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Chemoenzymatic syntheses of *cis*- and *trans*-3-hydroxy-5-methylpiperidin-2-ones

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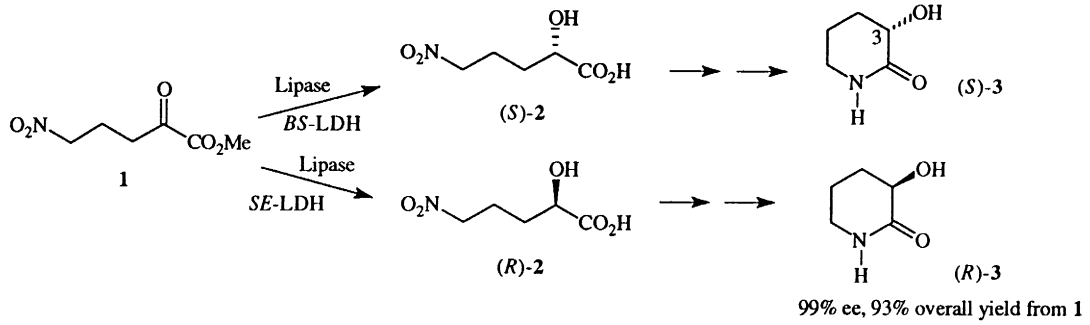
Abstract

An approach to the enantioselective synthesis of *cis*- and *trans*-3-hydroxy-5-methylpiperidin-2-ones from racemic methyl 4-methyl-5-nitro-2-oxopentanonate **8** is described via the first example of a lactate dehydrogenase catalysed combined kinetic resolution and reduction of a 2-oxo acid. In an alternative approach, stereoselective conjugate addition of nitromethane to a crotonyl camphorsultam gave access to the enantiopure 2-oxo esters (*S*)-**8** and (*R*)-**8** which, in turn, may be converted to the 3-hydroxy-5-methyl δ-lactams.

Hydroxylated six-membered ring nitrogen containing heterocycles are common features of many natural products and biologically active compounds;[1] we have reported an efficient method for the synthesis of 3-hydroxypiperidin-2-ones, valuable building blocks to these molecules.[2] Our strategy involved an enzyme catalysed reduction of 5-nitro-2-oxopentanoic acid to the corresponding 2-hydroxy acids (*S*)-**2** and (*R*)-**2** followed by esterification, catalytic hydrogenation of the nitro group using a platinum(IV) oxide catalyst and spontaneous intramolecular cyclisation as shown in Scheme 1.



Scheme 1.

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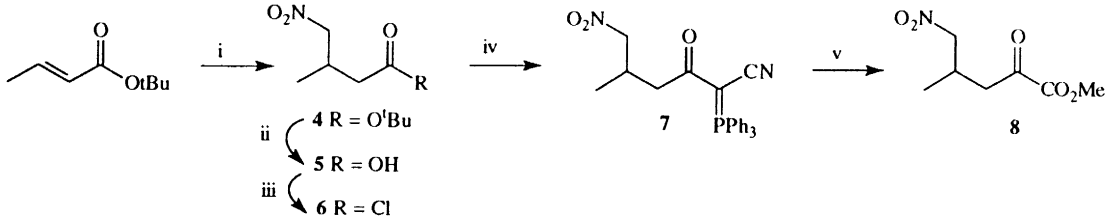
(*S*)-3-Hydroxypiperidin-2-one (*S*)-**3** was obtained using commercially available lactate dehydrogenase (LDH) from *Bacillus stearothermophilus* (*BS*-LDH) whilst the (*R*)-enantiomer, (*R*)-**3** was prepared using LDH from *Staphylococcus epidermidis* (*SE*-LDH). Recently we have been exploring further the utility of this approach to the enantioselective synthesis of more complex 3-hydroxypiperidin-2-ones such as those with a substituent at C-5. These investigations have led to some unexpected results which are now reported.

