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Review

Enzyme-catalysed Baeyer–Villiger oxidations

Stanley M. Roberts [a,*], Peter W.H. Wan [b]

[a] *Department of Chemistry, The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX, United Kingdom*
[b] *Department of Chemistry, Imperial College of Science, Technology and Medicine, Exhibition Road, South Kensington, London SW7 2AY, United Kingdom*

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Abstract

Preparative-scale biotransformations of cyclic and bicyclic ketones yielding optically active lactones are illustrated. The use of whole cell systems such as *Acinetobacter calcoaceticus* to stereoselectively oxidize bicycle[3.2.0]heptanones and bicyclo[2.2.1]heptanones to γ-lactones and δ-lactones respectively is typical of this increasingly popular strategy. Similarly isolated enzymes (e.g. from *Pseudomonas putida*) have been used to oxidize monocyclic ketones in an enantioselective fashion. The employment of these biotransformations in the synthesis of natural products such as lipoic acid, multifidene, cyclosarkomycin demonstrate the power of the methodology. A mechanistic rationale and an active site model are discussed.

1. Introduction and background information

The transformation of an acyclic ketone to an ester or a cyclic ketone to a lactone using an oxidant such as a peroxyacid (Scheme 1) was discovered by Baeyer and Villiger in 1899 [1]. Many developments that have been made to the reaction in the interim have been reviewed [2–4].

The accepted two-step mechanism for the Baeyer–Villiger oxidation is shown in Scheme 2 [3,5].

Thus addition of peroxyacid to the carbonyl group of the ketone (step 1) creates a tetrahedral 'Criegee' intermediate [5]. Subsequently (step 2), this intermediate rearranges to form the corresponding ester or lactone. When different substituents are attached to the carbonyl carbon atom, the one that can better accommodate a partial positive charge migrates to the incoming oxygen atom (R^2 in Scheme 2). Consequently, the usual migratory preference of alkyl groups in the Baeyer–Villiger oxidation is tertiary > secondary > primary > methyl [6,7]. This order has been attributed either to the greater electron-releasing power [8] of, or to the steric acceleration of migration by, the larger group [6]. Conformational, steric and electronic factors can all alter the normal migratory preference [3,4,9,10], though the regiochemistry of the reaction is usually predictable. However, problems arise when the two migrating groups are similar where upon both possible regioisomers of the product are often formed. Usually only one is required, and although it may be possible

* Corresponding author.

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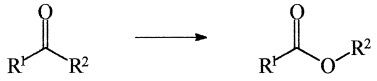
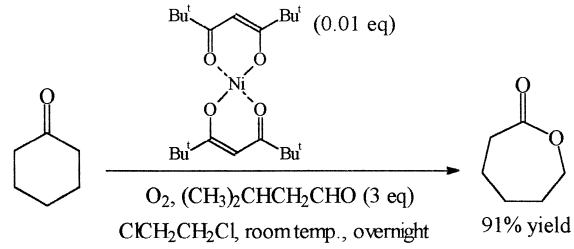


Scheme 1.

to influence the ratio of regioisomers in favour of that which is required by varying the reagents and conditions [2–4,11,12], this is not always the case. In terms of stereochemistry, the Baeyer–Villiger oxidation occurs with retention of configuration at the migrating centre [2], a very important feature for organic synthesis.

2. Chemical methods and reagents for the Baeyer–Villiger oxidation

Currently the most popular chemical oxidants for the Baeyer–Villiger reaction are *meta*-chloroperoxybenzoic acid (MCPBA), trifluoroperoxyacetic acid, peroxybenzoic acid, peroxyacetic acid and hydrogen peroxide. However, major problems may occur upon scaling up the reaction, and extreme caution must be exercised in some of these cases due to the intrinsic instability of many of these reagents. A variety of other, more stable chemical oxidants, such as bis(trimethylsilyl)peroxide [13] and magnesium monoperoxyphthalate [14,15], have been introduced in order to circumvent this problem. Many of the oxidising agents used in the Baeyer–Villiger oxidation also react with a variety of functional groups such as alkenes, amines, phosphines, sulfides and selenides, and as such, several reagents have been developed which allow chemoselective oxidation in the presence of other functional groups [4]. Within the last five years, another chemical oxidation system

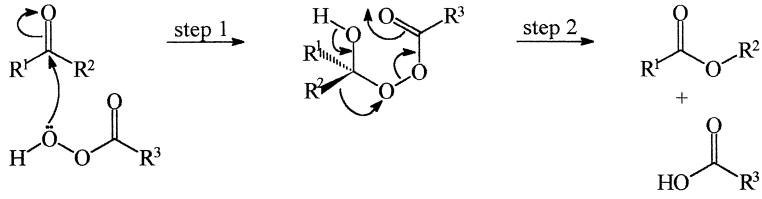


Scheme 3.

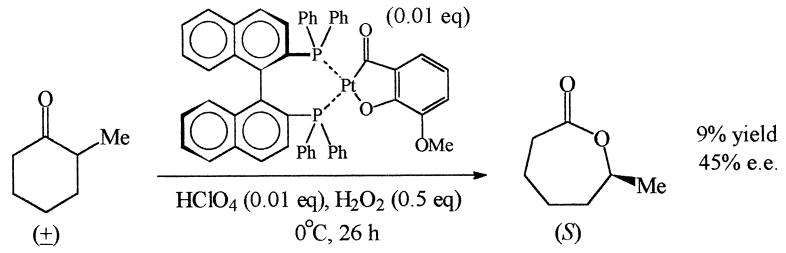
has been established. This new protocol uses molecular oxygen as the oxidant, aldehydes as reductants and transition metal complexes, oxides or salts as the catalysts [16]. For example, Mukaiyama [17] has reported the use of nickel (II) complexes as catalysts for the Baeyer–Villiger oxidation (Scheme 3).

In addition iron (III) oxide [18], copper (II) and nickel (II) acetate [19], heteropolyoxometalates [20], hydrotalcites [21], iron (III) complex [22], ruthenium (IV) and manganese (IV) dioxides [23] have been reported to catalyse the Baeyer–Villiger oxidation. Strukul [24] has reported the use of platinum (II) complexes as catalysts and hydrogen peroxide as oxidant for the Baeyer–Villiger oxidation. These catalytic oxidation systems were further developed so as to use only molecular oxygen and benzaldehyde (with no metal catalyst) for the Baeyer–Villiger oxidation [25–27]. Other oxidants, such as the nibocene ketene complex [28] and hypofluorous acid–acetonitrile complex ($HOF–CH_3CN$) [29], have been reported as oxygen atom transfer reagents for the Baeyer–Villiger oxidation.

With the upsurge in interest in the preparation of target molecules in single enantiomer form, efforts have been made to find a chemical method to achieve an asymmetric Baeyer–Vil-



Scheme 2.



Scheme 4.

liger oxidation. Strukul [30] has reported the use of hydrogen peroxide as the oxidant and various chiral platinum (II) complexes as catalysts for such an asymmetric oxidation of 2-alkyl cycloalkanones. However, both the enantiomeric excesses and yields of the products obtained were very poor (Scheme 4).

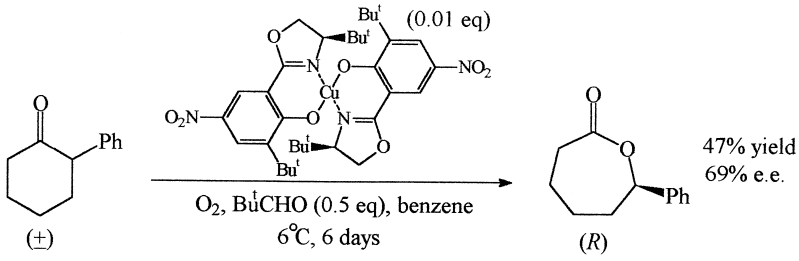
Bolm [31] has reported the use of molecular oxygen as the oxidant, aldehydes as the reductants and chiral copper (II) or nickel (II) complexes as catalysts for the oxidation/kinetic resolution of 2-aryl cycloalkanones (e.g. see Scheme 5). The enantiomeric excesses and yields of the lactones produced ranged between 47–69% and 21–65% respectively; recently Lopp et al. [32] have shown that modified Sharpless oxidation conditions convert substituted cyclobutanones into the corresponding γ-lactones (ee 34–75%).

