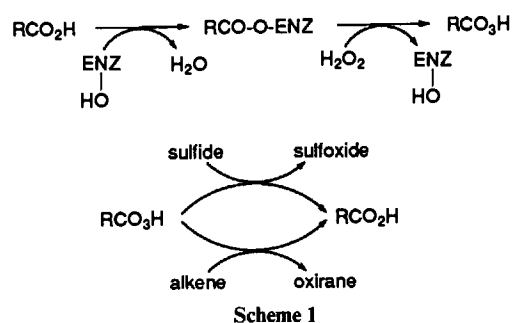# Lipase-catalysed Baeyer–Villiger Reactions

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The Baeyer–Villiger oxidation of some 2- and 3-substituted cyclopentanones and cyclohexanones using myristic acid and hydrogen peroxide is catalysed by *Candida anatarctica* lipase.

The use of lipases in organic synthesis is well-established.[1] For example Björkling *et al.* have shown that a lipase from a *Candida* species catalysed the epoxidation of alkenes and the conversion of sulfides into sulfoxides using hydrogen peroxide and a long-chain fatty acid.[2,3]

In fact, the lipase catalyses the formation of peracid through peroxide attack on the acylated enzyme (Scheme 1). The Danish


Scheme 1

workers did not report Baeyer–Villiger oxidations using the lipase system, save to comment that cyclopentanone gave a poor yield of oxidized product.[3] Given the importance of the Baeyer–Villiger reaction[4] we felt a more extensive study was justified.

Results and Discussion

A range of ketones was oxidized using 30% aqueous hydrogen peroxide and myristic acid in toluene (Table 1). The hydrogen peroxide was added over a period of 10 h using a syringe pump and the reaction was left for a further $5\frac{1}{2}$ days on completion of the addition. The myristic acid was removed at the end of the reaction by chromatography or by extraction into sodium hydroxide solution. 2-Hexylcyclopentanone, 2-octylcyclopent-anone, 2-undecylcyclopentanone, 2-methylcyclohexanone and 2-hexylcyclohexanone were oxidized to give the corresponding substituted lactones in 57–73% yield. These yields were, as a rule, slightly lower (5–10%) than those obtained in classical Baeyer–Villiger oxidations using *m*-chloroperoxybenzoic acid (MCPBA).

3-Hexylcyclopentanone and 3-hexylcyclohexanone gave equi-molar mixtures of isomeric lactones (*ca.* 50% yields) while cyclopentanone, 5-hexylcyclopent-2-enone and pentan-3-one were poor reactants. Cyclobutanone derivatives are trans-formed almost equally quickly in the absence of enzyme unless the carbonyl group is hindered, as in 2-*exo*-bromo-3-*endo*-hydroxy-7,7-dimethylbicyclo[3.2.0]heptan-6-one.
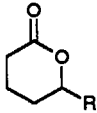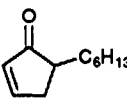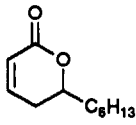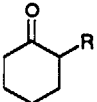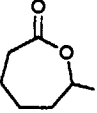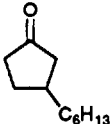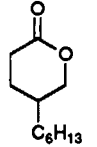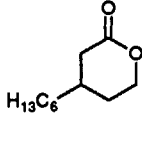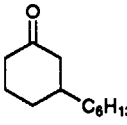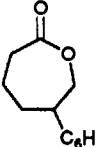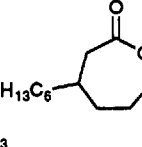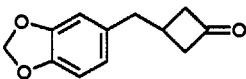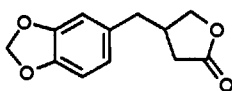
Not surprisingly, all the lactones described in Table 1 were obtained in racemic form; the peracid obviously migrates away from the surface of the enzyme before interacting with the ketone. In an effort to use the chiral nature of the catalyst to induce asymmetry into the Baeyer–Villiger reaction we have explored the lipase-catalysed oxidation of the ketone 1.