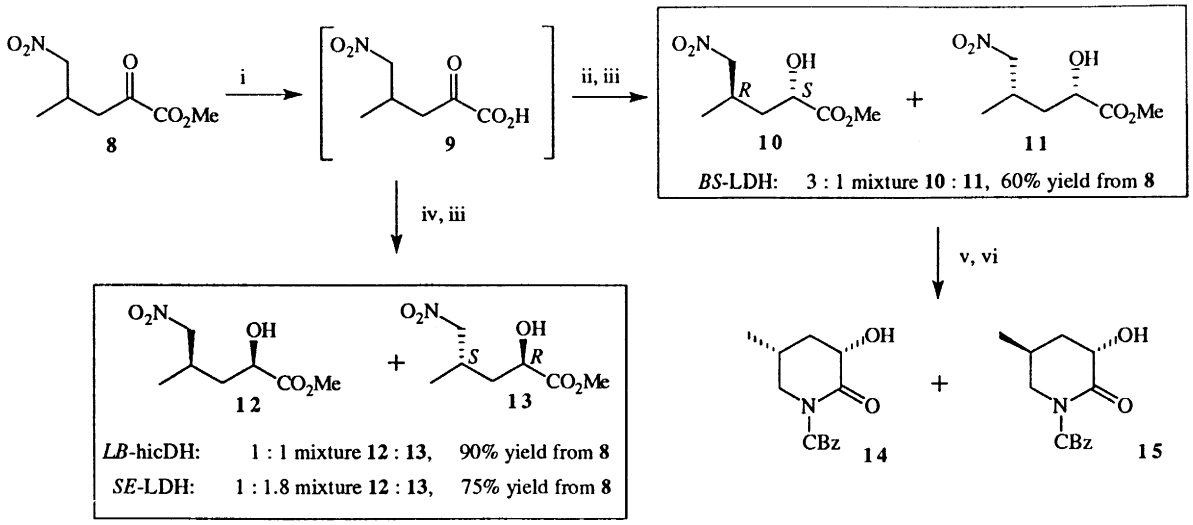
Our initial target compounds were the *cis*- and *trans*-isomers of 3-hydroxy-5-methylpiperidin-2-ones for which (*S*)- and (*R*)-4-methyl-5-nitro-2-oxopentanoic acids were required as the enzyme substrates. Before embarking on the enantioselective synthesis of these compounds, the racemic 2-oxo acid **9** was prepared to ensure that it was indeed a substrate for the LDHs. Conjugate addition of nitroalkanes to α,β-unsaturated carbonyl compounds is well precedented[3] and reaction of nitromethane with *tert*-butyl crotonate in the presence of DBU gave *tert*-butyl 3-methyl-4-nitrobutanoate **4** in excellent yield (Scheme 2). Acid catalysed hydrolysis of the ester, conversion of the resultant acid **5** to an acid chloride **6** and coupling with cyanomethylenetriphenylphosphorane in the presence of bis(trimethylsilyl)acetamide (BSA) as a proton scavenger[4] gave β-ketocyanophosphorane **7**. Ozonolysis of **7** gave the required 2-oxo ester **8** in 60% yield over the five steps.



Scheme 2. Reagents. (i) CH_3NO_2, DBU; (ii) H_2SO_4, $CHCl_3$; (iii) $SOCl_2$; (iv) Ph_3PCHCN, BSA, CH_2Cl_2; (v) O_3, MeOH, CH_2Cl_2

For recognition in the active site of LDH, it was necessary to convert ester **8** into the corresponding carboxylic acid **9**. We have found that a convenient method is to use a lipase to catalyse the hydrolysis under mild conditions and then, in the same pot, to reduce the ketone using LDH.[5] Thus **8** was incubated with a lipase from *Candida rugosa* (CRL) prior to addition of *BS*-LDH, NADH and a further enzyme, formate dehydrogenase (FDH), which is used to recycle the expensive cofactor NADH (Scheme 3).[6] After work-up, the products were methylated with diazomethane giving two diastereomeric hydroxy esters **10** and **11** which were inseparable by column chromatography. The ^{1}H NMR spectrum revealed that **10** and **11** had not been formed in equal amounts as expected but in a 3:1 ratio, indicating that both a kinetic resolution and reduction had occurred. It was not clear which stage gave the kinetic resolution, either the lipase catalysed hydrolysis or the LDH catalysed reduction. There are many reports in the literature of lipase catalysed resolution/hydrolysis of esters[7] but there are no examples of a combined reduction and kinetic resolution of a 2-oxo acid catalysed by a lactate dehydrogenase.