3. Monooxygenases enzymes as regio- and stereo-selective catalysts for the Baeyer–Villiger oxidation

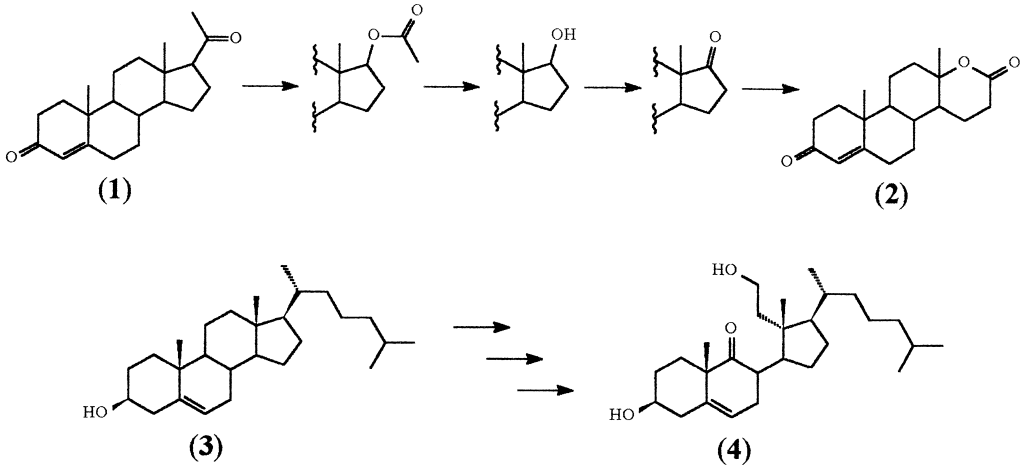
Oxygenases are classified broadly into monooxygenases and dioxygenases [33,34]. Monooxygenases catalyse the insertion of one oxygen atom from molecular oxygen into a substrate, the other oxygen atom undergoing reduction to furnish water. Dioxygenases catalyse the insertion of both oxygen atoms from molecular oxygen into a substrate. Depending on the type of substrate to be oxygenated, monooxygenases can be divided into two subclasses catalysing the following transformations: (1) hydroxylation of aromatic compounds, broadly named as hydroxylases; (2) peroxide oxygenation of either nucleophilic or electrophilic substrates. Baeyer–Villiger monooxygenases belong to this category.

Baeyer–Villiger monooxygenases (BVMOs) contain flavin as a prosthetic group (cofactor). BVMOs have been found to catalyse transformations such as Baeyer–Villiger oxidation [4,35], sulfoxidation [35–39], phosphoxidation [35], amine oxidation [35], boron oxidation [40] and selenoxidation [41].

In the early 1950s, Fried [42] and Peterson [43] noted that, during the incubation of progesterone (**1**) with *Penicillium* species and *Aspergillus flavus*, testololactone (**2**) was formed, apparently by sequential Baeyer–Villiger oxidations (Scheme 6). An acetone powder of the



Scheme 5.



Scheme 6.

gorgonian *Pseudopterogorgia americana* converts cholesterol (**3**) into the tricyclic compound (**4**) (78% yield) by a similar cascade of oxidations [44] (Scheme 6).

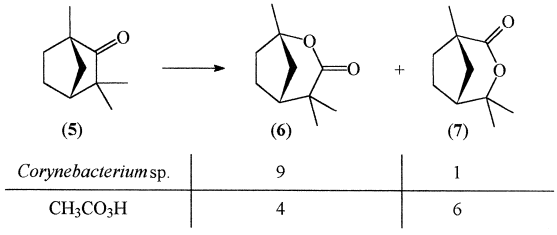
Although the enzyme(s) responsible was (were) not characterised, it was assumed that BVMOs were responsible for the ring-expansion reactions involved in these bioconversions. Other reviews provide further detail of these and other bioconversions involving steroids [45–48].

Regioselective Baeyer–Villiger oxidation of D-fenchone (**5**), catalysed by *Corynebacterium* species, has been reported [49]. The ratio of the two possible regioisomers 1,2-fencholide (**6**) and 2,3-fencholide (**7**) was 9:1; using peroxyacetic acid, the regioselectivity was very poor (Scheme 7).

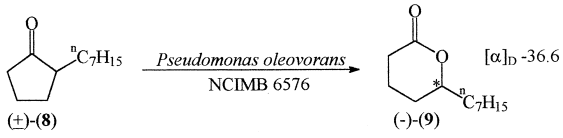
The first enzymic asymmetric Baeyer–Villiger oxidation was reported by Shaw [50] in 1966. (±)-2-heptylcyclopentanone (**8**) was found to be transformed to an optically active δ-heptyl valerolactone (**9**) by incubation with a whole-cell preparation of *Pseudomonas oleovorans* NCIMB 6576 (Scheme 8). The enzyme(s) responsible was (were) not characterised.

Regioselective Baeyer–Villiger oxidation of an acyclic ketone was demonstrated by the isolation of undecanol from a culture of *Pseudomonas multivorans* incubated with 2-tridecanone (Scheme 9) [51–53]. Similarly the ketone (**10**) was transformed into the alcohol (**11**) (40% yield; 65% ee) using *Beauvaria bassiana* (Scheme 9) [54].

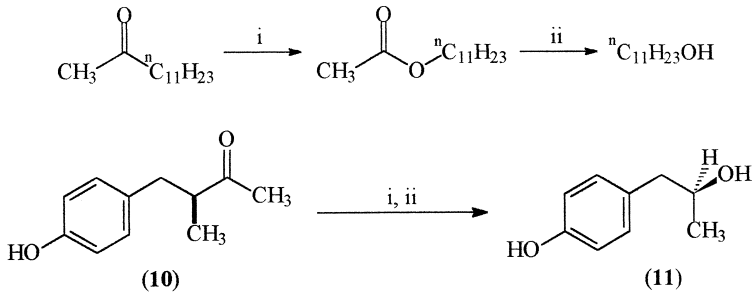
(1*R*)-(+)-Camphor (**12**) was found to be transformed to the corresponding lactone by incubation with a *Pseudomonas* species [55] and subsequently the complete degradation pathway of (1*R*)-(+)-camphor in *Pseudomonas putida* NCIMB 10007 (ATCC 17453) was re-



Scheme 7.



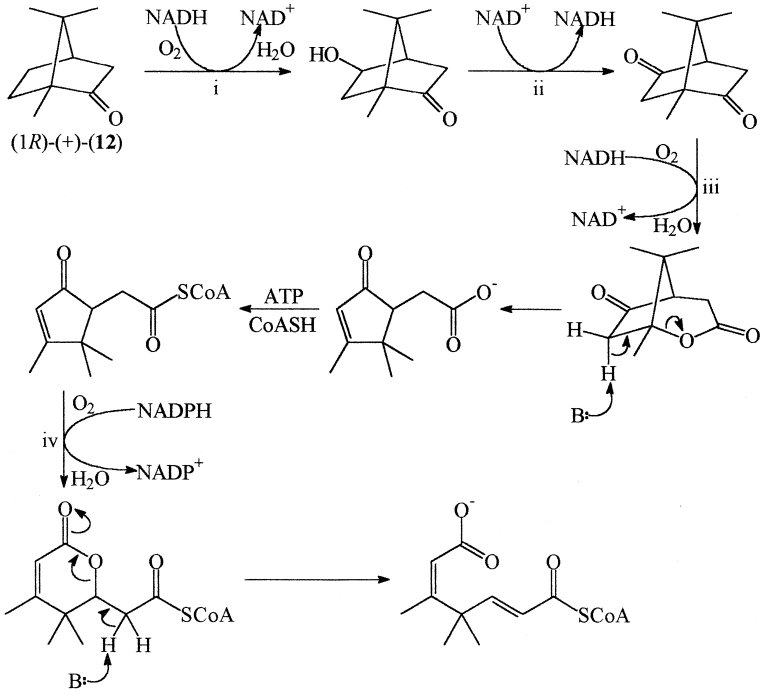
Scheme 8.



Enzymes: i, monooxygenase; ii, hydrolase.

