

## Lactonization reactions through hydrolase-catalyzed peracid formation. Use of lipases for chemoenzymatic Baeyer-Villiger oxidations of cyclobutanones.

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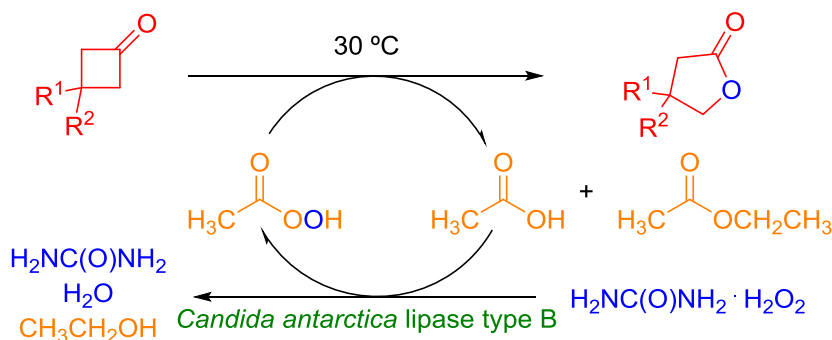
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### Graphical abstract:



**Abstract:** A *one-pot* chemoenzymatic method has been described for the synthesis of  $\gamma$ -butyrolactones starting from the corresponding ketones through a Baeyer-Villiger reaction. The approach is based on a lipase-catalyzed perhydrolysis for the formation of peracetic acid, which is the responsible for the ketone oxidation. Optimization studies have been performed in the oxidation of cyclobutanone, finding *Candida antarctica* lipase type B, ethyl acetate and urea-hydrogen peroxide complex as the best system. The relative ratio of these reagents has also been analyzed in depth. This synthetic approach has been successfully extended to a family of 3-substituted cyclobutanones in high substrate concentration, yielding the corresponding lactones with excellent isolated yields and purities, under mild reaction conditions and after a simple extraction protocol.

**Keywords:** Baeyer-Villiger reaction / *Candida antarctica* lipase type B / Cascade reactions / Cyclobutanones / Lactones

## 1. Introduction

Hydrolases are enzymes capable to naturally catalyze hydrolytic reactions for a vast number of organic compounds such as peptides, esters or amides.<sup>[1,2]</sup> Alternatively, and depending on the reaction conditions, they can also accelerate the reverse transformations leading to the corresponding esterification, aminolysis, ammonolysis, perhydrolysis, hydrazinolysis or thiolysis products, specially when working in non-aqueous media.<sup>[3,4]</sup> Within this class of enzymes, perhydrolases are able to efficiently catalyze perhydrolysis reactions for the formation of peracids,<sup>[5,6]</sup> but the unusual participation of lipases for global oxidative process has attracted the attention of different research groups in the last decade.<sup>[5,7,8]</sup> Thus, examples of lipase-mediated epoxidation,<sup>[9-14]</sup> Baeyer-Villiger reactions,<sup>[15-18]</sup> perhydrolysis of carboxylic acid and esters,<sup>[19]</sup> sequential Baeyer-Villiger reaction and ring-opening polymerization,<sup>[20]</sup> and also consecutive esterification and Baeyer-Villiger cascade reactions<sup>[21]</sup> have appeared in the literature, giving access to synthetically useful oxygenated heterocycles through clean and selective transformations under mild reaction conditions.

In this context, the synthesis of lactones is highly appealing because of their interesting properties as subunits for polymer industry, and their applications in medicinal chemistry, fragrance and food industry. Lipases provide useful possibilities for the synthesis of lactones by the proper combination of a peracid precursor, solvent and an oxidizing agent in mild reaction conditions,<sup>[7]</sup> avoiding the use and storage of peracids that are usually associated with explosion risks. This *in situ* formation of a peracid, commonly large aliphatic linear peracids or peracetic acid, provides an environmentally friendly alternative route to the desired oxygenated heterocycles.<sup>[22]</sup>

Examples described in the literature have been mainly focused on the oxidation of cyclopentanones and cyclohexanones.<sup>[15-18,23,24]</sup> Herein we have explored the possibility of using a cascade chemoenzymatic strategy for the production of  $\gamma$ -butyrolactones from cyclobutanones. With that purpose, different enzymes have been tested in order to find adequate oxidizing conditions, paying special attention to the oxygen source and the substrate concentration.

## 2. Experimental

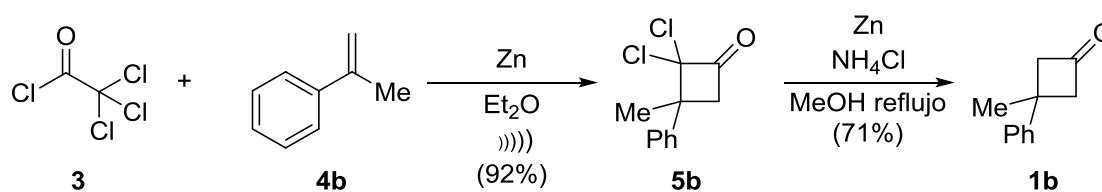
### 2.1. Material and methods

*Candida antarctica* lipase type B (CAL-B, Novozym-435, 7300 PLU/g) and *Rhizomucor miehei* lipase (RML, 150 IUN/g) were kindly gifted by Novo-Nordisk. *Pseudomonas cepacia* lipase supported on diatomite (PSL-SD, 23000 U/g), AK lipase from *Pseudomonas fluorescens* (AK, 23700 U/g) and *Candida rugosa* lipase (CRL, 1410 U/g) were acquired from Sigma-Aldrich. Other chemical reagents were used as purchased from Sigma-Aldrich, Acros or Fluka, without further additional purification. The only exceptions were phosphoryl chloride ( $\text{POCl}_3$ ) that was used freshly distilled, and distilled  $\text{Et}_2\text{O}$  and THF, which were dried over sodium under inert atmosphere using benzophenone as indicator.

NMR spectra were recorded on Bruker AV-300 and Bruker DPX-300 spectrometers (300.13 MHz for  $^1\text{H}$  and 75.5 MHz for  $^{13}\text{C}$ ). All chemical shifts ( $\delta$ ) are given in parts per million (ppm) and referenced to the residual solvent signal as internal standard. All coupling constants ( $J$ ) are reported in Hz. Mass spectra (MS) were recorded using a MAT-95 Finigan spectrometer by positive electrospray ionization ( $\text{ESI}^+$ ). High resolution mass spectra (HRMS) were obtained using a Bruker MicroQtof spectrometer by positive electrospray ionization ( $\text{ESI}^+$ ). Gas chromatography (GC) analyses were performed on a Hewlett Packard 6890 Series chromatograph equipped with FID. All the data have been included in the

supporting information file. IR spectra were recorded as thin films on NaCl plates on a Perkin-Elmer Spectrum 100 FT-IR and are reported in frequency of absorption ( $\text{cm}^{-1}$ ). Thin-layer chromatography (TLC) was conducted with Merck Silica Gel 60 F<sub>254</sub> precoated plates and visualized using a UV lamp and/or potassium permanganate stain. Column chromatography was performed using Merck Silica Gel 60 (230-400 mesh).