Scheme 2
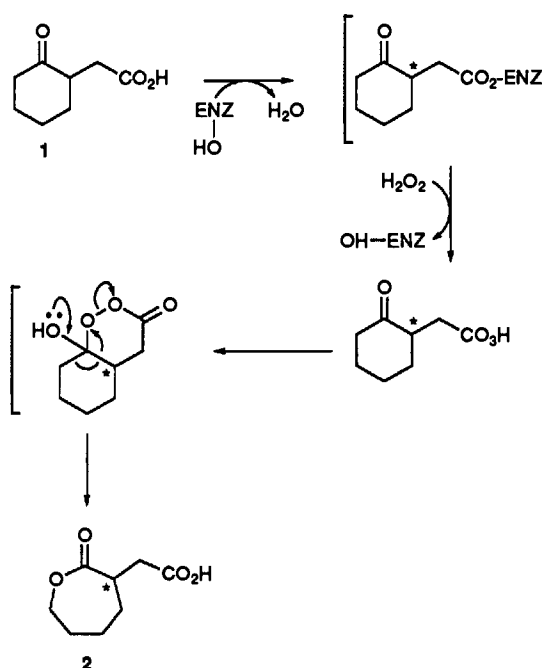
Baeyer–Villiger oxidation of ketone 1 has been studied by Chandrasekhar and Roy.[5] They report that the lactone 2 was the sole product of oxidation. Under the standard lipase-catalysed reaction conditions, the lactone 2 was obtained in optically active form (54% yield; 21% enantiomeric excess). Presumably the lipase is acylated slightly more rapidly by one enantiomer of the carboxylic acid and the peracid so formed undergoes intramolecular reaction (Scheme 2) as adumbrated by the Indian scientists. In accord with this hypothesis the ethyl ester of 1 was slowly hydro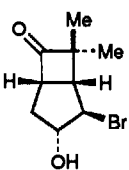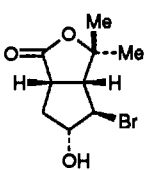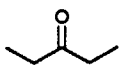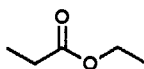lysed by *C. antarctica* in wet toluene to give the acid 1 with modest enantioselectivity (23% enantiomeric excess at *ca.* 10% conversion). The enantiomeric excesses were determined by ¹H NMR chiral shift analysis using [Eu(hfc)₃] {tris[(heptafluoropropylhydroxymethylene)-camphorato]europium(ɪɪɪ)} on the methyl ester of 2. The absolute configuration of the predominant enantiomer in the non-racemic samples of 2 was not determined.

In summary, some lipophilic cyclic ketones were oxidized to the corresponding lactones using myristic acid, peroxide and a lipase in yields which were comparable with those obtained in MCPBA oxidations. The enzyme system avoids the use of a relatively unstable peracid, but the long reaction times detract from the immediate usefulness of the biotransformation. 2-Oxocyclohexylacetic acid is oxidized with a very modest degree of enantioselectivity. In general, much better selectivity is obtained with other enzymes[6] and organometallic agents.[7]

Table 1

Substrate ketone	Product lactone(s)	% Yield [a]	
		Enzyme-catalysed reaction	Blank reaction (without enzyme)
	R = C₆H₁₃ R = C₈H₁₇ R = C₁₁H₂₃	73 64 66	0 0 0
		0	0
	R = CH₃ R = C₆H₁₃	57 69	0 0
		46 (ratio 1: 1)	0
		51 (ratio 1: 1)	0
		70	53
		74[c]	< 5
		20[b]	0

[a] All yields refer to isolated compounds, except [b] GC conversion. [c] Peroxide added over 1 h, reaction complete within 24 h.

Experimental

General Procedures for the Candida antarctica *catalysed Baeyer–Villiger Oxidation of Cyclic Ketones.*—To a solution of the ketone (1.11 mmol) in toluene (10 cm³) was added myristic acid (tetradecanoic acid) (0.32 g, 1.43 mmol) and immobilized *Candida antarctica* lipase (0.25 g). To this hydrogen peroxide (30%; 1 cm³, 4.4 mmol) was added over 10 h *via* syringe pump addition. The reaction was monitored by GC. After 6 days, the reaction mixture was filtered through a plug of Celite, and washed with dichloromethane (100 cm³). The filtrate was dried over MgSO₄ and the solvent removed. Column chromatography over silica afforded the pure lactone. Alternatively sodium hydroxide (2 mol dm⁻³; 3 cm³) can be

added at the end of the reaction. The resulting mixture was then filtered through Celite, the organic phase removed, dried and evaporated to afford the crude product, which was purified as above. The blank oxidations were carried out in an identical manner but without the enzyme.

Intramolecular Baeyer–Villiger Oxidation.—To a solution of the ketone 1 (1.11 mmol) in toluene (10 cm³) was added the lipase (0.25 g). To this hydrogen peroxide (30%; 1 cm³, 4.4 mmol) was added over 10 h *via* syringe pump addition. After 2 days, the reaction was filtered through a plug of Celite and washed with dichloromethane (100 cm³). The filtrate was dried over MgSO₄ and the solvent removed. Column chromatography

over silica affords the lactone **2**; $\nu_{max}(CHCl_3)/cm^{-1}$ 3200br and 1713; δ_H(250 MHz; $CDCl_3$) 1.29–1.76 (4 H, m), 1.95 (1 H, d, 9.2), 2.32–2.89 (5 H, m) and 4.63–4.74 (1 H, m, OCHCO); δ_C(62.9 MHz; $CDCl_3$) 22.7, 27.9, 34.2, 34.7, 40.8 (CH_2), 76.5 (CH), 175.1 and 177.1 (C=O) (Found: M^+, 172.0731. $C_8H_{12}O_4$ requires M, 172.0736).

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