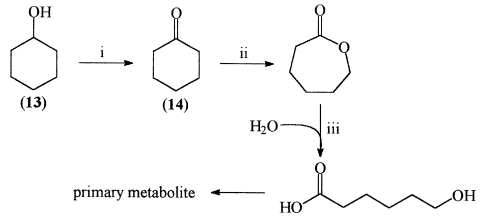
Scheme 9.

ported (Scheme 10) [33,56]. The BVMOs that are involved in this sequence, namely 2-oxa-4,5,5-trimethylcyclopent-3-enylacetyl CoA monooxygenase [57], 2,5-diketocamphane monooxygenase (2,5-DKCMO) [58] and 3,6-diketocamphane monooxygenase (3,6-DKCMO) [59] have been isolated and purified to homogeneity. The early characterisation of 2,5-DKCMO and 2-tridecanone monooxygenase as flavoproteins was confirmed by later investigations on these and other BVMOs. Indeed most, if not all, BVMOs require a flavin-based coen-



Degradation pathway of (1*R*)-(+)-camphor (**12**) in *Pseudomonas putida* NCIMB 10007
Enzymes: i, cytochrome P_{450} monooxygenase; ii, dehydrogenase; iii, 2,5-diketocamphane monooxygenase; iv, 2-oxa-4,5,5-trimethylcyclopent-3-enylacetyl CoA monooxygenase.

Scheme 10.



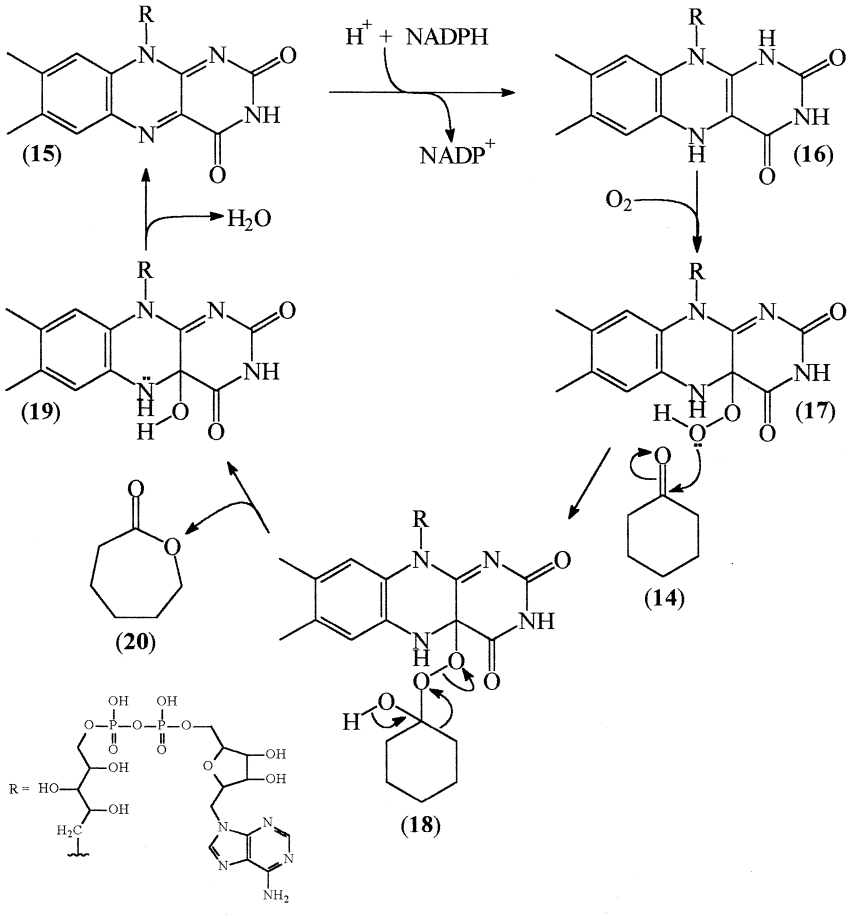
Degradation pathway of cyclohexanol (**13**) in various microorganisms
Enzymes: i, cyclohexanol dehydrogenase; ii, cyclohexanone monooxygenase (CHMO); iii, 2-oxepanone lactonase.

Scheme 11.

zyme, and none has yet been reported that utilises a transition metal [33].

Cyclohexanone monooxygenase (CHMO) enables a number of bacteria to grow on cyclohexanol (**13**) or cyclohexanone (**14**) as a sole source of carbon (Scheme 11) [33,34,60].

Initially isolated from *Acinetobacter calcoaceticus* NCIMB 9871 in 1975, a CHMO has been purified and characterised [61,62] and found to be an NADPH- and oxygen-dependent monomeric protein, dependent on flavin adenine dinucleotide (FAD) as a prosthetic group. The amino acid sequence of the monomeric protein has been determined and the gene responsible for the CHMO activity has been identified, cloned and expressed in *Escherichia coli* [63]. The mechanism of action of CHMO has been examined and results indicate that lactone formation occurs by a classic Baeyer–Villiger rearrangement (Scheme 12) [33,34,64–67]. The



Proposed mechanism of action of CHMO in the enzymic Baeyer-Villiger oxidation

Scheme 12.

prosthetic group FAD (**15**) (which is tightly bounded to the active site of the enzyme) is reduced to $FADH_2$ (**16**) by NADPH. Rapid reaction between $FADH_2$ (**16**) and molecular oxygen affords 4a-hydroperoxyflavin (**17**) which is a potent oxidising agent. Addition of 4a-hydroperoxyflavin (**17**) to the carbonyl group of cyclohexanone (**14**) creates a tetrahedral intermediate (**18**). This tetrahedral intermediate rearranges to give FAD-4a-OH (**19**) and ε-caprolactone (**20**). Finally, a water molecule is eliminated from FAD-4a-OH (**19**) to regenerate FAD (**15**) ready for a subsequent catalytic cycle.

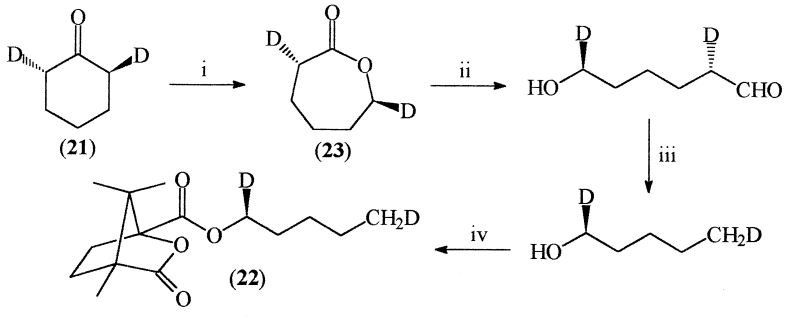
The absolute configuration at the migrating centre on the enzymic Baeyer–Villiger oxidation was found to be retained on using (2*S*,6*S*)-2,6-($^2H_1$)-cyclohexanone (**21**) in the biotransformation. Thus the camphanate ester (**22**), synthesised using the deuteriated ε-caprolactone (**23**) obtained from the enzymic transformation, was found to be a single diastereoisomer (Scheme 13) [68,69].

Some minor differences do occur between the various BVMOs; the reduced nicotinamide nucleotide cofactor can either be NADPH or NADH [58,59] and the prosthetic group can either be flavin adenine dinucleotide (FAD) or flavin mononucleotide (FMN) [58,59].

4. Preparative biotransformation using Baeyer–Villiger monooxygenases

After the above seminal studies, and up to the present time, BVMOs from a variety of microorganisms have been applied in many regioselective and enantioselective enzymic Baeyer–Villiger oxidations using a wide variety of natural and synthetic substrates. Particularly within the last ten years, BVMOs have been widely applied as chiral catalysts to catalyse the transformation of racemic or prochiral ketones to chiral lactones on a scale which has allowed the further manipulation of the products in many cases. These preparative-scale biotransformations may be carried out using either a whole-cell preparation of the appropriate microorganism, partially purified protein or a pure enzyme and some of the results obtained to date are summarised in the Table 1.

In 1987, Azerad [70] and co-workers reported preparative scale asymmetric enzymic Baeyer–Villiger oxidations using a whole-cell preparation of the fungus *Curvularia lunata* NRRL 2380 (Table 1, entry 1). Kinetic resolution of the racemic ketone (**24**) gave the corresponding lactone (**25**); the residual ketone (**24**) was found to be almost enantiomerically pure. Whitesides



Reagents and conditions: i, CHMO; ii, DIBAL-H, THF, -76 °C; iii, $(Ph_3P)_3RhCl$, benzene, reflux; iv, (-)-camphanyl chloride, pyridine.