## 2.2. Typical procedure for the synthesis of 3-methyl-3-phenylcyclobutanone (**1b**)



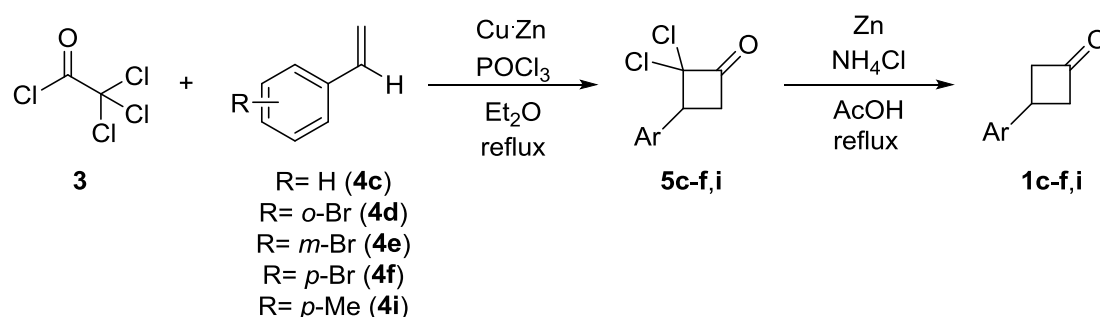
**Scheme 1.** Chemical synthesis of 3-phenyl-3-methylcyclobutanone (**1b**).

a) [2+2] cycloaddition reaction.<sup>[25]</sup> To a solution of  $\alpha$ -methylstyrene (**4b**, 650  $\mu\text{L}$ , 5.0 mmol) in dry  $\text{Et}_2\text{O}$  (50 mL), Zn (654 mg, 10.0 mmol) was added under inert atmosphere. The system was sonicated, while a solution of trichloroacetyl chloride (**3**, 837  $\mu\text{L}$ , 7.5 mmol) in dry  $\text{Et}_2\text{O}$  (25 mL) was carefully added under inert atmosphere, maintaining the bath temperature between 15 and 20  $^\circ\text{C}$ . Sonication was extended for an additional hour after the addition was completed, and after this time the reaction was stopped by filtration over celite. The reaction crude was washed with water ( $2 \times 25$  mL), an aqueous  $\text{NaHCO}_3$  saturated solution ( $5 \times 25$  mL) and brine (25 mL). The organic phase was dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent was evaporated under reduced pressure. The resulting crude was purified by column chromatography on silica gel (5%  $\text{EtOAc}$ /hexane), yielding the 2,2-dichloro-3-methyl-3-phenylcyclobutanone **5b** (92% yield).

b) Reduction with Zn. The 2,2-dichloro-3-methyl-3-phenylcyclobutanone (**5b**, 1.160 g, 5.06 mmol) was dissolved in MeOH (20 mL), and  $\text{NH}_4\text{Cl}$  was added until saturation. Then, Zn (1.987 g, 30.38 mmol) was added and the mixture stirred at 40  $^\circ\text{C}$  for 6 h. After this time,

the reaction was filtered over celite and the solvent was evaporated under reduced pressure. The reaction crude was redissolved in Et<sub>2</sub>O (100 mL) and washed with water (2 × 50 mL), an aqueous NaHCO<sub>3</sub> saturated solution (2 × 50 mL) and brine (50 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure. The resulting crude was purified by column chromatography on silica gel (10% EtOAc/hexane), yielding the cyclobutanone **1b** (71% yield; 65% global yield for the two steps). Colourless oil; *R<sub>f</sub>* (20% EtOAc/hexane): 0.68; IR (NaCl): ν 3059, 3026, 2958, 2921, 1785, 1602, 1496, 1445, 1381, 1080, 764 cm<sup>-1</sup>; <sup>1</sup>H RMN (CDCl<sub>3</sub>, 300.13 MHz): δ 1.62 (s, 3H, CH<sub>3</sub>), δ 3.07-3.17 (m, 2H, CHH), δ 3.42-3.53 (m, 2H, CHH), δ 7.23-7.42 (m, 5H) ppm; <sup>13</sup>C RMN (CDCl<sub>3</sub>, 75.5 MHz): δ 31.1 (CH<sub>3</sub>), δ 34.0 (C), δ 59.3 (2CH<sub>2</sub>), δ 125.7 (2CH), δ 126.3 (CH), δ 128.6 (2CH), δ 148.3 (C), δ 206.6 (CO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for (C<sub>11</sub>H<sub>12</sub>NaO) (M+Na)<sup>+</sup>: 183.0780, found: 183.0776.

### 2.3. Typical procedure for the synthesis of 3-arylcyclobutanones **1c-f,i**<sup>[26,27]</sup>



**Scheme 2.** General synthesis of  $\gamma$ -butyrolactones **1c-f,i**.

a) *Preparation of the Cu-Zn complex.* To a suspension of Zn (6.5 g, 99.4 mmol) in water (10 mL), a solution of CuSO<sub>4</sub>·5H<sub>2</sub>O (760 mg, 4.76 mmol) in water (5 mL) was added in two times. After one minute, the solid was filtered and washed with water (2 × 5 mL), acetone

(2 × 5 mL) and Et<sub>2</sub>O (2 × 5 mL). The resulting grey-black solid was dried in a Kugelrohr apparatus at 100 °C for 6 h, and stored under inert atmosphere.

*b) [2+2] cycloaddition reaction.* A suspension of the corresponding styrene **3c-f,i** (5.0 mmol) and Cu-Zn complex (1.31 g, 0.26 g/mmol styrene) in dry Et<sub>2</sub>O (20 mL) was prepared under inert atmosphere. A mixture composed by trichloroacetyl chloride (**3**, 1.116 mL, 10.0 mmol) and freshly distilled phosphoryl chloride (POCl<sub>3</sub>, 512 μL, 5.5 mmol) in dry Et<sub>2</sub>O (11 mL) was slowly added under inert atmosphere at room temperature, and once the addition was finished, the mixture was refluxed for 24 h. After this time, the mixture was left to cool down until room temperature, and filtered over celite. A major part of the Et<sub>2</sub>O was evaporated in the rotary evaporator, adding then hexane (100 mL). The mixture was vigorously stirred and then left unaltered, observing the formation of a precipitate. The supernatant was washed with an aqueous NaHCO<sub>3</sub> saturated solution (2 × 40 mL) and brine (40 mL). The organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent evaporated under reduced pressure, yielding the corresponding 2,2-dichloroketone **5c-f,i**.

