacial acetic acid (20 cm^3) was added slowly to concentrated sulphuric acid (37.5 cm^3). The solid ester **4c** (4 g, 15.89 mmol), was added in portions to the mixture, and the resulting solution was stirred at room temperature until total disappearance of the starting ester (TLC). After cooling to 0 ºC, the reaction mixture was quenched with water (150 cm^3 per 10 g of starting ester) and then was refluxed until decarboxylation was complete. The solid formed was filtered, washed with water and dried, yielding **5c** (2.97 g, 94%) as a yellow solid, mp 208-209 °C; ν_{max}(KBr)/cm^{-1} 3600-2200, 3490 and 1675; d_H(300 MHz; DMSO-*d_6*; Me_4Si) 13.21 (1 H, br s, COOH), 9.47 (1 H, br s, OH), 7.78 (2 H, d, *J* 8.54, ArH), 7.40 (2 H, d, *J* 8.54, ArH) and 6.40 (1 H, s, vinyl); δ_C (300 MHz; DMSO-*d_6*; Me_4Si) 166.09, 142.47, 133.93, 131.34, 130.81, 128.32 and 108.16.

3-(4-trifluoromethylphenyl)-2-oxopropanoic acid (5f). By the same procedure, **4f** (5.12 g, 17.96 mmol), yielded **5f** (3.99 g, 96%) as a white solid, mp 192-94 °C (from benzene); ν_{max}(KBr)/cm^{-1} 3640-2250, 3450, 1680 and 1315; d_H(300 MHz; DMSO-*d_6*; Me_4Si) 9.81 (1 H, s, OH), 7.95 (2 H, d, *J* 9.52, ArH), 7.69 (2 H, d, *J* 9.52, ArH) and 6.46 (1 H, s, vinyl).

3-(4-methylphenyl)-2-oxo-propanoic acid (5h). By the same procedure, **4h** (0,5 g, 2.16 mmol), yielded **5h** (0.33 g, 86%) as a yellow solid, mp 181 °C; ν_{max}(KBr)/cm^{-1} 3650-2300, 3500 and 1700; d_H(300 MHz; DMSO-*d_6*; Me_4Si) 9.10 (1 H, s, OH), 7.65 (2 H, d, *J* 7.94, ArH), 7.16 (2 H, d, *J* 7.94, ArH), 6.37 (1 H, s, vinyl) and 2.29 (3 H, s, CH_3); δ_C (300 MHz; DMSO-*d_6*; Me_4Si) 166.38, 141.10, 136.57, 132.1, 129.22, 128.92, 109.71 and 20.89.

N-[4-(2-methyl-5-oxooxazol-4-ylidenemethyl)-phenyl]-acetamide (7d). Aldehyde **6d** (4.39 g, 30.2 mmol), *N*-acetylglycine (4.24 g, 36.24 mmol), anhydrous NaOAc (3.22 g, 39.26 mmol) and Ac_2O (15.4 g, 151 mmol) were mixed and stirred at 120 ºC until the reaction was complete (6 h). The mixture was cooled to 0º C and water (1 cm^3 per 10 mmol of starting aldehyde) was added. The resulting precipitated was filtered and washed with 50% aq EtOH and acetone, to yield **7d** (4.50 g, 61%) as a white solid, mp 225-226 °C (from EtOH); ν_{max}(KBr)/cm^{-1} 3320, 1800, 1775, 1725, 1670 and 1655; d_H(300 MHz; DMSO-d_6; Me_4Si) 10.29 (1 H, s, NH), 8.13 (2 H, d, *J* 8.50, ArH), 7.70 (2 H, d, *J* 8.50, ArH), 7.15 (1 H, s, vinyl), 2.38 (3 H, s, CH_3) and 2.08 (3 H, s, CH_3).

4-(4-*tert*-butilbenzylidene)-2-methyl-4*H*-oxazol-5-ona (7e). By the same procedure, **6e** (3.25 g, 20.03 mmol) yielded **7e** (2.7 g, 55%) as a yellow solid, mp 231-233 °C; d_H(300 MHz; DMSO-d_6; Me_4Si) 8.10 (2 H, d, *J* 7.90, ArH), 7.51 (2 H, d, *J* 7.90, ArH), 7.19 (1 H, s, vinyl), 2.38 (3 H, s, CH_3) and 1.30 (9H, s, $3CH_3$)

3-(4-aminophenyl)-2-oxopropanoic acid hydrochloride (5d). A mixture of **7d** (4.5 g, 18.4 mmol) and 3N HCl (100 cm^3) was refluxed for 6 h. After cooling to room temperature, the resulting precipitated was filtered, yielding **5d** (3.85 g, 97%) as a white solid; ν_{max}(KBr)/cm^{-1} 3650-2300, and 1735; d_H(300 MHz; CD_3OD; Me_4Si) 7.93 (2 H, d *J* 8.50, ArH), 7.37 (2 H, d, *J* 8.50, ArH) and 6.50 (1 H, s, vinyl).