Scheme 13.

et al. [71] have reported a number of regioselective Baeyer–Villiger oxidations using pure cyclohexanone monooxygenase (CHMO) from *Acinetobacter calcoaceticus* NCIMB 9871 (Table 1, entries 2–6). It was found that the migratory preference in the enzymic Baeyer–Villiger oxidation was very similar to the equivalent chemical reaction. Taschner [72–75] and co-

Table 1
Asymmetric enzymic Baeyer–Villiger oxidations

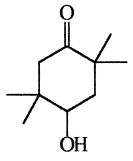
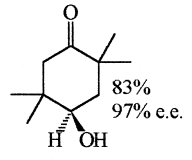
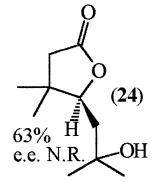
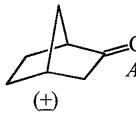
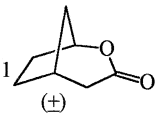
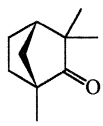
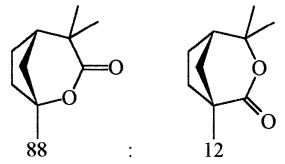
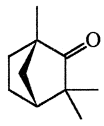
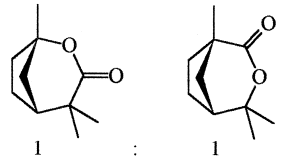
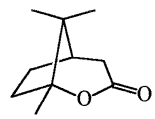
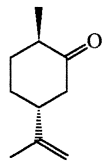
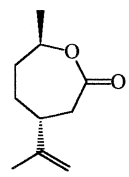
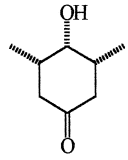
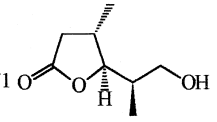
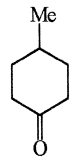
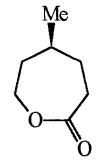
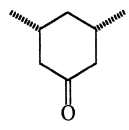
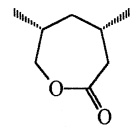
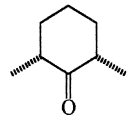
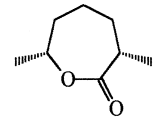
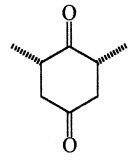
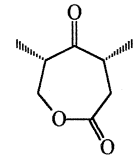
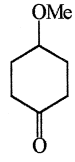
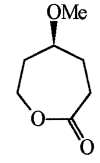
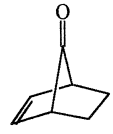
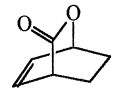
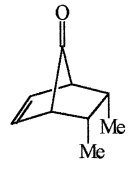
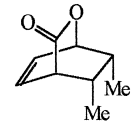
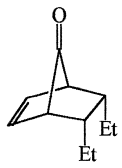
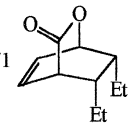
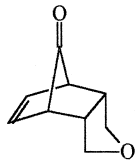
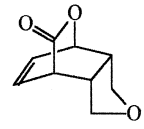
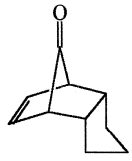
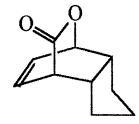
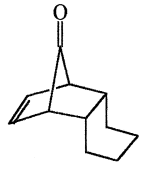
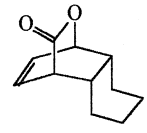
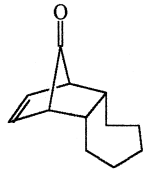
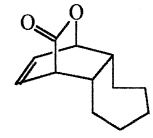
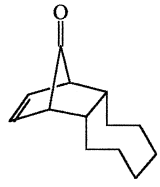
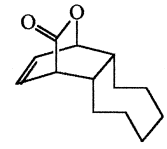
Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
1	 (±)-(**24**)	*Curvularia lunata* NRRL 2380 (whole-cell)	 83% 97% e.e. (**25**)  (**24**) 63% e.e. N.R.	[70]
2	 (±)	CHMO[a] (pure enzyme) from *Acinetobacter* NCIMB 9871	 (±) 81%	[71]
3		as above	 88 : 12 76% overall yield	[71]
4		as above	 1 : 1 79% overall yield	[71]
5		as above	 89%	[71]
6		as above	 75%	[71]

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
7		CHMO[a] (pure enzyme) from *Acinetobacter* NCIMB 9871	 88% > 98% e.e.	[72]
8		as above	 80% > 98% e.e.	[72]
9		as above	 73% > 98% e.e.	[72] [73]
10		as above	 27% > 98% e.e.	[72]
11		as above	 25% > 98% e.e.	[72]
12		as above	 76% 75% e.e.	[72]
13		as above	 62% 80% e.e.	[74]
14		as above	 70% > 98% e.e.	[74]

workers also used pure CHMO from *Acinetobacter calcoaceticus* NCIMB 9871 for asymmetric Baeyer–Villiger oxidations. A number of prochiral substituted cyclohexanones were assayed, and in most cases the corresponding lactones were obtained with good yields and

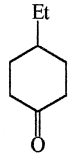
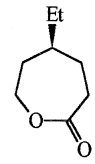
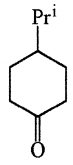
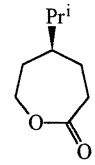
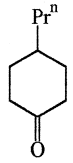
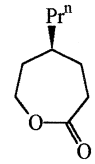
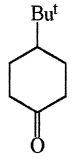
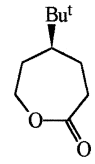
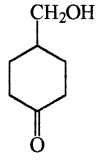
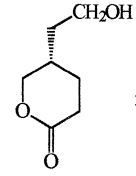
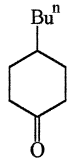
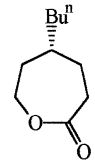
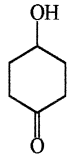
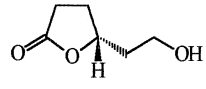
Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
15		CHMO[a] (pure enzyme) from *Acinetobacter* NCIMB 9871	 83% 93% e.e.	[74]
16		as above	 74% > 98% e.e.	[74]
17		as above	 80% 97% e.e.	[74]
18		as above	 78% > 98% e.e.	[74]
19		as above	 57% > 98% e.e.	[74]
20		as above	 55% 87% e.e.	[74]

excellent enantiomeric excesses (Table 1, entries 7–27). However, the major disadvantage of such a protocol is the cost of the reduced nicotinamide nucleotide cofactor, NADPH, on which CHMO depends for the oxygenation. In order to circumvent this problem, a catalytic amount of NADPH was used and, by incorporating an additional enzyme (glucose-6-phosphate dehydrogenase) and co-substrate (glucose-6-phosphate) the constant regeneration of NADPH was ensured (Scheme 14).

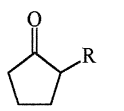
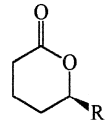
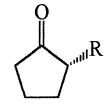
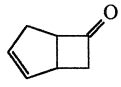
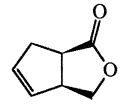
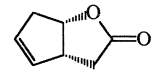
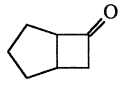
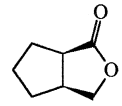
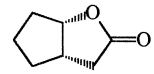
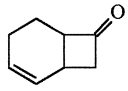
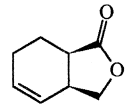
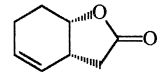
Furstoss [76–83] has been one of the staunchest advocates for the use of CHMOs in *Acinetobacter calcoaceticus* NCIMB 9871 and *Acinetobacter* TD 63 for asymmetric Baeyer–Villiger oxidations. Whole-cell preparations of

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
21		CHMO[a] (pure enzyme) from *Acinetobacter* NCIMB 9871	 84% > 98% e.e.	[75]
22		as above	 60% > 98% e.e.	[75]
23		as above	 80% > 98% e.e.	[75]
24		as above	 17% > 98% e.e.	[75]
25		as above	 80% > 98% e.e.	[75]
26		as above	 70% 52% e.e.	[75]
27		as above	 73% 9.6% e.e.	[75]

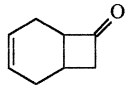
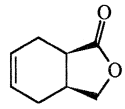
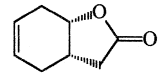
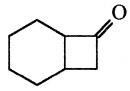
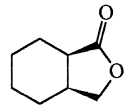
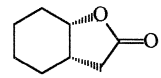
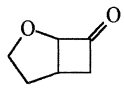
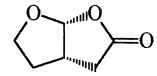
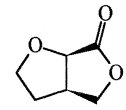
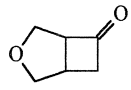
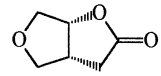
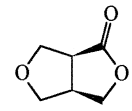
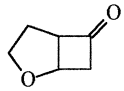
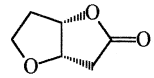
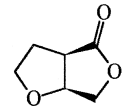
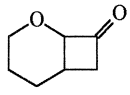
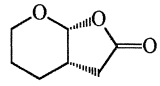
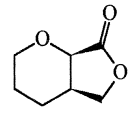
these microorganisms were used as biocatalysts allowing cofactor recycling in situ. The kinetic resolution of a series of 2-alkyl cyclopentanones were carried out; δ-alkyl valerolactones with moderate to excellent yields and enantiomeric excesses were obtained (Table 1, entry 28).