*c) Reduction with Zn.* The previous reaction crude containing the dichlorinated cyclobutanone **5c-f,i** (5.0 mmol) was dissolved in glacial acetic acid (20 mL) and Zn (1.34 g, 20.0 mmol) was added. The reaction was refluxed for 12 h, and after this time water (25 mL) was added. The solution was extracted with Et<sub>2</sub>O (2 × 15 mL), the organic phases were combined and washed with an aqueous NaHCO<sub>3</sub> saturated solution (4 × 15 mL) and brine (2 × 15 mL). The resulting organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (10-20% EtOAc/hexane), yielding the cyclobutanones **1c-f,i** (12-50% isolated yield).

**3-Phenylcyclobutanone (1c).** 34% yield. Colourless oil; *R<sub>f</sub>* (20% EtOAc/hexane): 0.45; IR (NaCl): ν 3062, 3029, 2975, 2923, 1785, 1603, 1496, 1380, 1104, 780 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300.13 MHz): δ 3.10-3.22 (m, 2H, CHH), 3.35-3.47 (m, 2H, CHH), 3.51-3.65 (m,

<sup>1</sup>H, CH), 7.13-7.31 (m, 5H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 28.5 (CH), 54.8 (2CH<sub>2</sub>), 126.6 (2CH), 126.7 (CH), 128.8 (2CH), 143.7 (C), 206.8 (CO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for (C<sub>10</sub>H<sub>10</sub>NaO) (M+Na)<sup>+</sup>: 169.0624, found: 169.0632.

**3-(2-Bromophenyl)cyclobutanone (1d).** 31% yield. Yellow oil; *R<sub>f</sub>* (20% EtOAc/hexane): 0.72; IR (NaCl): ν 3062, 2983, 2927, 1788, 1590, 1567, 1472, 1380, 1102, 1027, 755 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300.13 MHz): δ 3.16-3.29 (m, 2H, CHH), 3.46-3.59 (m, 2H, CHH), 3.87-4.02 (m, 1H, CH), 7.10-7.19 (m, 1H), 7.30-7.39 (m, 2H), 7.57-7.64 (m, 1H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 29.1 (CH), 53.2 (2CH<sub>2</sub>), 124.9 (CBr), 126.6 (CH), 127.8 (CH), 128.4 (CH), 133.3 (CH), 141.7 (C), 206.0 (CO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for (C<sub>10</sub>H<sub>9</sub>BrNaO) (M<sub>79Br</sub>+Na)<sup>+</sup>: 246.9729, found: 246.9703.

**3-(3-Bromophenyl)cyclobutanone (1e).** 32% yield. Pale yellow oil; *R<sub>f</sub>* (30% EtOAc/hexane): 0.77; IR (NaCl): ν 3062, 2975, 2923, 1785, 1636, 1596, 1566, 1477, 1378, 1102, 1074, 780 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300.13 MHz): δ 3.18-3.30 (m, 2H, CHH), 3.45-3.58 (m, 2H, CHH), 3.61-3.74 (m, 1H, CH), 7.22-7.27 (m, 2H), 7.36-7.43 (m, 1H), 7.45-7.48 (m, 1H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 28.3 (CH), 54.7 (2CH<sub>2</sub>), 122.9 (CBr), 125.3 (CH), 129.9 (2CH), 130.4 (CH), 146.0 (C), 205.7 (CO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for (C<sub>10</sub>H<sub>10</sub>BrO) (M<sub>79Br</sub>+H)<sup>+</sup>: 224.9910, found: 224.9889.

**3-(4-Bromophenyl)cyclobutanone (1f).** 50% yield. Yellowish-orangish solid. Mp: 49-51 °C; *R<sub>f</sub>* (30% EtOAc/hexane): 0.59; IR (nujol): ν 3055, 2987, 1786, 1489, 1422, 1395, 1101, 1075, 1009, 821 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300.13 MHz): 3.13-3.25 (m, 2H, CHH), 3.42-3.55 (m, 2H, CHH), 3.57-3.69 (m, 1H, CH), 7.13-7.19 (m, 2H), 7.42-7.48 (m, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz): δ 28.2 (CH), 54.8 (2CH<sub>2</sub>), 120.6 (CBr), 128.4 (2CH), 131.9 (2CH), 142.7 (C), 206.0 (CO) ppm; MS (ESI<sup>+</sup>, *m/z*): 225 (M<sub>79Br</sub>+H)<sup>+</sup>; 227 (M<sub>81Br</sub>+H)<sup>+</sup>.

**3-(4-Methylphenyl)cyclobutanone (1i).** 12% yield. Yellowish oil; *R<sub>f</sub>* (30% EtOAc/hexane): 0.79; IR (NaCl): ν 3023, 2974, 2922, 1785, 1608, 1516, 1450, 1417, 1379,

1167, 1109, 1020, 813  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  2.36 (s, 3H,  $\text{CH}_3$ ), 3.17-3.29 (m, 2H,  $\text{CHH}$ ), 3.42-3.55 (m, 2H,  $\text{CHH}$ ), 3.59-3.71 (m, 1H, CH), 7.15-7.23 (m, 4H);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  21.0 ( $\text{CH}_3$ ), 28.1 (CH), 54.8 ( $2\text{CH}_2$ ), 126.4 (2CH), 129.4 (2CH), 136.2 (CMe), 140.6 (C), 206.9 (CO) ppm; HRMS (ESI $^+$ ,  $m/z$ ): calculated for ( $\text{C}_{22}\text{H}_{24}\text{NaO}_2$ ) ( $2\text{M}+\text{Na}$ ) $^+$ : 343.1669, found: 343.1654.

#### 2.4. Synthesis of ethyl 3-oxocyclobutanecarboxylate (**1j**)

3-Oxocyclobutanecarboxylic acid (**6**, 200 mg, 1.75 mmol) was dissolved in dry THF (7 mL) and a drop of DMF was added under inert atmosphere. The solution was cooled down in an ice-bath, and oxalyl chloride (276  $\mu\text{L}$ , 3.51 mmol) was added, stirring the mixture for 30 minutes. After this time, the reaction was left to warm to room temperature, the solvent evaporated under reduced pressure and the residue redissolved in ethanol (7 mL). The solution was stirred for 1 h at room temperature. Then the solvent was evaporated in the rotary evaporator and the reaction crude purified by column chromatography on silica gel (20-30% EtOAc/hexane), yielding the cyclobutanone **1j** as a pale yellow oil (82% isolated yield).  $R_f$  (20% EtOAc/hexane): 0.30; IR (NaCl):  $\nu$  2985, 2937, 1797, 1733, 1467, 1375, 1346, 1215, 1193, 1099, 1052, 858  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  1.25 (t,  $^3J_{\text{HH}}=7.1$ , 3H,  $\text{CH}_3$ ), 3.12-3.43 (m, 5H,  $2\text{CH}_2+\text{CH}$ ), 4.17 (q,  $^3J_{\text{HH}}=7.1$ , 2H,  $\text{OCH}_2$ ) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  14.2 ( $\text{CH}_3$ ), 27.4 (CH), 51.6 ( $2\text{CH}_2$ ), 61.3 ( $\text{OCH}_2$ ), 174.1 (COO), 203.9 (CO) ppm; HRMS (ESI $^+$ ,  $m/z$ ): calculated for ( $\text{C}_7\text{H}_{10}\text{NaO}_3$ ) ( $\text{M}+\text{Na}$ ) $^+$ : 165.0522, found: 165.0531.