Various methods could be adopted to establish the stage of kinetic resolution, and we elected to repeat the reaction sequence changing just a single parameter, the oxidoreductase. The H205Q mutant of D-hydroxyisocaproate dehydrogenase from *Lactobacillus delbrueckii* (*LB*-hicDH) has broader substrate specificity than *BS*-LDH giving (*R*)-2-hydroxy acids in excellent yields and enantioselective excesses.[8] Hence, the hydrolysis/reduction/methylation protocol on **8** was repeated using *LB*-hicDH as the oxidoreductase (Scheme 3). After purification by column chromatography, a 1:1 mixture (by ^{1}H NMR spectroscopy) of (2*R*,4*R*)- and (2*R*,4*S*)-hydroxy esters **12** and **13** was isolated in 90% overall yield. This result confirmed that kinetic resolution is occurring with the *BS*-LDH catalysed reduction of 2-oxo acid **9** and not at the stage of the lipase catalysed hydrolysis of **8**.

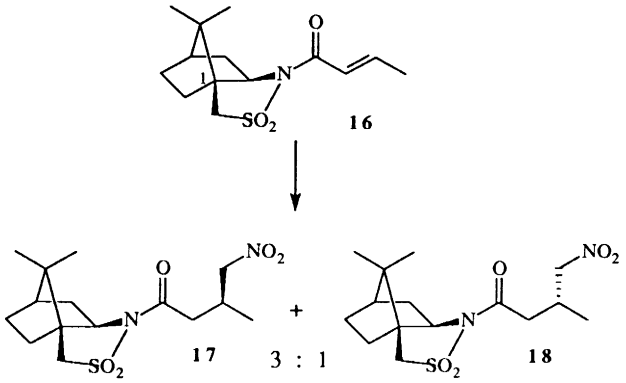


Scheme 3. Reagents. (i) *Candida rugosa* lipase; (ii) *BS*-LDH, NADH, FDH; (iii) CH_2N_2, MeOH; (iv) NADH, FDH and either *LB*-hicDH or *SE*-LDH; (v) H_2, PtO_2; (vi) $PhCH_2OCOCl$, Et_3N, CH_2Cl_2

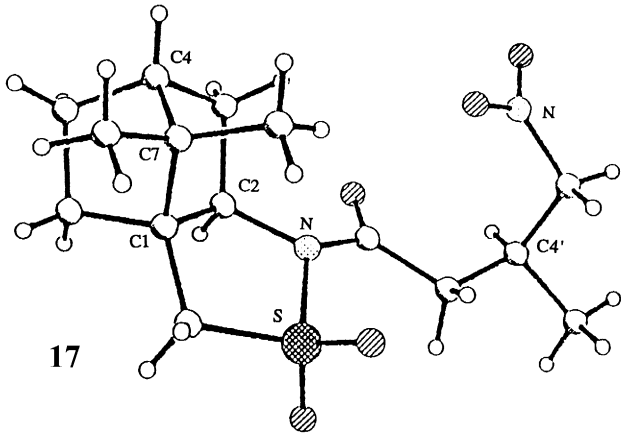
Next it was necessary to determine whether the *syn* or *anti* hydroxy acid was the major product from the *BS*-LDH catalysed reduction of **9**. Thus, the mixture of **10** and **11** was converted to the corresponding six-membered ring lactams **14** and **15** by catalytic hydrogenation and protection (Scheme 3). In the ^1H NMR spectrum of the major diastereomer, the signal (δ1.60) assigned to 4-H_{ax} appeared as a quartet with coupling J 12.5 arising from a geminal coupling with 4-H_{eq} and two axial–axial couplings to 5-H and 3-H in accord with the *cis*-lactam **14**.[9] By extrapolation, these results indicate that the *BS*-LDH catalysed reduction of **9** gave, after methylation, a 3:1 mixture of (2*S*,4*R*)- to (2*S*,4*S*)-hydroxy esters **10** and **11**.

Some caution is needed in the interpretation of these data as the hydroxylated lactams will not exist in a true chair conformation. To verify these conclusions, a single enantiomer of methyl 4-methyl-5-nitro-2-oxopentanoate **8** of known configuration at C-4 was required for the biotransformations. The required stereogenic centre was created by treatment of (1*S*,2*R*)-*N*-[(*E*)-crotonyl]bornane-10,2-sultam **16**[10] with nitromethane in the presence of DBU in THF and DMPU giving a 3:1 mixture of **17** and **18** in 90% yield (Scheme 4). Although **17** and **18** were inseparable by column chromatography, the major diastereomer **17** was readily isolated by crystallisation from methanol and its structure confirmed by X-ray crystallography. Cleavage of the auxiliary with lithium hydroperoxide gave (*S*)-3-methyl-4-nitrobutanoic acid which was converted to methyl (*S*)-4-methyl-5-nitro-2-oxopentanoate (*S*)-**8** by the same sequence of reactions as used for the racemic material (Scheme 2). The (*R*)-enantiomer, (*R*)-**8** was similarly prepared using (1*S*,2*R*)-*N*-[(*E*)-crotonyl]bornane-10,2-sultam as the starting material.