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)		Ref.
28	 (±)	*Acinetobacter calcoaceticus* NCIMB 9871 (whole-cell)			[77] [78]
	$R = {}^{n}C_5H_9$		4% (GC), e.e. N.R.	55% (GC), e.e. N.R.	
	$R = {}^{n}C_7H_{15}$		30% (GC), 92% e.e.	52% (GC), e.e. N.R.	
	$R = {}^{n}C_9H_{19}$		22% (GC), 82% e.e.	52% (GC), e.e. N.R.	
	$R = {}^{n}C_{11}H_{23}$		40% (GC), 60% e.e.	40% (GC), 71% e.e.	
		Acinetobacter TD 63 (whole-cell)			
	$R = {}^{n}C_5H_9$		10% (GC), 95% e.e.	68% (GC), e.e. N.R.	
	$R = {}^{n}C_7H_{15}$		30% (GC), 90% e.e.	50% (GC), e.e. N.R.	
	$R = {}^{n}C_9H_{19}$		26% (GC), 70% e.e.	55% (GC), e.e. N.R.	
	$R = {}^{n}C_{11}H_{23}$		45% (GC), 44% e.e.	50% (GC), 47% e.e.	
29	 (±)-(**26**)		 (**36**)	 (**31**)	[76] [80]
		Acinetobacter NCIMB 9871 (whole-cell)	33% > 95% e.e.	30% > 95% e.e.	
		Acinetobacter TD 63 (whole-cell)	35% > 95% e.e.	28% > 95% e.e.	
30	 (±)-(**27**)		 (**37**)	 (**32**)	[80]
		Acinetobacter NCIMB 9871 (whole-cell)	20% > 95% e.e.	19% > 95% e.e.	
		Acinetobacter TD 63 (whole-cell)	25% > 95% e.e.	21% > 95% e.e.	
31	 (±)-(**28**)		 (**38**)	 (**33**)	[80]
		Acinetobacter NCIMB 9871 (whole-cell)	35% > 95% e.e.	27% > 95% e.e.	
		Acinetobacter TD 63 (whole-cell)	37% > 95% e.e.	21% > 95% e.e.	

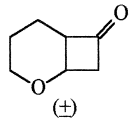
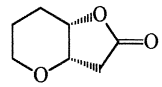
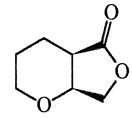
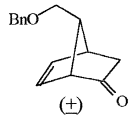
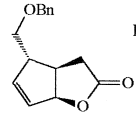
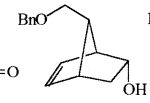
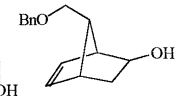
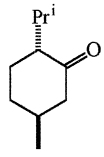
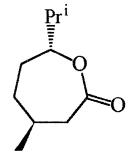
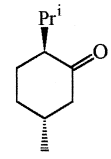
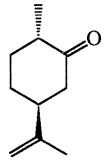
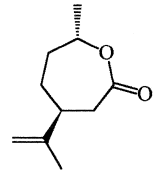
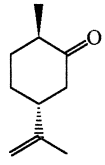
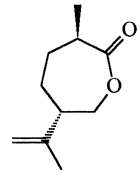
More interesting was the enantiodivergent transformation of [3 · 2 · 0] and [4 · 2 · 0] bicyclic ketones; in most cases both regioisomeric lactones were obtained with moderate yields and excellent enantiomeric excesses (Table 1, entries 29–38). A few examples of regioselective Baeyer–Villiger oxidations were also reported (Table 1, entries 39–42). Based on the results

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)		Ref.
32	 (±)-(**29**)		 (**39**)	 (**34**)	[80]
		Acinetobacter NCIMB 9871 (whole-cell)	22% > 95% e.e.	27% 86% e.e.	
		Acinetobacter TD 63 (whole-cell)	26% > 95% e.e.	20% 92% e.e.	
33	 (±)-(**30**)		 (**40**)	 (**35**)	[80]
		Acinetobacter NCIMB 9871 (whole-cell)	18% > 95% e.e.	30% 61% e.e.	
		Acinetobacter TD 63 (whole-cell)	12% > 95% e.e.	24% 53% e.e.	
34	 (±)	*Acinetobacter calcoaceticus* NCIMB 9871 (whole-cell)	 35% 90% e.e.	 32% > 98% e.e.	[82]
35	 (±)	as above	 35% 97% e.e.	 35% > 98% e.e.	[82]
36	 (±)	as above	 33% > 98% e.e.	 41% > 98% e.e.	[82]
37	 (±)	as above	 33% 70% e.e.	 33% > 98% e.e.	[82]

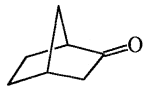
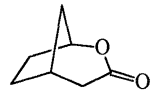
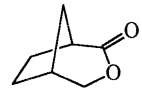
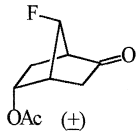
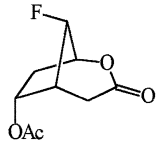
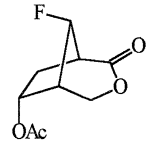
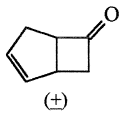
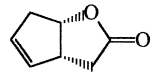
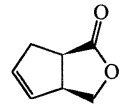
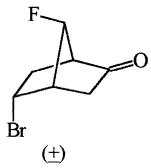
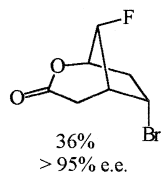
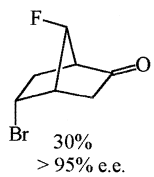
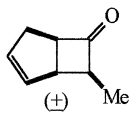
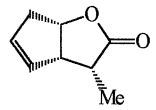
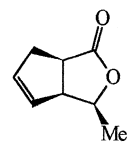
obtained from the enantiodivergent transformation of the bicyclic ketones (**26**)–(**30**) (Table 1, entries 29–33), Furstoss has proposed a model of the active site of CHMO [80]. In this hypothesis, and in accord with the proposed mechanism of action of CHMO (Scheme 12), 4a-hy-

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
38	 (±)	*Acinetobacter calcoaceticus* NCIMB 9871 (whole-cell)	 60% 33% e.e.  18% > 98% e.e.	[82]
39	 (±)	*Acinetobacter calcoaceticus* NCIMB 9871 (whole-cell)	 26% 85% e.e.  35% 95% e.e.  8% 89% e.e.	[79]
40	 (±)	*Acinetobacter* NCIMB 9871 (whole-cell) *Acinetobacter* TD 63 (whole-cell)	 45% > 98% e.e. 43% > 98% e.e.	 20% > 98% e.e. 20% > 98% e.e.	[81]
41		*Acinetobacter* NCIMB 9871 (whole-cell) *Acinetobacter* TD 63 (whole-cell)	80% 95%		[81]
42		*Acinetobacter* NCIMB 9871 (whole-cell) *Acinetobacter* TD 63 (whole-cell)	73% 66%		[81]

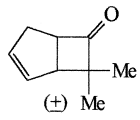
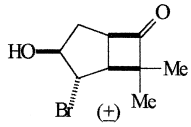
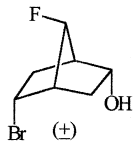
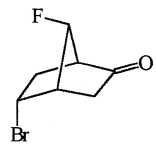
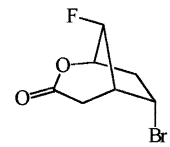
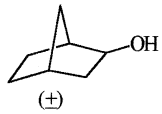
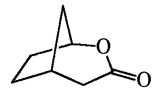
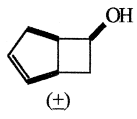
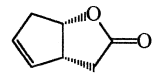
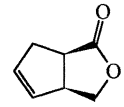
droperoxyflavin (**17**) is the oxygen transfer agent. The enantioselectivity of the reaction is due to the different positioning of each tetrahedral intermediate in the active site (Fig. 1). Furstoss supposed that the attack of the 4a-hydroperoxyflavin (**17**) should take place on the least hindered face of the ketones (**26**)–(**30**). On the other hand, the migrating C–C bond of the tetrahedral intermediate should be antiperiplanar to the peroxydic bond and to a non-bonded electron pair of the hydroxy group (as suggested by Deslongchamps [84] for chemical Baeyer–Villiger oxidations). Thus, the cycloalkyl part of the (*S*,*S*) enantiomer of the ketone (the one