#### 2.5. Synthesis of benzyl 3-oxocyclobutanecarboxylate (**1k**).

3-Oxocyclobutanecarboxylic acid (**6**, 200 mg, 1.75 mmol) was dissolved in dry THF (7 mL), and a drop of DMF was added under inert atmosphere. The solution was cooled down in an ice-bath, and oxalyl chloride (276  $\mu\text{L}$ , 3.51 mmol) was added, stirring the mixture for 30 minutes. After this time, the reaction was left to warm to room temperature and benzyl

alcohol (544  $\mu\text{L}$ , 5.26 mmol) was added. The solution was stirred overnight at room temperature. Then the solvent was evaporated in the rotary evaporator and the reaction crude purified by column chromatography on silica gel (20% EtOAc/hexane), yielding the cyclobutanone **1k** as a pale yellow oil (76% isolated yield).  $R_f$  (30% EtOAc/hexane): 0.56; IR (NaCl):  $\nu$  3034, 2926, 2854, 1792, 1732, 1498, 1456, 1380, 1347, 1186, 1100, 1051, 752  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  3.20-3.50 (m, 5H,  $2\text{CH}_2+\text{CH}$ ), 5.19 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 7.33-7.39 (m, 5H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  27.5 (CH), 51.7 ( $2\text{CH}_2$ ), 67.2 ( $\text{OCH}_2$ ), 128.4 ( $2\text{CH}$ ), 128.6 (CH), 128.7 ( $2\text{CH}$ ), 135.5 (C), 173.9 (COO), 203.6 (CO) ppm; HRMS (ESI $^+$ ,  $m/z$ ): calculated for ( $\text{C}_{12}\text{H}_{12}\text{NaO}_3$ ) ( $\text{M}+\text{Na}$ ) $^+$ : 227.0679, found: 227.0660

#### 2.6. General procedure for the synthesis of lactones **2b-l** with *m*-chloroperbenzoic acid (MCPBA).

To a solution of the corresponding 3-arylcyclobutanone **1b-l** (0.25 mmol) in  $\text{CH}_2\text{Cl}_2$  (1.0 mL), MCPBA (88 mg, 0.50 mmol) was added and the mixture was stirred for 20 h. The mixture was washed with an aqueous  $\text{NaHCO}_3$  saturated solution (6 x 5 mL), the organic phase dried over  $\text{Na}_2\text{SO}_4$ , filtered and the solvent evaporated under reduced pressure. The reaction crude was purified by column chromatography on silica gel (10-30% EtOAc/hexane), yielding the lactones **2b-l** (44-99% isolated yield: 93% for **2b**; 83% for **2c**; 72% for **2d**; 99% for **2e**; 85% for **2f**; 86% for **2g**; 88% for **2h**; 44% for **2i**; 77% for **2j**; 75% for **2k**; 96% for **2l**). These standards were used for the development of GC analysis methods prior to carry out the chemoenzymatic reactions.

#### 2.7. General procedure for the chemoenzymatic synthesis of lactones **2a-l** using CAL-B, UHP and EtOAc.

Over a solution of the corresponding cyclobutanone **1a-l** (0.25 mmol) in EtOAc (379  $\mu\text{L}$ , 30.0 mmol), complex urea-hydrogen peroxide (UHP, 35 mg, 0.38 mmol) and CAL-B

(12.5 mg) were added. The suspension was shaken for 20 h at 30 °C and 250 rpm, then an aliquot was analyzed by GC. The reaction was left shaken until complete conversion was reached, then water was added (2 mL) and the enzyme filtered off. The solution was extracted with EtOAc (3 × 5 mL) and the organic phases combined and washed with water (2 × 5 mL) and brine (5 mL). The resulting organic phase was dried over Na<sub>2</sub>SO<sub>4</sub>, filtered and the solvent was evaporated under reduced pressure to obtain the corresponding lactones **2a-l** (51-99% isolated yield). For fluorinated lactone **2k** a column chromatography on silica gel (30% EtOAc/hexane) was necessary, as the reaction did not lead to complete conversion.

**4-Methyl-4-phenyldihydrofuran-2(3H)-one (2b).** 93% yield; White solid; Mp: 49-51 °C; *R<sub>f</sub>* (30% EtOAc/hexane): 0.43; IR (nujol):  $\nu$  3024, 2969, 2930, 2904, 1773, 1601, 1497, 1305, 1173, 1094, 1020, 767 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300.13 MHz):  $\delta$  1.54 (s, 3H, CH<sub>3</sub>), 2.68 (dd, <sup>2</sup>*J*<sub>HH</sub> = 16.8, <sup>4</sup>*J*<sub>HH</sub> = 0.4, 1H, CHH), 2.93 (dd, <sup>2</sup>*J*<sub>HH</sub> = 16.8, <sup>4</sup>*J*<sub>HH</sub> = 0.6, 1H, CHH), 4.39-4.47 (m, 2H, OCH<sub>2</sub>), 7.18-7.23 (m, 2H), 7.27-7.33 (m, 1H), 7.36-7.42 (m, 2H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz):  $\delta$  28.1 (CH<sub>3</sub>), 42.1 (CH<sub>2</sub>), 44.2 (C), 78.5 (OCH<sub>2</sub>), 125.2 (2CH), 127.3 (CH), 129.1 (2CH), 144.4 (C), 176.2 (CO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for (C<sub>11</sub>H<sub>12</sub>NaO<sub>2</sub>) (M+Na)<sup>+</sup>: 199.0730, found: 199.0781.