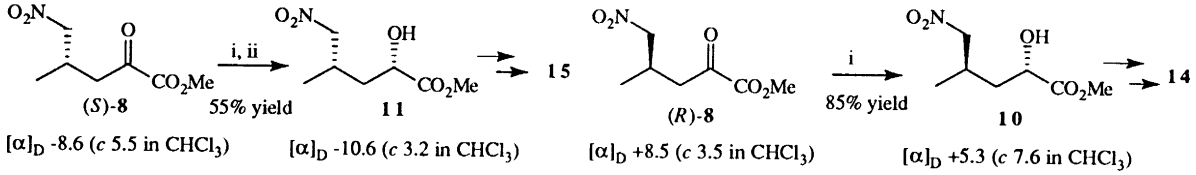
Each 2-oxo ester was then subjected to the three stage hydrolysis/*BS*-LDH catalysed reduction/methylation procedure (Scheme 5). Reduction of the (*S*)-enantiomer was slow and eventually gave the (2*S*,4*S*)-diastereomer **11** in 55% yield over the 3 steps. Reduction of the (*R*)-enantiomer proceeded smoothly to give the (2*S*,4*R*)-2-hydroxy ester **10** in 85% yield from (*R*)-**8**. All spectral data were in accord with those previously obtained thus confirming that the (*R*)-2-hydroxy acid was indeed favoured over the (*S*)-enantiomer for reduction by *BS*-LDH.



Scheme 4. Reagents. CH_3NO_2 (6 equiv.), DBU (6 equiv.), THF, DMPU



Finally, the reduction of racemic 4-methyl-5-nitro-2-oxopentanoic acid **9** with *SE*-LDH was examined (Scheme 3). This reaction also led to both a kinetic resolution and reduction but the resolution was less pronounced than in the case of *BS*-LDH giving a 1.8:1 mixture of the (2*R*,4*S*)- and (2*R*,4*R*)-diastereomers **12** and **13**. Interestingly, in contrast to the reaction with *BS*-LDH, the (*S*)-enantiomer was the preferred substrate for *SE*-LDH.



Scheme 5. Reagents. (i) *Candida rugosa* lipase then *BS*-LDH, NADH, FDH; (ii) CH_2N_2

In conclusion, we have reported the first examples of a lactate dehydrogenase catalysed combined kinetic resolution and reduction of a 2-oxo acid. These reactions have interesting potential in organic synthesis, enabling the creation of two asymmetric centres in a single pot process as demonstrated here by the enantioselective synthesis of the *cis*- and *trans*-3-hydroxy-5-methylpiperidin-2-ones **14** and **15**. In addition, these 2-oxo acids (*S*)-**9** and (*R*)-**9** are valuable substrates to further probe the active sites of both *SE*- and *BS*-LDHs.

Acknowledgements

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9. ^{1}H NMR data: Lactam **14**, δ (300 MHz, $CDCl_3$) 1.11 (3H, d, *J* 6.5, 5-CH_3), 1.60 (1H, q, *J* 12.5, 4H_{ax}), 2.30–2.40 (2H, m, 5-H and 4-H_{eq}), 3.40 (1H, t, *J* 11, 6-H_{ax}), 3.63 (1H, ddd, *J* 11, 5, 6-H_{eq}), 4.24 (1H, dd, *J* 12.5, 6, 3-H), 5.28 (2H, s, PhCH_2), 7.38 (5H, m, aromatics). Lactam **15**, δ (300 MHz, $CDCl_3$) 1.19 (3H, d, *J* 6.5, 5-CH_3), 1.96 (2H, m, 4-H_2), 2.51 (1H, oct, *J* 6.5, 5-H), 3.41 (1H, dd, *J* 11, 6.5, 6-*H*H), 3.79 (1H, dd, *J* 11, 6.5, 6-H*H*), 4.37 (1H, t, *J* 6, 3-H), 5.28 (2H, s, PhCH_2), 7.38 (5H, m, aromatics).
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