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
43		*Pseudomonas* sp. NCIMB 9872 (whole-cell)	  38 : 1 100% overall yield (GC)	[88]
		Chemically using peroxyacid	9 : 1 100% overall yield (GC)	
44	 (±)	*Acinetobacter* sp. NCIMB 9871 (whole-cell)	  100 : 1 11%	[89]
		Chemically using peroxyacid	1 : 4	
45	 (±)	Various dematiaceous fungi of the genera *Drechslera* and *Curvularia* (whole-cell) e.g., *Curvularia intermedia*	  86% e.e. 98% e.e. 95% overall yield (GC)	[90] [91]
46	 (±)	*Acinetobacter* sp. NCIMB 9871 (whole-cell)	 36% > 95% e.e.  30% > 95% e.e.	[93]
47	 (±)	*Acinetobacter* NCIMB 9871 (whole-cell)	  1 : 1 > 96% e.e. > 96% e.e. 55% overall yield	[94] [95]
		Chemically using peroxyacetic acid	1 : 10 (±) 75% overall yield (±)	

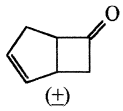
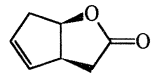
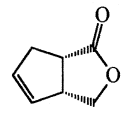
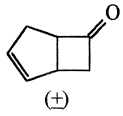
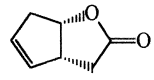
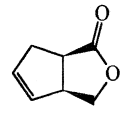
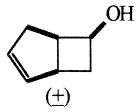
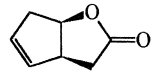
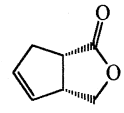
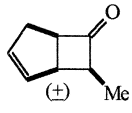
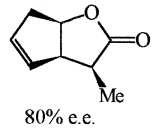
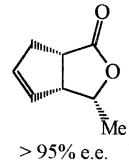
leading to 2-oxo-lactone (**31**)–(**35**)) could be accommodated in only one region of the active site (position 1). Position 2 would never be adopted due to some steric hindrance within the active site (dotted cube). In the case of the (*R*,*R*) enantiomer (leading to 2-oxo-lactones

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
48		*Acinetobacter* NCIMB 9871 (whole-cell)	N.D.	63% 29% e.e.	[94] [95]
		Pseudomonas sp. NCIMB 9872 (whole-cell)	1 : 20 41% overall yield, e.e. N.R.	
		Chemically using peroxyacetic acid	N.D.	56% (±)	
49		*Acinetobacter* NCIMB 9871 (whole-cell)	31% > 98% e.e.	30% 96% e.e.	[94] [95]
		Chemically using peroxyacetic acid	61% (±)	N.D.	
50		*Acinetobacter calcoaceticus* NCIMB 9871 (fractured cell)	 15% (GC) e.e. N.R.	 50% (GC) e.e. N.R.	[96]
51		Alcohol dehydrogenase from *Thermoanaerobium brockii* & CHMO[a] (pure enzyme) from *Acinetobacter calcoaceticus* NCIMB 9871		16% 56% e.e.	[96]
52		same conditions	 :  2 : 1 86% e.e. e.e. N.R. 41% overall yield		[96]

(**31**)–(**35**) and 3-oxo-lactones (**36**)–(**40**)), the molecule could adopt two orientations (position 3 and 4), although position 4 (which leads to 3-oxo-lactones (**36**)–(**40**)) is favoured over position 3 because of electronic interactions with the active site. Furstoss suggested that this hypothe-

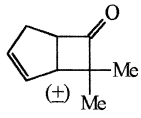
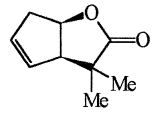
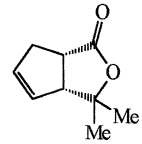
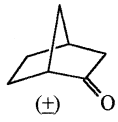
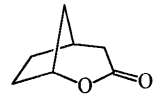
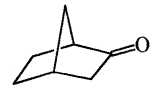
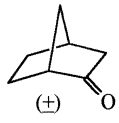
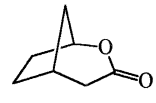
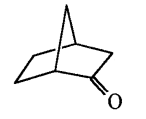
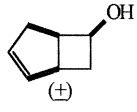
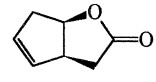
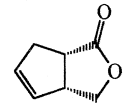
Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)		Ref.
53	 (±)	*Ps. putida* NCIMB 10007 (whole cell)	 50% e.e. 86% overall yield	 > 95% e.e.	[97] [98] [99] [100]
		MO 1[b] from *Ps. putida* NCIMB 10007	53% (GC) 89% e.e.	47% (GC) > 99% e.e.	
		2,5-DKCMO[d] from *Ps. putida* NCIMB 10007	57% (GC) 82% e.e.	43% (GC) 100% e.e.	
		3,6-DKCMO[e] from *Ps. putida* NCIMB 10007	17% (GC) 10% e.e.	13% (GC) 72% e.e.	
	 (±)				
		MO 2[c] from *Ps. putida* NCIMB 10007	72% (GC) 35% e.e.	28% (GC) 95% e.e.	
		CHMO[a] from *Acinetobacter* NCIMB 9871	92% e.e.	95% e.e.	
54	 (±)	Alcohol dehydrogenase from *Pseudomonas* sp. NCIMB 9872 & MO 1[b] from *Ps. putida* NCIMB 10007	 59% (GC) 79% e.e.	 41% (GC) > 98% e.e.	[97] [98]
55	 (±) Me	*Pseudomonas putida* NCIMB 10007 (whole-cell)	 80% e.e. 63% overall yield	 > 95% e.e.	[98]

sis could also explain the difference of behaviour observed between the [3 · 2 · 0] bicyclic ketones (**26**), (**27**), and the [4 · 2 · 0] bicyclic ketones (**28**)–(**30**). The tetrahedral intermediates of ketone (**26**) and (**27**) could not adopt position 3, because these molecules are more concave than those of the [4 · 2 · 0] bicyclic ketones (**28**)–(**30**), and would be partially situated in the 'forbidden zone' (dotted cube). The active site model of CHMO from *Acinetobacter calcoaceticus* NCIMB 9871 has been developed further by Ottolina et al. [85]; however, since the 3-dimensional structure of CHMO has not yet been determined, such models must remain purely speculative.

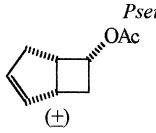
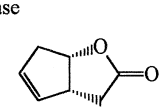
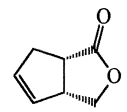
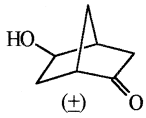
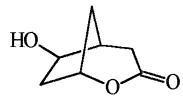
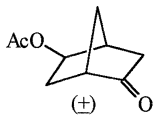
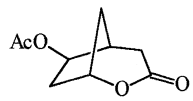
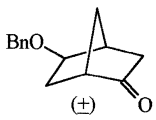
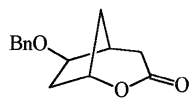
One of the most interesting features of the biocatalysed oxidation of bicycloheptanones (**26**) and (**27**) is the formation of the 3-oxabicyclo[3

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)		Ref.
56					[98] [99]
		Ps. putida NCIMB 10007 (whole cell)	80% e.e.	> 95% e.e.	
			73% overall yield		
		MO 1[b] from *Ps. putida* NCIMB 10007	89% e.e.	> 95% e.e.	
			100% overall yield (GC)		
		MO 2[c] from *Ps. putida* NCIMB 10007	60% e.e.	> 95% e.e.	
			100% overall yield (GC)		
57					[98] [99] [100]
		Ps. putida NCIMB 10007 (whole cell)	60% (GC)	40% (GC)	
			53% e.e.	70% e.e.	
		MO 1[b] from *Ps. putida* NCIMB 10007	53% e.e.	e.e. N.R.	
		2,5-DKCMO[d] from *Ps. putida* NCIMB 10007	20% (GC)	80% (GC)	
			60% e.e.	20% e.e.	
		3,6-DKCMO[e] from *Ps. putida* NCIMB 10007	48% (GC)	52% (GC)	
			> 90% e.e.	> 90% e.e.	
					