3-(4-*tert*-butylphenyl)-2-oxopropanoic acid (5e). By the same procedure, **7e** (0.522 g, 2.0 mmol) yielded **5e** (0.403 g, 92%) as a white solid, mp 184-186 °C (from benzene); ν_{max}(KBr)/cm^{-1} 3690-2400, 3475 and 1725; d_H(300 MHz; DMSO-d_6; Me_4Si) 9.13 (1 H, s, OH), 7.68 (2 H, d, *J* 8.50, ArH), 7.37 (2 H, d, *J* 8.50, ArH), 6.37 (1 H, s, vinyl) and 1.27 (9 H, s, 3 CH_3).

Synthesis of a-ketoesters (1); **General Procedure A**. To a solution of α-hydroxycynnamic acid **5** (5 mmol) in DMF (20 cm^3) at 0 ºC was added DBU (5 mmol)

and MeI (25 mmol) and the mixture was stirred for 2.5 h at the same temperature. The reaction mixture was acidified with 1 M HCl and extracted with Et_2O (2 x 25 cm^3). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to dryness. The obtained compounds were used in the following step without further purification.

General Procedure B. A solution of α-hydroxycinnamic acid (**5**) in methanol at 0 ºC was saturated with HCl gas and stirred until total disappearance of the starting material (TLC). The obtained compounds were used in the following step without further purification.

Methyl 3-phenyl-2-oxopropanoate (1a). By method A, **5a** (2 g, 12.18 mmol), DBU (1.85 g, 12.18 mmol) and MeI (8.65 g, 60.9 mmol) yielded **1a** (1.99 g, 92%) as a yellow oil; ν_{max}(film)/cm^{-1} 3380, and 1690; δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.05 (1 H, s, OH), 7.76 (2 H, d, *J* 9.18, ArH), 7.30 (3 H, m, ArH), 6.53 (1 H, s, vinyl) and 3.92 (3 H, s, CH_3).

Methyl 3-(4-hydroxyphenyl)-2-oxopropanoate (1b). By method A, **5b** (1.32 g, 7.32 mmol), DBU (1.11 g, 7.32 mmol) and MeI (5.2 g, 36.60 mmol) yielded **1b** (1.131 g, 86%); δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.68 (2 H, d, *J* 8.52, ArH), 6.85 (2 H, d, *J* 8.52, ArH), 6.49 (1 H, s, vinyl), 6.28 (1 H, s, OH) and 3.90 (3 H, s, CH_3).

Methyl 3-(4-chlorophenyl)-2-oxopropanoate (1c). By method A, **5c** (0.473 g, 2.38 mmol), DBU (0.362 g, 2.38 mmol) and MeI (1.69 g, 11.9 mmol) yielded **1c** (0.45 g, 89%); ν_{max}(KBr)/cm^{-1} 3400, and 1690; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.69 (2 H, d, *J* 8.81, ArH), 7.32 (2 H, d, *J* 8.81, ArH), 6.67 (1 H, s, OH), 6.47 (1 H, s, vinyl) and 3.91 (3 H, s, CH_3).

Methyl 3-(4-aminophenyl)-2-oxopropanoate hydrochloride (1d). By method B, **5d** (3.85 g, 17.85 mmol) yielded **1d** (4.0 g, 99%); δ_H(300 MHz; CD_3OD; Me_4Si) 7.94 (2

H, d, *J* 8.55, ArH), 7.38 (2 H, d, *J* 8.55, ArH), 6.49 (1 H, s, vinyl) and 3.87 (3 H, s, CH_3).

Methyl 3-(4-*tert*-butylphenyl)-2-oxopropanoate (1e). By method B, **5e** (3.0 g, 13.62 mmol) yielded **1e** (3.19 g, 100%) as a white solid; $_{max}$(KBr)/cm^{-1} 3400, 2950 and 1675; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.70 (2 H, d, *J* 8.25, ArH), 7.39 (2 H, d, *J* 8.25, ArH), 6.52 (1 H, s, vinyl), 3.91 (3 H, s, CH_3) and 1.32 (9 H, s, $3CH_3$).

Methyl 3-(4-trifluoromethylphenyl)-2-oxopropanoate (1f). By method A, **5f** (2.205 g, 9.50 mmol), DBU (1.45 g, 9.50 mmol) and MeI (6.75 g, 47.5 mmol) yielded **1f** (1.60 g, 68%) as a white solid, mp 122-124 ºC; ν_{max}(KBr)/cm^{-1} 3400, 1695 and 1440; δ_H(300 MHz; $CDCl_3$; Me_4Si) 7.85 (2 H, d, *J* 7.50, ArH), 7.61 (2 H, d, *J* 7.50, ArH), 6.60 (1 H, s, OH), 6.53 (1 H, s, vinyl) and 3.94 (3 H, s, CH_3).

