Chemo-enzymatic Baeyer-Villiger oxidation of 4-methylcyclohexanone *via* kinetic resolution of racemic carboxylic acids: direct access to enantioenriched lactone

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Materials

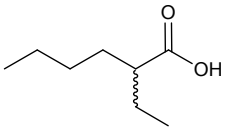
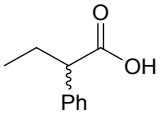
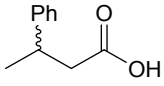
Cyclohexanones, carboxylic acids, esters and native CALB [5, 000 LU/G] were purchased from Sigma Aldrich. Novozyme-435 was donated by Novozymes. Synthesis of 3-phenylcyclobutanone was performed according to a previously described method (A. Drożdż, A. Foreiter and A. Chrobok, *Synlett*, 2014, **25**, 559).

Instrumentation

^{1}H-NMR and ^{13}C-NMR spectra of the lactone were recorded at 300 MHz in $CDCl_3$ (Varian Unity Inova plus spectrometer with a TMS internal standard). GC analysis was performed using a Perkin Elmer Clarus 500 chromatograph with a SUPELCOWAX™ 10 column (30 m×0.2 mm×0.2 μm) with *n*-decane as an external standard or Astec CHIRALDEX™ G-TA capillary column (30 m×0.25 mm×0.12 μm).

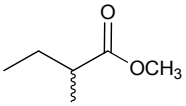
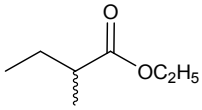
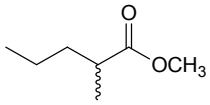
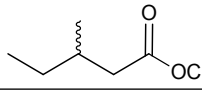
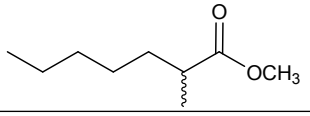
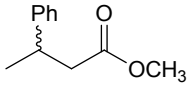
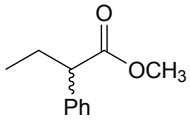
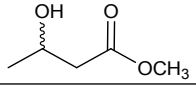
General method for Baeyer-Villiger oxidation: the ketone (0.5 mmol), carboxylic acid (1 mmol) and 1 ml of toluene were introduced into a 25 ml round-bottom flask and the contents of the flask was shaken. Next, 0.1 g of native CALB was introduced, and 30% H_2O_2 (1 mmol) was added dropwise. The flask was sealed with a septum and mixed in a thermostatted shaker (±0.5ºC) with orbital stirring at 250 rpm at 18 and 25°C for 3-8 days, depending on the reaction rate. Periodically, 15 μl of the sample diluted with 1 ml of dichloromethane was collected during the reaction to monitor the progress of the reaction (yield and *ee*) utilising GC (SUPELCOWAX™ 10 column (30 m×0.2 mm×0.2 μm) with *n*-decane as an external standard or Astec CHIRALDEX™ G-TA capillary column (30 m×0.25 mm×0.12 μm)). When the reaction was completed, the post-reaction mixture was washed with 5 ml of a 10% $NaHCO_3$ solution in water, dried over anhydrous $MgSO_4$ and concentrated under vacuum. The yield of 4-methylcaprolactone after purification by column chromatography with a hexane:ethyl acetate ratio of 4:1 as an eluent was 93%.

Table S1 The influence of the structure of peracid precursor on the yield and *ee* of (*R*)-4-methylcaprolactone [a]

No.	Carboxylic acid	25°C		18°C	
		Yield [%]	*ee (R)* [%]	Yield [%]	*ee* (*R*) [%]
1		21 (8 days)	37	16 (8 days)	41
2		47 (3 days)	40	82 (8 days)	57
3		31 (4 days)	48	33 (8 days)	47

[a] *Reaction conditions:* 4-methylcyclohexanone (0.5 mmol), 30% aq. H_2O_2 (1 mmol), acid (1 mmol), 0.10 g of CALB, toluene (1 ml), yields and *ee* determined by GC.

Table S2 The influence of the structure of peracid precursor on the yield and *ee* of (*R*)-4-methylcaprolactone [a]

No.	Ester	25°C	
		Yield [%]	*ee (R)* [%]
1		92 (8 days)	66
2		90 (8 days)	65
3		86 (8 days)	59
4		95 (8 days)	55
5		39 (7 days)	54
6		12 (7 days)	34
7		9 (7 days)	23
8		23 (7 days)	24

[a] *Reaction conditions:* 4-methylcyclohexanone (0.5 mmol), 30% aq. H_2O_2 (1 mmol), ester (1 mmol), 0.10 g of CALB, 25 °C, toluene (1 ml), yields and *ee* determined by GC.