**4-Phenyldihydrofuran-2(3H)-one (2c).** 83% yield; White solid; Mp: 46-47 °C; *R<sub>f</sub>* (20% EtOAc/hexane): 0.20; IR (nujol):  $\nu$  3064, 3032, 2973, 2904, 1763, 1601, 1456, 1355, 1163, 1010, 761 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 300.13 MHz):  $\delta$  2.67 (dd, <sup>2</sup>*J*<sub>HH</sub> = 17.5, <sup>3</sup>*J*<sub>HH</sub> = 9.1, 1H, CHH), 2.92 (dd, <sup>2</sup>*J*<sub>HH</sub> = 17.5, <sup>3</sup>*J*<sub>HH</sub> = 8.3, 1H, CHH), 3.73-3.85 (m, 1H, CH), 4.26 (dd, <sup>2</sup>*J*<sub>HH</sub> = 9.0, <sup>3</sup>*J*<sub>HH</sub> = 8.1, 1H, OCHH), 4.66 (dd, <sup>2</sup>*J*<sub>HH</sub> = 9.0, <sup>3</sup>*J*<sub>HH</sub> = 8.3, 1H, OCHH), 7.21-7.40 (m, 5H) ppm; <sup>13</sup>C NMR (CDCl<sub>3</sub>, 75.5 MHz):  $\delta$  35.8 (CH<sub>2</sub>), 41.2 (CH), 74.1 (OCH<sub>2</sub>), 126.8 (2CH), 127.8 (CH), 129.2 (2CH), 139.5 (C), 176.5 (COO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for (C<sub>10</sub>H<sub>10</sub>NaO<sub>2</sub>) (M+Na)<sup>+</sup>: 185.0573, found: 185.0592.

**4-(2-Bromophenyl)dihydrofuran-2(3H)-one (2d).** 72% yield; White solid; Mp: 56-57 °C; *R<sub>f</sub>* (20% EtOAc/hexane): 0.41; IR (nujol):  $\nu$  3064, 2990, 2914, 1779, 1568, 1473, 1440,

1372, 1168, 1023, 753  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz): 2.67 (dd,  $^2J_{\text{HH}} = 17.6$ ,  $^3J_{\text{HH}} = 6.7$ , 1H, *CHH*), 2.97 (dd,  $^2J_{\text{HH}} = 17.6$ ,  $^3J_{\text{HH}} = 8.6$ , 1H, *CHH*), 4.17-4.24 (m, 2H, *CH+OCHH*), 4.71 (dd,  $^2J_{\text{HH}} = 9.0$ ,  $^3J_{\text{HH}} = 7.2$ , 1H, *OCHH*), 7.17 (ddd,  $^3J_{\text{HH}} = 8.0$ ,  $^3J_{\text{HH}} = 7.1$ ,  $^4J_{\text{HH}} = 1.9$ , 1H), 7.26-7.35 (m, 2H), 7.61 (dd,  $^3J_{\text{HH}} = 8.0$ ,  $^4J_{\text{HH}} = 1.3$ , 1H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  34.9 ( $\text{CH}_2$ ), 40.3 (CH), 73.0 ( $\text{OCH}_2$ ), 124.5 (CBr), 126.8 (CH), 128.4 (CH), 129.3 (CH), 133.6 (CH), 140.0 (C), 176.2 (COO) ppm; HRMS ( $\text{ESI}^+$ ,  $m/z$ ): calculated for ( $\text{C}_{10}\text{H}_9\text{BrNaO}_2$ ) ( $\text{M}_{79\text{Br}} + \text{Na}$ ) $^+$ : 262.9678, found: 262.9670.

**4-(3-Bromophenyl)dihydrofuran-2(3*H*)-one (2e).** 99% yield; Yellowish oil;  $R_f$  (30% EtOAc/hexane): 0.50; IR (NaCl):  $\nu$  3058, 2971, 2913, 1781, 1597, 1568, 1479, 1266, 1169, 1024, 737  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz): 2.64 (dd,  $^2J_{\text{HH}} = 17.5$ ,  $^3J_{\text{HH}} = 8.8$ , 1H, *CHH*), 2.93 (dd,  $^2J_{\text{HH}} = 17.5$ ,  $^3J_{\text{HH}} = 8.7$ , 1H, *CHH*), 3.70-3.82 (m, 1H, CH), 4.25 (dd,  $^2J_{\text{HH}} = 9.1$ ,  $^3J_{\text{HH}} = 7.6$ , 1H, *OCHH*), 4.66 (dd,  $^2J_{\text{HH}} = 9.1$ ,  $^3J_{\text{HH}} = 7.8$ , 1H, *OCHH*), 7.16 (dt,  $^3J_{\text{HH}} = 7.7$ ,  $^4J_{\text{HH}} = 1.2$ , 1H), 7.25 (t,  $^3J_{\text{HH}} = 7.8$ , 1H), 7.38 (t,  $^4J_{\text{HH}} = 1.8$ , 1H), 7.42 (ddd,  $^3J_{\text{HH}} = 7.8$ ,  $^4J_{\text{HH}} = 1.8$ ,  $^4J_{\text{HH}} = 1.2$ , 1H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  35.6 ( $\text{CH}_2$ ), 40.8 (CH), 73.7 ( $\text{OCH}_2$ ), 123.3 (CBr), 125.4 (CH), 130.1 (CH), 130.9 (CH), 131.0 (CH), 141.9 (C), 175.9 (COO) ppm; HRMS ( $\text{ESI}^+$ ,  $m/z$ ): calculated for ( $\text{C}_{10}\text{H}_9\text{BrNaO}_2$ ) ( $\text{M}_{79\text{Br}} + \text{Na}$ ) $^+$ : 262.9678, found: 262.9657.

**4-(4-Bromophenyl)dihydrofuran-2(3*H*)-one (2f).** 85% yield; White solid; Mp: 72-74  $^\circ\text{C}$ ;  $R_f$  (30% EtOAc/hexane): 0.31; IR (nujol):  $\nu$  3016, 2930, 2901, 1767, 1589, 1487, 1424, 1221, 1158, 1016, 826  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  2.62 (dd,  $^2J_{\text{HH}} = 17.5$ ,  $^3J_{\text{HH}} = 8.8$ , 1H, *CHH*), 2.93 (dd,  $^2J_{\text{HH}} = 17.5$ ,  $^3J_{\text{HH}} = 8.7$ , 1H, *CHH*), 3.68-3.83 (m, 1H, CH), 4.23 (dd,  $^2J_{\text{HH}} = 9.1$ ,  $^3J_{\text{HH}} = 7.6$ , 1H, *OCHH*), 4.65 (dd,  $^2J_{\text{HH}} = 9.1$ ,  $^3J_{\text{HH}} = 7.8$ , 1H, *OCHH*), 7.08-7.14 (m, 2H), 7.46-7.52 (m, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  35.7 ( $\text{CH}_2$ ), 40.7 (CH), 73.8 ( $\text{OCH}_2$ ), 121.7 (CBr), 128.5 (2CH), 132.4 (2CH), 138.6 (C), 176.0 (COO) ppm; HRMS ( $\text{ESI}^+$ ,  $m/z$ ): calculated for ( $\text{C}_{10}\text{H}_9\text{BrNaO}_2$ ) ( $\text{M}_{79\text{Br}} + \text{Na}$ ) $^+$ : 262.9678, found: 262.9673.