Methyl 3-(4-methoxyphenyl)-2-oxopropanoate (1g). By method A, **5g** (1.745 g, 8.98 mmol), DBU (1.367, 8.98 mmol) and MeI (6.37 g, 44.9 mmol) yielded **1g** (1.70 g, 91%) as a yellow oil; δ_H(300 MHz; DMSO-d_6; Me_4Si) 9.28 (1 H, s, OH), 7.73 (2 H, d, *J* 9.18, ArH), 6.93 (2 H, d, *J* 9.18, ArH), 6.41 (1 H, s, vinyl), 3.78 (3 H, s, CH_3) and 3.76 (3 H, s, CH_3).

Methyl 3-(4-methylphenyl)-2-oxopropanoate (1h). By method A, **5h** (2 g, 12.22 mmol), DBU (1.86 g, 12.22 mmol) and MeI (8.67 g, 61.1 mmol) yielded **1h** (1.70 g, 79%); ν_{max}(KBr)/cm^{-1} 3395, and 1695; δ_H(300 MHz; $CDCl_3$; Me_4Si) 8.02 (1 H, s, OH), 7.66 (2 H, d, *J* 7.80, ArH), 7.18 (2 H, d, *J* 7.80, ArH), 6.51 (1 H, s, vinyl), 3.91 (3 H, s, CH_3) and 2.35 (3 H, s, CH_3).

References

(1) Cagniant, D. Contribution a l´etude des acides phénylpyruviques para-substitués *Ann. Chim.* 1952, 442-457.

Table 2. Ab Initio 6-31G*\\3-21G Electrostatic Potential Atomic Charges for Butyrolactone I

Butyrolactone I *R*			Butyrolactone I *S*		
Atom number	Atom type	charge	Atom number	Atom type	charge
O1	OS	-0.425602	O1	OS	-0.539805
C2	C	0.718280	C2	C	0.786617
O3	O	-0.527768	O3	O	-0.543172
C4	C2	0.277611	C4	C2	0.158981
O5	OH	-0.589578	O5	OH	-0.565305
H6	HO	0.455408	H6	HO	0.430126
C7	C2	-0.261021	C7	C2	-0.038574
C8	CA	-0.135571	C8	CA	-0.124486
C9	CA	0.000000	C9	CA	0.000000
H10	HA	0.123665	H10	HA	0.110948
C11	CA	-0.327343	C11	CA	-0.310246
H12	HA	0.191613	H12	HA	0.189966
C13	CA	0.439999	C13	CA	0.403659
O14	OH	-0.603085	O14	OH	-0.588900
H15	HO	0.437806	H15	HO	0.429373
C16	CA	-0.370203	C16	CA	-0.328550
H17	HA	0.161549	H17	HA	0.152504
C18	CA	-0.014645	C18	CA	-0.022854
H19	HA	0.141254	H19	HA	0.109849
C20	80	0.100603	C20	80	0.127792
C21	C	0.784560	C21	C	0.697492
O22	O	-0.540530	O22	O	-0.542851
O23	OS	-0.288738	O23	OS	-0.281889
C24	CT	-0.108880	C24	CT	-0.154597
H25	HC	0.091762	H25	HC	0.113236
H26	HC	0.091762	H26	HC	0.113236
H27	HC	0.091762	H27	HC	0.113236
C28	CT	-0.018533	C28	CT	-0.018855
H29	HC	0.038545	H29	HC	0.043116
H30	HC	0.074913	H30	HC	0.082352
C31	CA	-0.043058	C31	CA	-0.040719
C32	CA	-0.156266	C32	CA	-0.200441
H33	HA	0.171062	H33	HA	0.176058
C34	CA	-0.277678	C34	CA	-0.309320
H35	HA	0.147156	H35	HA	0.149730
C36	C	0.298257	C36	C	0.319066
O37	OH	-0.596523	O37	OH	-0.608946
H38	HO	0.440574	H38	HO	0.442182
C39	CA	-0.014419	C39	CA	0.007245
C40	CA	-0.183335	C40	CA	-0.235126
H41	HA	0.147009	H41	HA	0.236851
C42	CT	-0.031407	C42	CT	0.054334
H43	HC	0.053139	H43	HC	0.049224
H44	HC	0.072577	H44	HC	0.071759
C45	C2	-0.236152	C45	C2	-0.357054
H46	HC	0.153788	H46	HC	0.145116
C47	C2	0.089317	C47	C2	0.084562
C48	CT	-0.180130	C48	CT	-0.167544
H49	HC	0.063309	H49	HC	0.056292
H50	HC	0.063309	H50	HC	0.056292
H51	HC	0.063309	H51	HC	0.056292
C52	CT	-0.361033	C52	CT	-0.175078
H53	HC	0.102533	H53	HC	0.062275
H54	HC	0.102533	H54	HC	0.062275
H55	HC	0.102533	H55	HC	0.062275

