Application of Enzymic Baeyer–Villiger Oxidations of 2-Substituted Cycloalkanones to the Total Synthesis of (*R*)-(+)-Lipoic Acid

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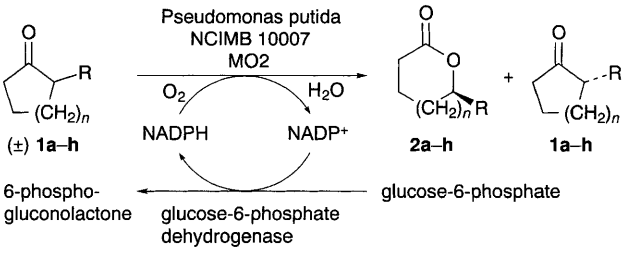
Oxidation of ketones **1a–h** using a monooxygenase from *Pseudomonas putida* NCIMB 10007 gave the lactones **2a–h** in optically active form: lactone **2h** was converted into (*R*)-(+)-lipoic acid **9**.

Kinetic resolution of cyclic ketones *via* enzymic Baeyer–Villiger oxidation provides chiral lactones which are valuable synthons for use in synthetic organic chemistry.[1] Our previous studies using NADH and NADPH-dependent monooxygenases (labelled MO1 and MO2, respectively) from *Pseudomonas putida* NCIMB 10007 proved MO2 was able to catalyse the Baeyer–Villiger oxidation of (*S*)-2-alkyl cyclopentanones to the (*S*)-δ-lactones. Excellent enantiomeric excesses (92–95%) and enantioselectivies (E_p2† = *ca.* 52–>100) were obtained.[1a]

We now report enantioselective bio-Baeyer–Villiger oxidations on a wider variety of cycloalkanones **1a–h** (Scheme 1) and the application of this technique to the total synthesis of naturally occurring (*R*)-(+)-lipoic acid. The ketones **1a–h** were oxidised enantioselectively using MO2 from *Pseudomonas putida* NCIMB 10007 and a non-stoichiometric amount of NADPH to give the lactones **2a–h**. Recycling of NADPH was effected using glucose-6-phosphate plus glucose-6-phosphate dehydrogenase. The results in Table 1 show the ketones **1a** and **1b** were oxidised to the corresponding lactones (*S*)-**2a** and (*S*)-**2b** with a lower enantioselectivity in comparison to the oxidations of the corresponding 2-alkyl cyclopentanones.[1a] It is known that 3,4,4-trimethyl-5-carboxymethylcyclopent-2-enone, probably in the form of the CoA-ester, **3** is the natural metabolite transformed by MO2 in the living cells to the corresponding lactone.[3] Since **3** is a 5-membered ring ketone, this seemed to suggest that MO2 is more enantioselective towards the oxidation of compounds closely related to the natural substrate. With this in mind and considering ketone **3** contains a polar side chain ($CH_2CO_2^-$/$CH_2COSCoA$), we decided to investigate the effect that such a polar functional group would have on the oxidation of cyclopentanones and cyclohexanones. The results in Table 1 show that cycloalkanones **1c**, **d**, **e** and **g** with polar and non-bulky side chains give excellent enantiomeric excesses (>90%) and enantioselectivities (E_p *ca.* 58–>100). In contrast, the ketone **1f** with a bulkier and less polar side chain was oxidised with very poor enantioselectivity. The high volatility of the starting material and the product account for the low recoveries in runs involving the ketones **1e** and **f**. No attempt was made to optimise the work-up conditions.

Of particular interest was the oxidation of cyclohexanone **1h** using MO2 which afforded the lactone **2h** with an e.e. of 83% and enantiomeric ratio of *ca.* 17. The decrease in enantioselectivity for this conversion compared with the conversion of compound **1e** may be due to the increased



a *n* = 2 R = C_6H_{13}
b *n* = 2 R = C_8H_{17}
c *n* = 2 R = CH_2CO_2Et
d *n* = 1 R = CH_2CO_2Et
e *n* = 1 R = CH_2OAc
f *n* = 1 R = $CH_2OSiBu^tMe_2$
g *n* = 1 R = $CH_2OCH_2O(CH_2)_2OMe$
h *n* = 2 R = CH_2CH_2OAc