**4-(4-Chlorophenyl)dihydrofuran-2(3*H*)-one (2g).** 86% yield; Pale yellow solid; Mp: 54-56  $^\circ\text{C}$ ;  $R_f$  (30% EtOAc/hexane): 0.41; IR (nujol):  $\nu$  3055, 2987, 2914, 1782, 1496, 1423,

1170, 1094, 1025, 828  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  2.61 (dd,  $^2J_{\text{HH}}=17.5$ ,  $^3J_{\text{HH}}=8.9$ , 1H, *CHH*), 2.92 (dd,  $^2J_{\text{HH}}=17.5$ ,  $^3J_{\text{HH}}=8.7$ , 1H, *CHH*), 3.70-3.82 (m, 1H, CH), 4.23 (dd,  $^2J_{\text{HH}}=9.1$ ,  $^3J_{\text{HH}}=7.7$ , 1H, *OCHH*), 4.65 (dd,  $^2J_{\text{HH}}=9.1$ ,  $^3J_{\text{HH}}=7.8$ , 1H, *OCHH*), 7.13-7.19 (m, 2H), 7.30-7.36 (m, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  35.7 ( $\text{CH}_2$ ), 40.6 (CH), 73.9 ( $\text{OCH}_2$ ), 128.2 (2CH), 129.4 (2CH), 133.6 (CCl), 138.1 (C), 176.1 (COO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for ( $\text{C}_{10}\text{H}_9\text{ClNaO}_2$ ) ( $\text{M}+\text{Na}$ )<sup>+</sup>: 219.0183, found: 219.0156.

**4-(4-Fluorophenyl)dihydrofuran-2(3*H*)-one (2h).** 88% yield; White solid; Mp: 65-67 °C;  $R_f$  (30% EtOAc/hexane): 0.38; IR (nujol):  $\nu$  3068, 2914, 1777, 1602, 1514, 1433, 1219, 1165, 1013, 843  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  2.62 (dd,  $^2J_{\text{HH}}=17.5$ ,  $^3J_{\text{HH}}=8.9$ , 1H, *CHH*), 2.92 (dd,  $^2J_{\text{HH}}=17.5$ ,  $^3J_{\text{HH}}=8.7$ , 1H, *CHH*), 3.71-3.84 (m, 1H, CH), 4.23 (dd,  $^2J_{\text{HH}}=9.1$ ,  $^3J_{\text{HH}}=7.7$ , 1H, *OCHH*), 4.65 (dd,  $^2J_{\text{HH}}=9.1$ ,  $^3J_{\text{HH}}=7.8$ , 1H, *OCHH*), 7.00-7.09 (m, 2H), 7.16-7.24 (m, 2H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  35.9 ( $\text{CH}_2$ ), 40.6 (CH), 74.1 ( $\text{OCH}_2$ ), 116.2 (d,  $^2J_{\text{CF}}=21.5$ , 2CH), 128.4 (d,  $^3J_{\text{CF}}=8.0$ , 2CH), 135.3 (d,  $^4J_{\text{CF}}=2.9$ , C), 162.2 (d,  $^1J_{\text{CF}}=246.6$ , CF), 176.2 (COO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for ( $\text{C}_{10}\text{H}_9\text{FNaO}_2$ ) ( $\text{M}+\text{Na}$ )<sup>+</sup>: 203.0479, found: 203.0474.

**4-(4-Methylphenyl)dihydrofuran-2(3*H*)-one (2i).** 44% yield; White solid; Mp: 40-42 °C; IR (nujol):  $\nu$  2978, 2948, 2916, 1761, 1608, 1519, 1484, 1455, 1427, 1350, 1214, 1158, 1008, 827  $\text{cm}^{-1}$ ;  $R_f$  (30% EtOAc/hexane): 0.54;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  2.34 (s, 3H,  $\text{CH}_3$ ), 2.65 (dd,  $^2J_{\text{HH}}=17.5$ ,  $^3J_{\text{HH}}=9.2$ , 1H, *CHH*), 2.90 (dd,  $^2J_{\text{HH}}=17.5$ ,  $^3J_{\text{HH}}=8.6$ , 1H, *CHH*), 3.69-3.82 (m, 1H, CH), 4.24 (dd,  $^2J_{\text{HH}}=9.1$ ,  $^3J_{\text{HH}}=8.0$ , 1H, *OCHH*), 4.65 (dd,  $^2J_{\text{HH}}=9.1$ ,  $^3J_{\text{HH}}=7.9$ , 1H, *OCHH*), 7.10-7.20 (m, 4H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  21.1 ( $\text{CH}_3$ ), 35.9 ( $\text{CH}_2$ ), 40.9 (CH), 74.3 ( $\text{OCH}_2$ ), 126.7 (2CH), 129.9 (2CH), 136.4 (CMe), 137.6 (C), 176.6 (COO) ppm; HRMS (ESI<sup>+</sup>, *m/z*): calculated for ( $\text{C}_{11}\text{H}_{12}\text{NaO}_2$ ) ( $\text{M}+\text{Na}$ )<sup>+</sup>: 199.0730, found: 199.0728.

**Ethyl 5-oxotetrahydrofuran-3-carboxylate (2j).** 77% yield; Yellowish liquid;  $R_f$  (40% EtOAc/hexane): 0.30; IR (NaCl):  $\nu$  2986, 2941, 1783, 1733, 1477, 1375, 1348, 1198, 1176, 1024, 845  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  1.25 (t,  $^3J_{\text{HH}} = 7.1$ , 3H,  $\text{CH}_3$ ), 2.70 (dd,  $^2J_{\text{HH}} = 17.9$ ,  $^3J_{\text{HH}} = 9.6$ , 1H,  $\text{CHH}$ ), 2.83 (dd,  $^2J_{\text{HH}} = 17.9$ ,  $^3J_{\text{HH}} = 7.2$ , 1H,  $\text{CHH}$ ), 3.36-3.47 (m, 1H, CH), 4.17 (q,  $^3J_{\text{HH}} = 7.1$ , 2H,  $\text{OCH}_2\text{CH}_3$ ), 4.37-4.52 (m, 2H,  $\text{OCH}_2$ ) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  14.1 ( $\text{CH}_3$ ), 30.9 ( $\text{CH}_2$ ), 40.0 (CH), 61.9 ( $\text{OCH}_2\text{CH}_3$ ), 69.1 ( $\text{OCH}_2$ ), 171.2 ( $\text{CO}_2\text{Et}$ ), 175.3 (COO) ppm; HRMS (ESI $^+$ ,  $m/z$ ): calculated for ( $\text{C}_7\text{H}_{10}\text{NaO}_4$ ) ( $\text{M}+\text{Na}$ ) $^+$ : 181.0471, found: 181.0477.

