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# ENZYME MEDIATED OPTICAL RESOLUTION OF *endo*-NORBORNENE LACTONE

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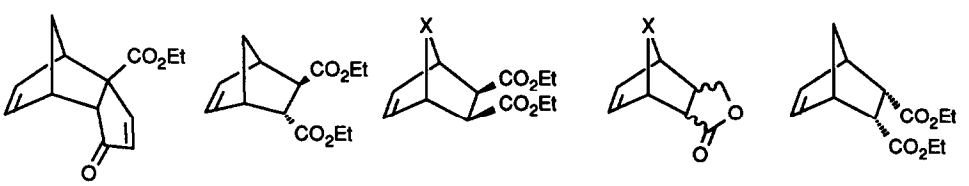
*Abstract: The enzymatic resolution of some norbornene esters, -carboxylic acids and -methanols was evaluated. Good results were obtained for the Porcine Pancreatic Lipase (PPL) catalyzed transesterification of norbornene methanols* **12** *and* **13** *in methyl acetate. A formal kinetic resolution of* endo*-norbornene lactone* **7** *could be achieved through the PPL-catalyzed transesterification of iodolactone* **15** *in methyl acetate. Both enantiomers of lactone* **7** *were obtained enantiomerically pure in good overall yields.*

The use of enzymes as chiral catalysts in the synthesis of optically active compounds from either chiral or prochiral substrates has gained considerable importance during the last few years[1]. In particular, the readily available and therefore relatively cheap hydrolases such as pig liver esterase (PLE)[2] and porcine pancreatic lipase (PPL)[3] have been recognized as powerful synthetic tools for the preparation of valuable chirons.

In relation with our studies aimed at modifying polycyclic structures to chirons for natural product synthesis, we recently reported the efficient enzymatic resolution of tricyclodecadienone **1** and norbornene diester **2** using PLE[4,5]. Bloch *et al.*[6] described a similar high enantioselectivity for the PLE-catalyzed hydrolysis of the prochiral oxygen bridged diester **3**. The obtained optically active half-ester was readily converted into the synthetically valuable *exo*-oxabicyclo[2.2.1]heptene lactone **4**. In contrast, the methylene bridged *cis*-diesters **5** and **6** hardly show any enantioselectivity upon hydrolysis with PLE[5,6]. Consequently, a convenient route to optically active annelated lactones[7,8] **7**, which are useful chirons in the synthesis of natural and pharmaceutical products[9], is blocked. In this paper we report the evaluation of other biocatalysts, *viz.* the lipases Candida Cylindracea Yeast Lipase (CCL) and Porcine Pancreatic Lipase (PPL), in a synthetic sequence leading to homochiral *endo*-lactone **7**.

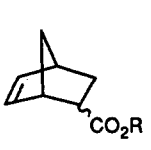



**1** **2** **3** X= O; X= $CH_2$ **4** X= O; X= $CH_2$ **6**

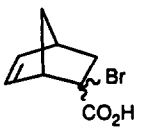
**5** **7**

The enzymatic hydrolysis of tricyclodecadienone ester **1** and *trans*-norbornene diester **2** using either CCL or PPL under standard conditions (pH 7.8, 0.1 M phosphate buffer, ambient temperature) could not be accomplished, which strongly contrasts the behavior of PLE (*vide supra*). Only for the mono-ester **8** (*endo* as well as *exo*) some hydrolysis was observed, however with a very low rate and with virtually no enantioselec-

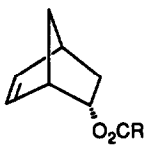
tivity. Disappointing results were also obtained when carboxylic acid **9** was subjected to enzymatic esterification: attempts to esterify **9** with methanol or n-butanol applying CCL in hexane as the solvent failed completely, even after reacting for several weeks. An explanation for this failure could be the inappropriate functionalization of the substrate. Literature reports suggest that for an efficient yeast lipase catalyzed esterification of carboxylic acids, these acids should preferably contain an electron withdrawing substituent, such as a halogen or a halophenoxy group, at the α-position[10]. Therefore, *endo*- and *exo*-α-bromo carboxylic acids **10**, which were synthesized from α-bromo-acrylic acid and cyclopentadiene, were also subjected to CCL catalyzed esterification in hexane, with methanol as well as n-butanol. In neither case any esterification was