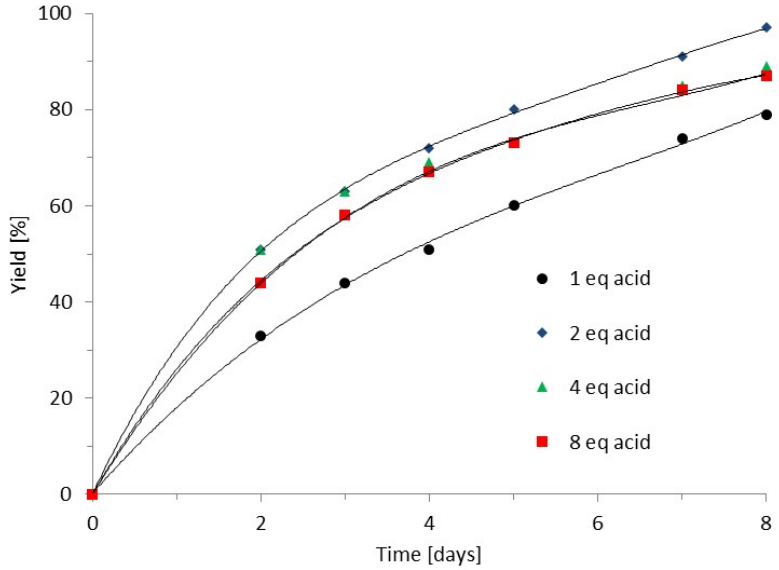


Fig. S1. The influence of the amount of (±)-4-methyloctanoic acid on the yield of 4-methylcaprolactone obtained during the chemo-enzymatic oxidation of 4-methylcyclohexanone (0.5 mmol) with 30% aq. H_2O_2 (1 mmol) in the presence of 0.10 g of CALB at 18 °C in toluene (1 ml).

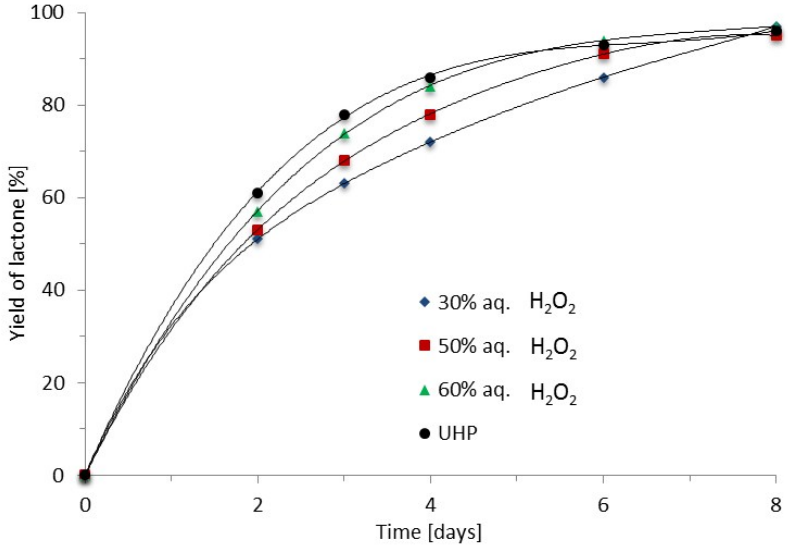


Fig. S2. The influence of the structure of primary oxidant on the yield of 4-methylcaprolactone obtained during the chemo-enzymatic oxidation of 4-methylcyclohexanone (0.5 mmol) in the presence of oxidant (1 mmol) and (±)-4-methyloctanoic acid (1 mmol) and 0.10 g of CALB at 18 °C in toluene (1 ml).