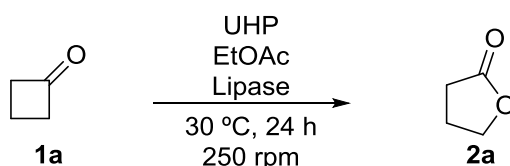
**Benzyl 5-oxotetrahydrofuran-3-carboxylate (2k).** 75% yield; White gummy solid;  $R_f$  (30% EtOAc/hexane): 0.33; IR (NaCl):  $\nu$  3066, 3034, 2959, 1779, 1736, 1636, 1498, 1456, 1383, 1350, 1175, 1013, 754  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  2.74 (dd,  $^2J_{\text{HH}} = 17.9$ ,  $^3J_{\text{HH}} = 9.6$ , 1H,  $\text{CHH}$ ), 2.88 (dd,  $^2J_{\text{HH}} = 17.9$ ,  $^3J_{\text{HH}} = 7.3$ , 1H,  $\text{CHH}$ ), 3.44-3.56 (m, 1H, CH), 4.42-4.56 (m, 2H,  $\text{OCH}_2$ ), 5.20 (s, 2H,  $\text{CH}_2\text{Ph}$ ), 7.33-7.44 (m, 5H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  30.9 ( $\text{CH}_2$ ), 40.1 (CH), 67.7 ( $\text{CH}_2\text{Ph}$ ), 69.0 ( $\text{OCH}_2$ ), 128.5 (2CH), 128.8 (3CH), 135.0 (C), 171.0 ( $\text{CO}_2\text{Bn}$ ), 175.1 (COO) ppm; HRMS (ESI $^+$ ,  $m/z$ ): calculated for ( $\text{C}_{12}\text{H}_{12}\text{NaO}_4$ ) ( $\text{M}+\text{Na}$ ) $^+$ : 243.0628, found: 243.0671.

**4-(Benzyloxy)dihydrofuran-2(3H)-one (2l).** 96% yield; White gummy solid;  $R_f$  (40% EtOAc/hexane): 0.30; IR (NaCl):  $\nu$  3066, 3034, 2923, 1779, 1603, 1455, 1401, 1374, 1333, 1166, 1086, 1050, 993, 886, 747  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 300.13 MHz):  $\delta$  2.58-2.73 (m, 2H), 4.34-4.41 (m, 3H,  $\text{CH}+\text{OCH}_2$ ), 4.49-4.57 (m, 2H,  $\text{OCH}_2\text{Ph}$ ), 7.27-7.40 (m, 5H) ppm;  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ , 75.5 MHz):  $\delta$  35.0 ( $\text{CH}_2$ ), 71.2 ( $\text{OCH}_2\text{Ph}$ ), 73.2 ( $\text{OCH}_2$ ), 73.9 (CH), 127.8 (2CH), 128.2 (CH), 128.7 (2CH), 137.0 (C), 175.6 (COO) ppm; HRMS (ESI $^+$ ,  $m/z$ ): calculated for ( $\text{C}_{11}\text{H}_{12}\text{NaO}_3$ ) ( $\text{M}+\text{Na}$ ) $^+$ : 215.0679, found: 215.0726.

### 3. Results and discussion

To start with, a screening of biocatalysts for the oxidation of cyclobutanone (**1a**) was made, considering a representative set of lipases such as CAL-B, RML, AK, PSL-SD and CRL. Searching for a simple catalytic cascade system, ethyl acetate (EtOAc) was selected as both solvent and peracetic acid precursor, using the stable and safe urea-hydrogen peroxide (UHP) complex as oxidizing agent. Initially, the reactions were carried out with 1 equivalent of UHP complex and a 0.66 M concentration of **1a** in EtOAc at 30 °C (Table 1).

**Table 1.** Baeyer-Villiger reaction of cyclobutanone (**1a**) using 1 equivalent of UHP, different lipases (50 mg enzyme/mmol **1a**) in EtOAc (0.66 M of **1a**) after 24 h at 30 °C and 250 rpm.



Entry	Lipase	Conversion (%) <sup>a</sup>
1	----	3
2	CAL-B	77
3	RML	32
4	AK	34
5	PSL-SD	46
6	CRL	42

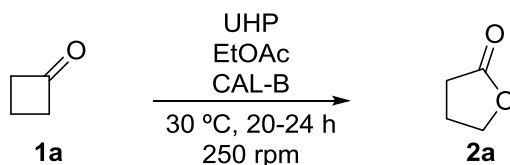
<sup>a</sup> Calculated by GC analysis of the reaction crudes.

In all cases conversions into the lactone **2a** were much higher (>30%, entries 2-6) compared to that in absence of enzyme, which just proceeded in 3% conversion (entry 1). Moreover, **2a** was found to be the unique final product, not detecting any other side reactions. Remarkably, the use of an aqueous 30% H<sub>2</sub>O<sub>2</sub> solution<sup>[28,29]</sup> led to the formation of various by-products and poor reproducibility. CAL-B came out as the most efficient catalyst,<sup>[30]</sup>

reaching a 77% conversion after 24 h (entry 2), while RML, AK, PSL-SD and CRL did not overcome a 46% yield (entries 3-6).

In order to obtain complete conversions, different reaction parameters were studied such as the amount of UHP or the substrate concentration, maintaining CAL-B as biocatalyst (Table 2).<sup>[28]</sup> Thus, the amount of UHP was varied between 1.0 and 2.0 equivalents, **1a** being used in a really high concentration if compared to other classes of enzymes (0.5-1.0 M). Regarding previous results (entry 1), doubling the amount of UHP led to a complete conversion in the same reaction time (entry 2). It must be noticed that 24 h were necessary to reach complete conversion, as a 91% conversion was achieved after 20 h (entry 3). Satisfactorily, 1.5 equivalents of the oxidizing agent allowed the formation of **2a** quantitatively after 20 h (entry 4), which suggests a deactivation of the enzyme during the timeframe at higher UHP concentration. This reaction was performed with both 0.25 mmol and 0.5 mmol of **1a** observing identical results. Unfortunately a decrease of UHP to only 1 equivalent at both lower (0.5 M, entry 5) or very high substrate concentration (0.8 and 1.0 M, entries 7 and 8), led to modest 64-75% conversion values after 20 h (entries 5-8). Finally, a 1.0 M substrate concentration was studied. Hence, after examining the influence of UHP ratio (1-2 equivalents, entries 8-11), it was observed that an almost complete conversion could only be achieved using 2 equivalents of the oxidizing agent (entry 11).

**Table 2.** Baeyer-Villiger reaction of cyclobutanone (**1a**) using UHP complex and CAL-B (50 mg/mmol **1a**) in EtOAc at 30 °C and 250 rpm.



Entry	Time (h)	UHP (eq)	[ <b>1a</b> ] (M)	Conversion (%) <sup>a</sup>
1	24	1.0	0.66	77
2	24	2.0	0.66	>99
3	20	2.0	0.66	91
4	20	1.5	0.66	>99
5	20	1.0	0.5	64
6	20	1.0	0.66	71
7	20	1.0	0.8	74
8	20	1.0	1.0	75
9	20	1.2	1.0	79
10	20	1.5	1.0	83
11	20	2.0	1.0	96

<sup>a</sup> Calculated by GC analyses of the reaction crudes. Lactone **2a** was the only product detected.