Scheme 1

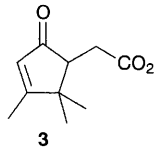


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Table 1

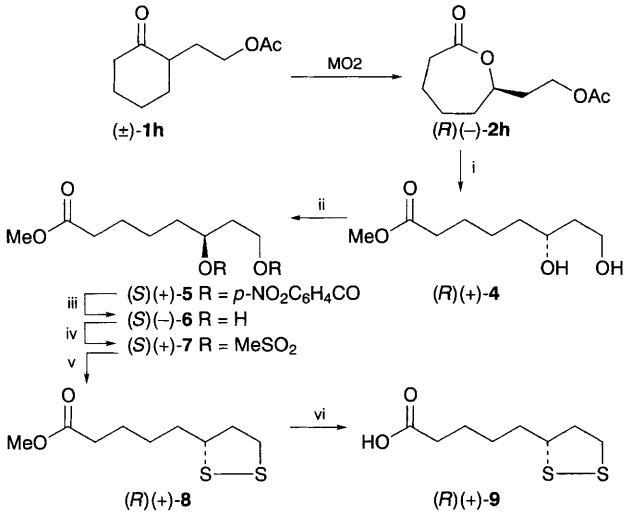
	2a–h					1a–h		
Substrate	Conv.[a] (%)	Yield[b] (%)	E.e.$_p$[c] (%)	E_p2†	Config.[e]	Yield[e] (%)	E.e.$_s$[d] (%)	Config.[e] (%)
1a	47	36	72	~12	*S*	30	65	*R*
b	44	34	77	~14	*S*	49	61	*R*
c	45	30	93	~63	*R*	33	89	*S*
d	37	27	>98	>100	*R*	37	75	*S*
e	40	16	>98	>100	*R*	19	65	*S*
f	40	18	45	~3	*R*	25	22	*S*
g	50	45	>90	~58	*R*	47	88	*S*
h	36	34	83[f]	~17	*R*	13	75[f]	*S*

[a] Conv. = conversion of ketone to lactone based on GC analysis of the isolated crude products using a capillary column, BP 1 (25 m), and helium as the carrier gas (error ±2%). [b] Yield = isolated yield after purification by flash column chromatography. [c] E.e.$_p$ = enantiomeric excesses of the product were determined by converting the lactones into the corresponding hydroxy esters using sodium methoxide in methanol. The hydroxy groups were then esterified with Mosher's acid chloride. [d] E.e.$_s$ = enantiomeric excesses of the substrate were determined by oxidising the residue ketones using MCPBA to the corresponding lactones and then reacted as above. [e] Config. = absolute configuration. [f] The enantiomeric excess of **2h** was determined using chiral GC and a capillary column, Lipodex® E (25 m), and helium as the carrier gas. Oxidation of the ketone **1h**, using MCPBA gave the corresponding lactone **2h**; the optical purity of this sample was determined as described above.

distance between the chiral centre and the polar functional group. While the yield of lactone was acceptable, the overall mass balance was low due to the formation of cyclohexanol derivatives as side products (*ca.* 20%). Obviously, using partially purified MO2 enzyme some NADPH-linked dehydrogenase activity was being observed. Further purification of the enzyme (MO2) by FPLC gave protein which gave only one product, the lactone **2h** 43% (78% e.e.), on oxidation of ketone **1h**. No cyclohexanols were observed by gas chromatography and the mass balance was >90%. It is noteworthy that the stereochemistry of all the biotransformations described above was consistent with that observed in the 2-alkyl cyclopentanone series.[1a]

(*R*)-(+)-Lipoic acid, which has been reported to be a growth factor for a variety of microorganisms,[4] has previously been synthesised from 'chiral pool' starting materials or by asymmetric synthesis.[5] To secure a novel route to (*R*)-(+)-lipoic acid (Scheme 2), ε-lactone **2h** was transesterified to (*R*)-(+)-methyl 6,8-dihydroxyoctanoate **4** in 80% yield. Inversion by the Mitsunobu reaction[6] gave the corresponding (*S*)-(+)-ester **5** (97% yield). Reaction with potassium carbonate in methanol afforded (*S*)-(−)-methyl 6,8-dihydroxyoctanoate **6** (82% yield). Using a prescribed procedure,[5] the (*S*)-(−)-diol **6** was converted into the (*S*)-(+)-methyl 6,8-bis(methylsulfonyloxy)octanoate **7** in 92% yield; disulphide displacement in DMF gave (*R*)-(+)-methyl lipoate **8** (83% yield). Finally, hydrolysis using aqueous potassium hydroxide gave (*R*)-(+)-lipoic acid **9** (70% yield after recrystallisation), mp 44–46 °C (lit.,[5c] 44–46 °C), $[\alpha]_D$ +87 (*c* 0.071 in benzene) (lit.,[5c] $[\alpha]_D$ + 107, *c* 0.88 in benzene). ^1H and ^{13}C NMR spectra were identical to those of the racemic authentic sample obtained from Aldrich.

The necessity to effect the Mitsunobu reaction in the above sequence (Scheme 2) could be circumvented if a bio-oxidant was available that was selective for the (*S*)-ketone. In fact the pure monooxygenase from *Pseudomonas* NCIMB 9872[7] transformed the ketone **1h** into the (*S*)-lactone **2h** [E_p = *ca.* 5] and this lactone was transformed with methoxide into the laevorotatory ester (*S*)-(−)-**6** directly.



Scheme 2 *Reagents and conditions*: i, MeONa, MeOH; ii, *p*-$NO_2C_6H_4CO_2H$, PPh_3, diethyl azodicarboxylate, THF; iii, K_2CO_3, MeOH; iv, $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; v, $Na_2S{\cdot}9H_2O$, S, DMF, 80 °C; vi, KOH (0.1 mol dm^{-3}), MeOH

In summary, we have extended the use of monooxygenases, obtained from *Pseudomonas* in the bio-Baeyer–Villiger reaction and we have demonstrated their application to the synthesis of enantiomerically enriched (*R*)-(+)-lipoic acid.

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Footnote

† E_p = Enantiomeric ratio = $\dfrac{\ln[1 - c(1 + \text{e.e.}_p)]}{\ln(1 - c(1 - \text{e.e.}_p)]}$

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