		MO 2[c] from *Ps. putida* NCIMB 10007	14% e.e.	e.e. N.R.	
		CHMO[a] from *Acinetobacter* NCIMB 9871	(±)	(±)	
58		Horse liver alcohol dehydrogenase & MO 1[b] from *Ps. putida* NCIMB 10007	 58% (GC) 79% e.e.	 42% (GC) 97% e.e.	[100]

· 3 · 0]octan-2-ones (**36**) and (**37**) since these compounds are formed to only a minor extent ($\leq$ 10%) using chemical oxidants. Difficulties in separating the lactones (**31**) and (**36**) encouraged Furtoss to search for, and find, an organism that would enantioselectively oxidise racemic ketone (±)-(**26**). The required oxidation was provided by *Cunninghamella echinulata* NRRL 3655 which provided the lactone (**36**) in 30% yield and > 98% ee [86]. With

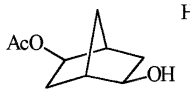
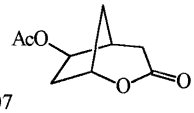
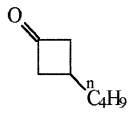
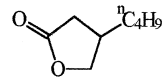
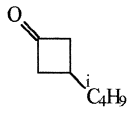
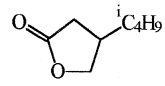
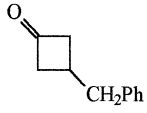
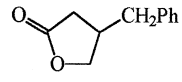
Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
59		*Pseudomonas cepacia* lipase & Horse liver alcohol dehydrogenase & MO 1[b] from *Ps. putida* NCIMB 10007	 9% (GC) 93% e.e.  33% (GC) 100% e.e.	[100]
60		MO 1[b] from *Ps. putida* NCIMB 10007	 11% > 95% e.e.	[102]
		2,5-DKCMO[d] from *Ps. putida* NCIMB 10007	0%	
		3,6-DKCMO[e] from *Ps. putida* NCIMB 10007	33% (GC) > 95% e.e.	
61		*Ps. putida* NCIMB 10007 (whole-cell)	 27% > 95% e.e.	[102]
		MO 1[b] from *Ps. putida* NCIMB 10007	35% > 95% e.e.	
		MO 2[c] from *Ps. putida* NCIMB 10007	39% (GC) >95% e.e.	
		2,5-DKCMO[d] from *Ps. putida* NCIMB 10007	35% (GC) > 95% e.e.	
		3,6-DKCMO[e] from *Ps. putida* NCIMB 10007	0%	
62		*Ps. putida* NCIMB 10007 (whole-cell)	 11% > 95% e.e.	[102]
		MO 1[b] from *Ps. putida* NCIMB 10007	39% > 95% e.e.	
		MO 2[c] from *Ps. putida* NCIMB 10007	50% (GC) 87% e.e.	

useful supplies of compound (**36**) available, the Furtoss team completed syntheses of (+)-virdene [86], (+)-multifidene [86], (−)-cyclosarkomycin [87] (Scheme 15).

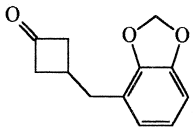
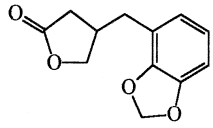
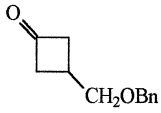
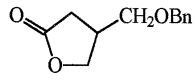
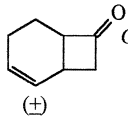
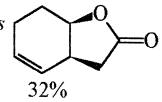
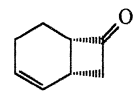
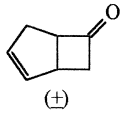
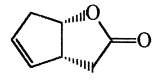
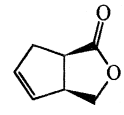
Acinetobacter calcoaceticus NCIMB 9871, *Pseudomonas* species NCIMB 9872 and *Pseudomonas putida* NCIMB 10007 have been employed as the biocatalysts for the Baeyer–Vil-

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
63		Horse liver alcohol dehydrogenase & MO 1[b] from *Ps. putida* NCIMB 10007	 15% (GC) > 95% e.e.	[102]
64				[103]
		Acinetobacter calcoaceticus NCIMB 9871 (whole-cell)	68% 17% e.e.	(*S*)-lactone
		MO 1[b] from *Ps. putida* NCIMB 10007	100% (GC) 69% e.e.	(*R*)-lactone
		MO 2[c] from *Ps. putida* NCIMB 10007	93% (GC) 54% e.e.	(*R*)-lactone
65				[103]
		Acinetobacter calcoaceticus NCIMB 9871 (whole-cell)	56% 84% e.e.	(*S*)-lactone
		MO 1[b] from *Ps. putida* NCIMB 10007	78% (GC) 91% e.e.	(*R*)-lactone
		MO 2[c] from *Ps. putida* NCIMB 10007	97% (GC) 85% e.e.	(*R*)-lactone
66				[103]
		Acinetobacter calcoaceticus NCIMB 9871 (whole-cell)	57% 82% e.e.	(*S*)-lactone
		MO 1[b] from *Ps. putida* NCIMB 10007	40% 15% e.e.	(*S*)-lactone
		MO 2[c] from *Ps. putida* NCIMB 10007	26% 20% e.e.	(*S*)-lactone

liger oxidations of substituted bicyclo[3 · 2 · 0]heptanones and bicyclo[2 · 2 · 1]heptanones (Table 1, entries 43–52) [88–96]. *Ps. putida* NCIMB 10007 contains at least three BVMOs: 2,5-diketocamphane monooxygenase (2,5-DKCMO), 3,6-diketocamphane monooxygenase (3,6-DKCMO) and 2-oxa-4,5,5-trimethylcyclopent-3-enylacetyl CoA monooxygenase (Scheme 10). 2,5-DKCMO and 3,6 DKCMO (MO 1) are FMN- and NADH-dependent monooxygenases while 2-oxa-4,5,5-trimethylcyclopent-3-enylacetyl CoA monooxygenase (MO 2) was found to be FAD- and NADPH-dependent. Both MO 1 and MO 2 may be used in the form of partially purified enzyme preparations from cell-free extracts. On addition of the relevant

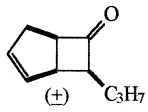
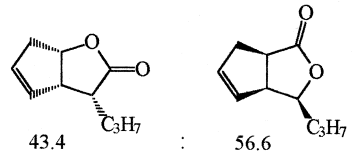
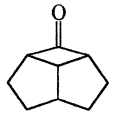
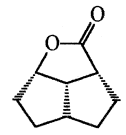
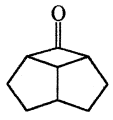
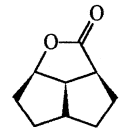
Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
67				[103]
		Acinetobacter calcoaceticus NCIMB 9871 (whole-cell)	83% (*S*)-lactone 95% e.e.	
		MO 1[b] from *Ps. putida* NCIMB 10007	38% (*R*)-lactone 7% e.e.	
		MO 2[c] from *Ps. putida* NCIMB 10007	69% (GC) (*S*)-lactone 14% e.e.	
68				[103]
		Acinetobacter calcoaceticus NCIMB 9871 (whole-cell)	89% (*S*)-lactone 55% e.e.	
		MO 1[b] from *Ps. putida* NCIMB 10007	74% (GC) (*S*)-lactone 74% e.e.	
		MO 2[c] from *Ps. putida* NCIMB 10007	95% (GC) (*R*)-lactone 90% e.e.	
69	 (±)	*Cylindrocarpon destructans* ATCC 11011 (whole-cell)	 32% 27% e.e.  28% e.e.	[111]
70	 (±)		 	[112]
		Pseudomonas putida AS 1 (whole-cell)	89.0% e.e. 99.6% e.e. 86% overall yield	
		Acinetobacter junii (whole-cell)	87.4% e.e. 99.3% e.e. 79% overall yield	
		Rhodococcus coprophilus WT 1 (whole-cell)	89.1% e.e. 99.6% e.e. 69% overall yield	
		Rhodococcus fasciens WT 13 (whole-cell)	89.1% e.e. 99.0% e.e. 63% overall yield	
		Acinetobacter NCIMB 9871 (whole-cell)	93.7% e.e. 99.2% e.e. 67% overall yield	
		CHMO[a] from *Acinetobacter* NCIMB 9871	94.3% e.e. 98.9% e.e. 98% overall yield	

cofactor (NADH or NADPH) to the partially purified enzyme (a crude mixture of MO 1 and MO 2 monooxygenases), it is possible to discriminate between the different activities (Table 1, entries 53–68) [97–103].