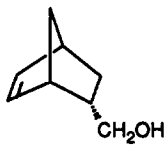

**8** R= $CH_3$
**9** R= H



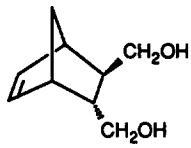

**10**




**11** R= $CH_3$, n-$C_3H_7$




**12**




**13**

observed. The negative results with **8**, **9** and **10** clearly indicate that carboxylic acids or esters in which the norbornene skeleton forms part of the acyl moiety, are not suitable substrates for lipases. Entirely different results are obtained when the norbornenyl system constitutes the alkyl part of an ester, *e.g.* **11**. These esters of *endo*-norborneol are efficiently hydrolyzed by CCL[11]. Apparently, the mere presence of the bulky norbornene unit in the substrate is on itself not prohibiting the acceptance by yeast lipase, rather the relative position in the ester, acid or alcohol is determinant. Therefore, the hydroxymethyl substituted norbornenes **12** and **13** were considered as substrates in a transesterification reaction now using PPL as the catalyst, because it is known that PPL has a better affinity for alcohols than CCL[10].

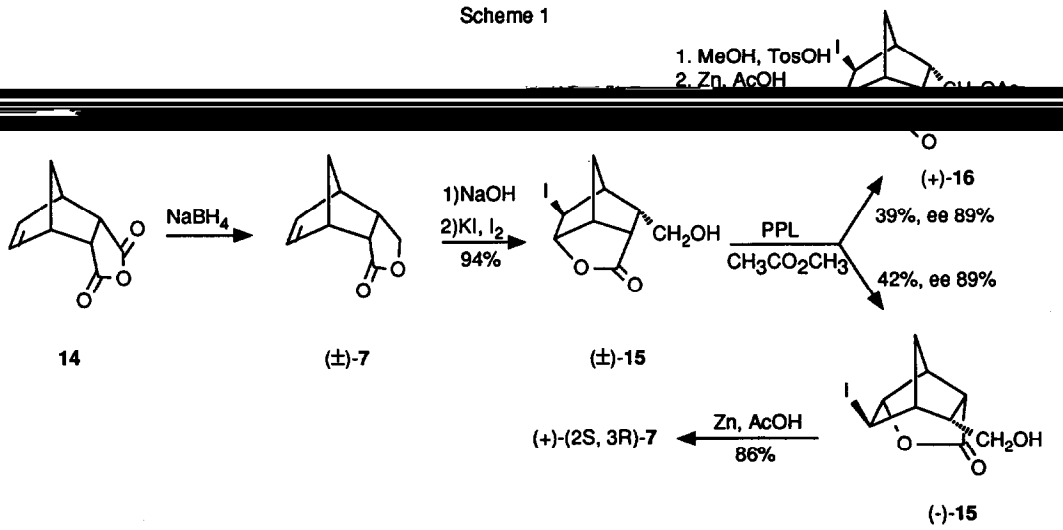
Reaction of *endo*-norbornene methanol **12**, prepared by $LiAlH_4$ reduction of *endo*-acid **9**, in methyl acetate in the presence of PPL for 44 hrs at room temperature afforded the corresponding acetate in a yield of 56% with an appreciable enantioselectivity. Comparison of the optical rotation of the recovered alcohol **12**, $[\alpha]^{25}_D$ +61.9° (c 0.6, 95% ethanol), with that reported[12], reveals an ee of 68%. In addition, its absolute configuration could be deduced as to be R, implying that the S-hydroxymethyl compound had been esterified preferentially.

A considerably higher enantioselectivity was observed for *trans*-bis(hydroxymethyl)norbornene **13**. After stirring for 44 hrs at room temperature with PPL in methyl acetate, a conversion of 60% was attained. Analysis of the reaction product showed that a mixture of *exo*- and *endo*-mono-acetates and the corresponding di-acetate had been formed. Unreacted diol **13**, which could be readily isolated from the mixture by chromatography, was obtained in a high optical purity: $[\alpha]^{25}_D$ +52.3° (c 1.4, ethanol), ee 91%. Its absolute configuration was established as (2S,3S) by comparison of its optical properties with those reported[13]. Chromatographic analysis of the ester mixture showed that the mono-esters were the major products (total yield of 49%) with a minor amount of the di-ester (10%). The observed ratio of 3:1 for *exo*-mono-acetate and *endo*-mono-acetate illustrates the stereochemical preference of PPL for the *exo*-methanol function in **13**.