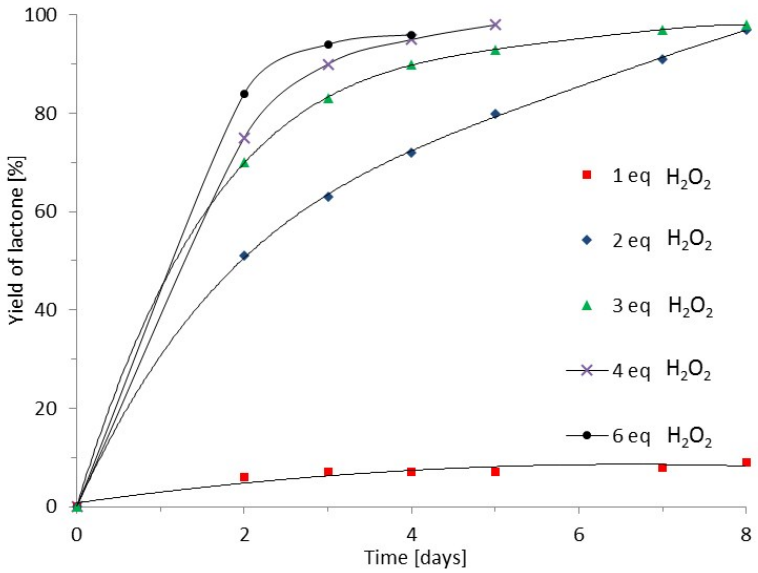


Fig. S3. The influence of the amount of 30% aq. H_2O_2 on the yield of 4-methylcaprolactone obtained during the chemo-enzymatic oxidation of 4-methylcyclohexanone (0.5 mmol) in the presence of (±)-4-methyloctanoic acid (1 mmol) and 0.10 g of CALB at 18 °C in toluene (1 ml).

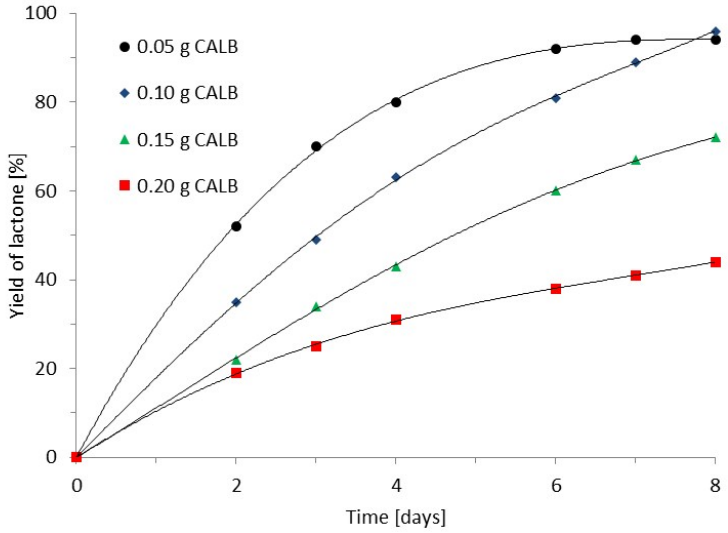


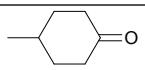
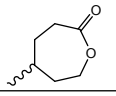
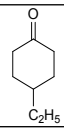
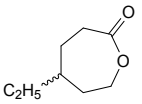
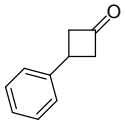
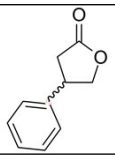
Fig. S4. The influence of the amount of CALB on the yield of 4-methylcaprolactone obtained during the chemo-enzymatic oxidation of 4-methylcyclohexanone (0.5 mmol) with 30% aq. H_2O_2 (1 mmol) in the presence of (±)-4-methyloctanoic acid (1 mmol) at 18 °C in toluene (1 ml).

Table S3 The influence of the solvent on the reaction [a]

No.	Solvent	V [ml]	Time [days]	Yield [%]	*ee* (*R*) [%]
1	toluene	0.5	8	95	87
	toluene	1.0	8	97	96
2	diethyl ether	1.0	6	79	37
	diethyl ether	1.0	7	79	48
	diethyl ether	1.0	8	79	56
3	hexane	1.0	6	86	40
	hexane	1.0	7	88	45
	hexane	1.0	8	89	55

[a] *Reaction conditions:* 4-methylcyclohexanone (0.5mmol), 30% aq. H_2O_2 (1 mmol), (±)-4-methyloctanoic acid (1mmol), 0.10g of CALB, 18 °C,

Table S4 The influence of the structure of ketone on the yield and *ee* of lactone [a]

No.	Ketone	Lactone	Time [h]	Yield [%]	*ee (R)* [%]
1			4 8	69 97	63 96
2			4 6	85 99	35 69
3			4 6	72 99	39 76

[a] *Reaction conditions:* ketone (0.5 mmol), 30% aq. H_2O_2 (1 mmol), (±)-4-methyloctanoic acid (1 mmol), 0.10 g of CALB, 18 °C, toluene (1 ml), yields and *ee* determined by GC.