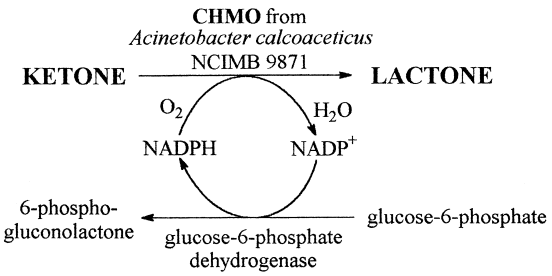
While all the previous examples have illus-

Table 1 (continued)

Entry	Substrate	Biocatalyst	Product(s), yield(s) and e.e.(s)	Ref.
71		*Xanthobacter autotrophicus* NCIMB 10811 (whole-cell)	 43.4 100% e.e. : 56.6 100% e.e.	[113]
72		CHMO[a] (pure enzyme) from *Acinetobacter* sp. NCIMB 9871	 100% (GC) > 98% e.e.	[114] [115]
73		MO 1[b] from *Pseudomonas putida* NCIMB 10007	 100% (GC) > 98% e.e.	[114] [115]

[a] CHMO, cyclohexanone monooxygenase.
[b] MO 1, NADH stimulated activities of the partially purified enzyme isolated from *Pseudomonas putida* NCIMB 10007.
[c] MO 2, NADPH stimulated activities of the partially purified enzyme isolated from *Pseudomonas putida* NCIMB 10007.
[d] 2,5-DKCMO, 2,5-diketocamphane monooxygenase.
[e] 3,6-DKCMO, 3,6-diketocamphane monooxygenase.
N.D., not detected; N.R., not reported. When NCIMB 9871 is quoted, *Acinetobacter* and *Acinetobacter* sp. are equivalent to *Acinetobacter calcoaceticus*. When NCIMB 10007 is quoted, *Ps. putida* is equivalent to *Pseudomonas putida*.

trated the Baeyer–Villiger oxidation of ketones to lactones, it has been reported that through the use of a coupled enzyme system [96–98,100,102], the oxidation of alcohols to lactones via the corresponding ketone is also possible. Matched alcohol dehydrogenase and monooxygenase were used to catalyse the transformation and simultaneously recycle the cofactor, either NADH or NADPH (Scheme 16) (Table 1, entries 50–52, 54, 58, 59 and 63).



Scheme 14.

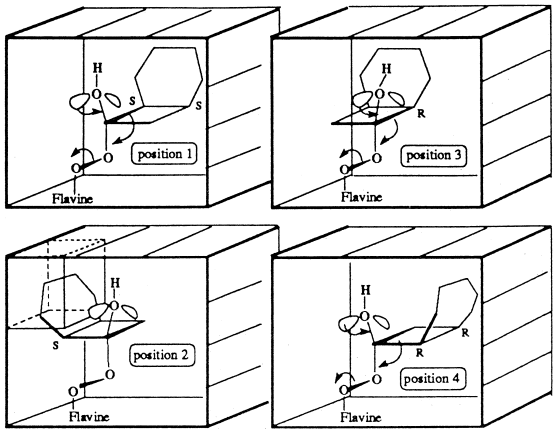
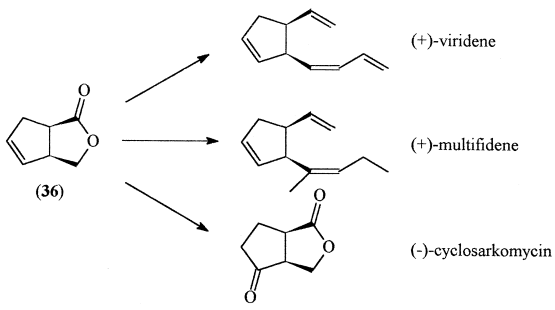
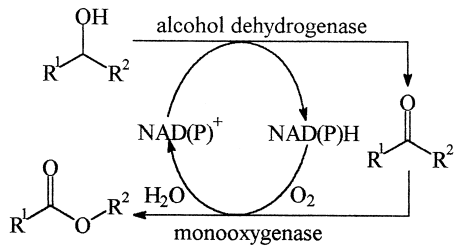


Fig. 1.



Scheme 15.



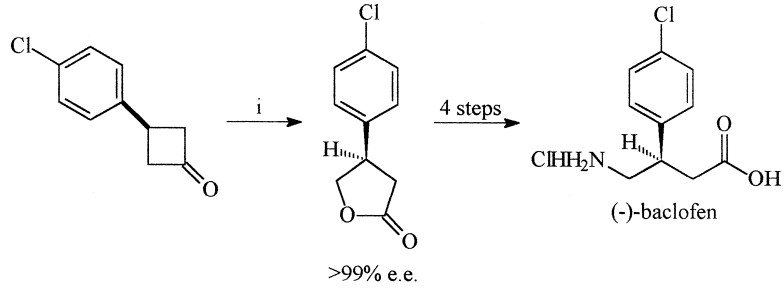
Scheme 16.

Very recently, a series of prochiral 3-substituted cyclobutanones have been subjected to the bio-Baeyer–Villiger reaction; the corresponding lactones were obtained, often in good to excellent yield and enantiomeric excess (Table 1, entries 64–68) [103] and this work formed the basis of an efficient synthesis of baclofen (Scheme 17) [104].

The relative merits of using a whole cell system (*Acinetobacter*) and an isolated enzyme (MO 2) for the kinetic resolution of 2-substituted cyclohexanones have been surveyed [105]. The enantioselective Baeyer–Villiger oxidation of the ketone (**41**) using the MO 2 system was scaled up to provide quantities of the lactone (**42**) for its conversion into (*R*)-(+)-lipoic acid (Scheme 18) [106–108].

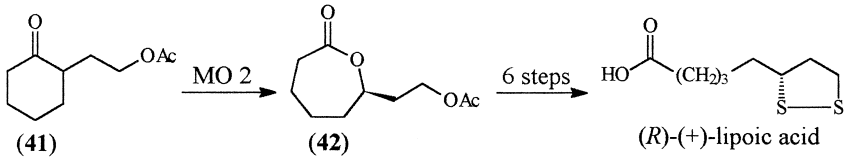
In two noteworthy papers Steward et al. have reported that Bakers' yeast expressing CHMO from *Acinetobacter* provides a simple alternative whole cell system for the kinetic resolution of 2-alkylcyclohexanones [109,110].

Griengl [111], Knowles [112] and Kelly [113] have reported enantiodivergent transformations of bicyclo[3 · 2 · 0]- and bicyclo[4 · 2 · 0]-ketones (Table 1, entries 69–71) using biocatalysts derived from various microorganisms. In most cases, lactones were obtained with excellent yields and enantiomeric excesses. Hence the range of biocatalysts for use in the area of enzymic asymmetric Baeyer–Villiger oxidations is now very broad. Very recently, Kelly [114,115] has designed a *meso*-ketone which could possibly help in the mapping of the functional active site of many of the BVMOs. Almost optically pure lactone was obtained from the biotransformations using either pure CHMO from *Acinetobacter calcoaceticus* NCIMB 9871 or MO 1 from *Pseudomonas putida* NCIMB



Reagents and conditions: i, *Cunninghamella echinulata*, H_2O, 24 h, 30% yield.

Scheme 17.



Scheme 18.

10007 (Table 1, entries 72 and 73). On the basis of these, and other results, an active site model for the MO 1 monooxygenase enzyme has been proposed and a rationale for the origin of stereoselectivity for a whole raft of such enzyme-catalysed Baeyer–Villiger oxidations has been put forward [116,117].

5. Conclusions and outlook

The monooxygenase-catalysed Baeyer–Villiger reaction often provides products in optically active form; some of these products are difficult to obtain by other strategies. Certainly other bioconversions (e.g., lipase-catalysed reactions [118]) and biomimetic transformations [119] are decidedly inferior. Variations of Bolm's non-natural catalysts are the most likely to provide alternatives to the biocatalysts in the not-too-distant future.

However, at the present time, biotransformations provide the best methodology for accomplishing asymmetric Baeyer–Villiger reactions. The most popular whole cell biocatalyst is *Acinetobacter calcoaceticus* NCIMB 9871. The monooxygenase(s) in the whole cell system is (are) well documented in terms of substrate-, regio-, and stereo-selectivities. The fact that *A. calcoaceticus* is a Class 2 organism and hence should be used in a properly sealed and ventilated laboratory restricts its use from the non-specialist. Hence the recent availability of monooxygenase enzymes (e.g., CHMO, MO 1, MO 2 et al.) from a commercial supplier (Fluka) provide helpful encouragement for other scientists wishing to experiment in this field.

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