On the basis of these results, which show that norbornene substituted methanols are suitable substrates for PPL in transesterification reactions, the optical resolution of iodolactone **15** was attempted. As is outlined

in Scheme 1, an efficient resolution of this alcohol would provide an easy access to *endo*-norbornene lactone **7** in high optical purity. This route starts from the readily available anhydride **14** which is conveniently reduced to racemic **7** using $NaBH_4$ in THF. Opening this lactone using aqueous base and subsequent iodolactonisation, afforded the *endo*-methanol **15** in a yield of 94%. Reconversion of this iodolactone **15** into the bicyclic lactone **7** could readily be achieved in high yield by eliminative reduction with zinc in acetic acid.

Scheme 1




Gratifyingly, the enzymatic esterification of iodolactone **15** using PPL in methyl acetate at room temperature indeed led to a highly enantioselective esterification, albeit at a relatively slow rate. After 16 days a conversion of only 30% was obtained. By enhancing the temperature to 40°C, the reaction time could be reduced to 8 days in which the desired conversion of 40% was reached; the high degree of enantioselectivity was retained. In a typical experiment, a suspension of 11.8 g (40 mmoles) of iodolactone (±)-**15** and 16 g of commercially available PPL (predried during 4 hrs at 0.2 mbar) in 120 ml of dry methyl acetate (predried on molsieves 4Å) was stirred at 40°C in the dark until a conversion of about 40% was obtained (about 8 days). The lipase was filtered off, washed with acetone and dried, as described above, for further use. The procuced ester (+)-**16** and remaining alcohol (-)-**15** were readily isolated by chromatography (silicagel / $CH_2Cl_2$ - acetone (9:1)) in 39% and 60% yield, respectively. Acetate (+)-**16**, $[\alpha]^{25}_D$ +53.1° (c 1.0, chloroform), was obtained in an excellent optical yield of 89% ee[14]. Acidic hydrolysis of acetate (+)-**16** led to alcohol (+)-**15**, $[\alpha]^{25}_D$ +62.7° (c 1.0, chloroform), in 86% yield. As a consequence of the 40% conversion in this esterification process, the optical purity of the recovered alcohol (-)-**15**, $[\alpha]^{25}_D$ -35.1° (c 1.0, chloroform), is relatively low (55% ee). However, repeating the enzymatic procedure with this optically enriched alcohol for another 8 days, eventually afforded (-)-**15** in an excellent overall chemical yield of 42% and an enantiomeric excess of 89% ($[\alpha]^{25}_D$ -63.8° (c 1.0, chloroform)). These results clearly point to a high enantioselectivity of PPL towards iodolactone **15**. Although the long reaction times may seem disadvantageous, this is not a serious synthetic drawback as the enzymatic esterification can be carried out on a large scale, the enzyme does not lose much of its activity during this period and can be used for a next batch.

The synthesis of both antipodes of bicyclic lactone **7** was completed by zinc reduction of either enantiomer **15**. Treating (-)-**15** with zinc in acetic acid afforded (+)-**7** in 87% yield. Crystallization from hexane

gave optically pure lactone (+)-(2S,3R)-**7**, $[\alpha]^{25}_D$ +148.3° (c 1.0, chloroform), lit.[8] $[\alpha]^{26}_D$ +147.52° (c 0.52, chloroform). Its optically pure antipode (-)-(2S,3R)-**7**, $[\alpha]^{25}_D$ -147.9° (c 1.0, chloroform), lit.[8] $[\alpha]^{26}_D$ -148.20° (c 0.52, chloroform), was similarly obtained from alcohol (+)-**15**. The absolute configurations of the respective lactones **7**, as shown in Scheme 1, were established by comparison of their optical data with those reported[8]. Based on these assignments, it may be concluded that PPL preferentially esterifies the (R)-hydroxymethyl group in (±)-**15**.

In conclusion, it has been demonstrated that PPL can be used in the enzymatic kinetic resolution of norbornenyl substituted methanols by transesterification in methyl acetate. A formal kinetic resolution of *endo*-norbornene lactone **7** can be accomplished via enzymatic transesterification of iodolactone **15**.

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