With these results in hand, the strategy was extended to a broad panel of 3-substituted cyclobutanones, some of them commercially available and other synthesized through conventional chemical protocols (see experimental section). For this study, prochiral cyclobutanones, such as the 3,3-disubstituted **1b**, 3-aryl-substituted **1c-h**, ketoesters **1i-j** and the alkoxy substituted **1l**, were considered. Prior to the performance of the chemoenzymatic studies, lactones **2b-l** were synthesized by reaction of the corresponding cyclobutanone **1b-l** with *m*-chloroperbenzoic acid in dichloromethane, developing adequate GC methods for the

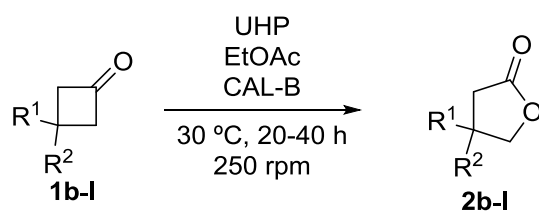
analysis of the lipase-mediated oxidations of **1b-l** (see experimental section and supporting information). Table 3 shows the results achieved for the Baeyer-Villiger reaction of 3-substituted cyclobutanones **1b-l** using CAL-B, UHP complex and EtOAc. Control experiments in the absence of the enzyme led in all cases to poor conversions (lower than 22%), the highest value being obtained with the brominated derivative **1d**. This observation demonstrates the efficiency of the chemoenzymatic system here employed. Lower conversion values (< 5%) were reached with ketoesters **1j-k**, and in the presence of unsubstituted phenyl derivatives **1b-c**.

Remarkably after 20 h, conversions were equal or higher than 90% in all cases except for the fluorinated derivative in the *para*-position of the phenyl ring **1h** (entry 7). A periodic time course analysis was performed in order to reach complete conversions, which facilitates the purification of the final products, avoiding column chromatography separations. Thus, high to excellent isolated yields were achieved for the final  $\gamma$ -butyrolactones after a simple and effective extraction protocol following the enzyme filtration, which is in contrast with traditional oxidative processes using metal complexes or inorganic salts. It is also worthy to mention that ketoesters **1j** and **1k** (entries 9 and 10) led to the lactones without formation of any undesired hydrolytic products in spite of using a hydrolase in the transformation.

Complete conversions were found for seven out of the eleven tested substrates after 20 h, requiring 30 h for the 3-phenyl-cyclobutanones **1b-c** and 40 h for the 3-(benzyloxy)cyclobutanone (**1l**). Nevertheless, the oxidation of the 3-(4-fluorophenyl)cyclobutanone (**1h**) did not proceed to complete conversion after prolonged time periods. The chemoenzymatic global oxidative approach was extremely effective for ketones presenting substitutions in the phenyl ring such as alkyl rests (methyl, **1i**) or halogen atoms (bromine or chlorine, **1d-g**) in different positions (*orto*, *meta* or *para*), but also when alkyl carboxylates (**1j,k**) and the benzyloxy rest (**1l**) was considered. All the final products were racemic, probing that the enzyme is only responsible for the perhydrolysis reaction leading to

the formation of non chiral peracetic acid, which is in turn the responsible for the non enantioselective oxidation.<sup>[8]</sup> The scalability of the process was probed at a 250 mg-scale using 3-(4-methylphenyl)cyclobutanone (**1i**) as substrate. Gratifyingly, it was quantitatively transformed after 20 h.

**Table 3.** Baeyer-Villiger reaction of 3-substituted cyclobutanones **1b-l** using 1.5 equivalents of UHP and CAL-B (50 mg/mmol **1b-l**) in EtOAc (0.66 M) at 30 °C and 250 rpm.



Entry	Substrate	R <sup>1</sup>	R <sup>2</sup>	t (h)	Conversion (%) <sup>a</sup>	Yield (%) <sup>c</sup>
1	<b>1b</b>	Me	Ph	30	>99 (94) <sup>b</sup>	93
2	<b>1c</b>	H	Ph	30	>99 (94) <sup>b</sup>	99
3	<b>1d</b>	H	2-Br-C <sub>6</sub> H <sub>4</sub>	20	>99	98
4	<b>1e</b>	H	3-Br-C <sub>6</sub> H <sub>4</sub>	20	>99	97
5	<b>1f</b>	H	4-Br-C <sub>6</sub> H <sub>4</sub>	20	>99	99
6	<b>1g</b>	H	4-Cl-C <sub>6</sub> H <sub>4</sub>	20	>99	87
7	<b>1h</b>	H	4-F-C <sub>6</sub> H <sub>4</sub>	20	78	51
8	<b>1i</b>	H	4-Me-C <sub>6</sub> H <sub>4</sub>	20	>99	97
9	<b>1j</b>	H	COOEt	20	>99	84
10	<b>1k</b>	H	COOBn	20	>99	96
11	<b>1l</b>	H	OBn	40	>99 (90) <sup>b</sup>	94

<sup>a</sup> Calculated by GC analyses of the reaction crudes.

<sup>b</sup> Conversion values after 20 h appears in parentheses.

<sup>c</sup> Isolated yields after purification by extraction of the final products, once complete conversions were detected by GC. For **1h** none significant improvements in the conversion value were observed over the time, so **2h** was purified by column chromatography on silica gel.

## 4. Conclusions

The development of cascade reactions is a challenging task for organic chemists since they simplify the overall process, allowing the participation of unstable intermediates and improving the yields of the final products. Herein, we have described a chemoenzymatic strategy for the synthesis of  $\gamma$ -butyrolactones starting from the corresponding cyclobutanones. This Baeyer-Villiger reaction is based on two sequential steps carried out in *one-pot*. Firstly, a lipase-catalyzed perhydrolysis of ethyl acetate allows the formation of peracetic acid, which smoothly performs the oxidation of the ketones into the lactones in a non-enzymatic fashion. Cyclobutanone was selected for simplicity and commercial availability as model substrate, finding *Candida antarctica* lipase type B as the most efficient enzyme to carry out this transformation, while the stable UHP complex has served as a mild oxidative agent. The influence of the substrate concentration and the amount of UHP has also been studied in depth. Satisfyingly, 1.5 equivalents of UHP allowed the preparation of  $\gamma$ -butyrolactones in good to excellent yields after a simple extraction protocol, from a previously acquired or synthesized representative number of cyclobutanones in a 0.66 M concentration. Finally, the reaction has been satisfactorily scaled-up, demonstrating the efficiency of this chemoenzymatic cascade approach.

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