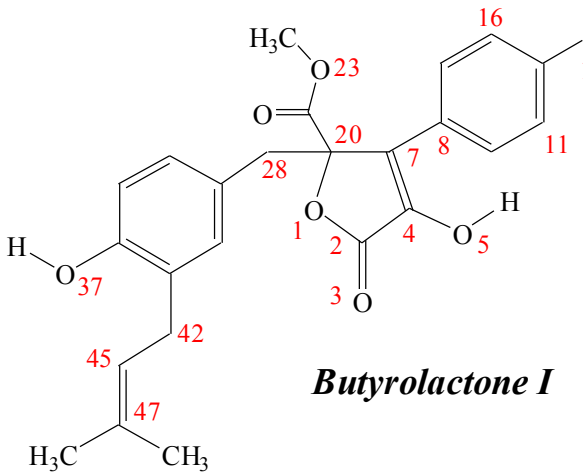
Table 3. Additional force field parameters for butyrolactone I

Bond	*K_r (Kcal/mol A^2)*	*r_{eq} (Å)*
C -80	317.0	1.522
C -C2	447.0	1.419
C2-80	317.0	1.510
C2-C2	549.0	1.350
C2-CT	317.0	1.510
C2-OH	450.0	1.364
C2-CA	350.0	1.485
C2-HC	367.0	1.080
CT-C2	317.0	1.510
80-CT	310.0	1.526
OS-80	320.0	1.410

Dihedral angle	*idivf*	*$V_n/2$ (Kcal/mol)*	*g (d*
X -C2-C2-X	4	4.00	180
X -C2-C -X	4	12.00	180
X -C2-OH-X	2	1.80	180
X -C2-CA-X	4	0.0	0.
X -OS-80-X	3	0.50	0.
X -CT-C2-X	6	0.00	0.
X -80-CT-X	9	1.40	0.
X -80-C2-X	6	0.00	0.
X -80-C -X	6	0.00	0.

Angle	*K_θ (Kcal/mol rad^2)*	*r_{eq} (Å)*
O -C -C2	80.0	123.72
C -C2-OH	70.0	124.25
C2-C2-CA	70.0	123.96
C -C2-C2	70.0	106.21
C2-OH-HO	50.0	111.36
OS-C -C2	60.0	110.63
OS-80-C	60.0	107.17
80-C -O	60.0	124.49
80-C –OS	60.0	109.08
80-CT-HC	60.0	110.07
80-CT-CA	60.0	113.45
C –OS-80	60.0	108.27
OS-80-C2	60.0	104.83
OS-80-CT	60.0	108.59
OS-CT-HC	60.0	109.85
OH-C2-C2	60.0	129.53
C2-C2-80	60.0	110.04
C2-CA-CA	60.0	120.17
C2-80-C	60.0	111.69
C2-80-CT	60.0	112.39
CA-C2-80	60.0	125.98
C -80-CT	60.0	111.80
C –CA-CT	60.0	121.08
CA-CT-C2	60.0	109.99
CT-C2-HC	60.0	114.30

Van der Waals	*R* (Å)*	*€ (Kcal/mol)*
C2	1.9080	0.0860



Butyrolactone I

Table 4. Autodock parameters used for the flexible docking.

Genetic algorithm (GA) and Lamarckian Genetic Algorithm (LGA) parameters.		
ga_pop_size	***Number of individuals in population***	50
ga_num_evals	Maximum number of energy evaluations	250000
ga_num_generations	Maximum number of generations	27000
ga_elitism	Num. of top individuals that automatically	1
ga_mutation_rate	Rate of gene mutation	0.02
ga_crossover_rate	Rate of crossover	0.80
ga_window_size	Num. of generations for picking worst individual	10
ga_cauchy_alpha	Mean of cauchy distribution for gene mutation	0
ga_cauchy_beta	Variance of cauchy distribution for gene mutation	1
	Local search parameters	
sw_max_its	***Number of iterations of Solis & Wets local search***	300
sw_max_succ	Number of consecutive successes before changing rho	4
sw_max_fail	Number of consecutive failures before changing rho	4
sw_rho	Size of local search space to sample	1.0
sw_lb_rho	Lower bound on rho	0.01
ls_search_freq	Probability of performing local search on an indiv.	0.06