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# Enzymatic Preparation of Homochiral 2-(N-Carbobenzyloxypiperid-4-yl)-1,3-propanediol Monoacetate. A Facile Entry to Both Enantiomers of 3-Hydroxymethylquinuclidine.

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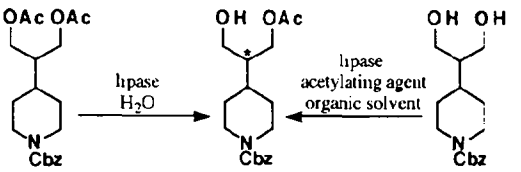
**Abstract**: Both enantiomers of monoacetate 1 have been prepared in high ee by lipase catalyzed monohydrolysis of the prochiral diacetate **3** and by monoacetylation of the corresponding diol **4**. 3-Hydroxymethylquinuclidine **2** was then synthesized in both enantiomeric forms with an ee up to 98% starting from (+)-**1**.

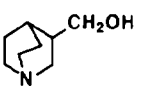
Enantiomerically pure molecules containing a nitrogen-heterocycle are useful units that can be used as starting material in the synthesis of alkaloids and many other important biologically active targets.[1] Unfortunately their number is rather limited and continuous efforts are currently made in order to improve the so called "heterocycle chiral pool".[2]

Biocatalysis is a very powerful tool in organic synthesis for the high chemo, regio and stereoselectivity often exhibited by many enzyme assisted processes.[3] Lipases have proved to be one of the most effective class of biological catalysts being easily available, inexpensive and requiring no cofactor. Moreover, they accept a broad range of substrates often still maintaining high stereoselectivity.[3,4]

As part of our ongoing programme on the use of enzymes in the asymmetric synthesis of new chiral building blocks starting from prochiral substrates with two enantiotopic groups,[1a,4a,5] we report here our results on the lipase-catalyzed preparation of both enantiomers of 3-acetoxy-2-(N-carbobenzyloxypiperid-4-yl)-1-propanol **1**,[6] a new piperidine ring containing chiral building block useful for many synthetic applications. Afterwards, as a first example of the usefulness and stereochemical versatility of **1**, we report herein the synthesis of both enantiomers of 3-hydroxymethylquinuclidine **2**, an intermediate of considerable interest for the synthesis of mequitazine and other 3-substituted quinuclidine derived drugs.[7]




**3** **1** **4**




**2**

First we studied the enantioselective hydrolysis in the presence of PPL of the diester **3**,[8] a derivative of 2-(4-piperidyl)-1,3-propanediol in which the two hydroxy groups were acetylated and the nitrogen of the piperidine ring was protected as carbobenzyloxy derivative. When the reaction was stopped at 47% conversion, monoacetate (-)-**1** was isolated in 49% chemical yield and in 44% ee (Table 1). Some attempts to improve either chemical yield and enantiomeric excess using different lipases and degrees of conversion were made: the best outcome, in terms of enantiomeric excess, was achieved using PPL and stopping the reaction at 73% conversion (entry 2); in these conditions the monoacetate (-)-**1** was obtained in 74% ee, but only in 39% chemical yield.

Since the results were acceptable but not excellent we turned our attention to the enantioselective esterification of the prochiral diol **4** in organic solvent. We examined in all cases the acetylation reaction, using various lipases and different series of conditions (solvent, acylating agent, degree of conversion, weight ratio enzyme/diol, enzyme supportation). The most significant results are reported in Table 2. As expected the

**Table 1**: Lipase Catalyzed Monohydrolysis of Diacetate **3**[a]

diacetate **3** —(Enzyme, Phosphate buffer 0.02 M (pH 7) / $Pr_2O$, 85/15)→ monoacetate (-)-**1** + diol **4**

| entry | lipase[b] | reaction time (h) | conversion[c] (%) | (-)-**1** (yield %) | ee[d] (%) |
|---|---|---|---|---|---|
| 1 | PPL | 5.5 | 47 | 49 | 44 |
| 2 | PPL | 19 | 73 | 39 | 74 |
| 3 | CCL | 18 | 65 | 45 | 56 |
| 4 | AYL | 8 | 45 | 45 | 60 |

a) All reactions were carried out on a 0.6 mmol scale using a ponderal ratio enzyme/diacetate = 0.75. b) See note 9. c) Conversion means the percentage of initial acetyl groups which have been hydrolysed. d) Determined by formation of Mosher's esters and $^1$HNMR analysis of diastereoisomeric compositions. Major enantiomer was always (-)-**1** (abs. conf. S).

**Table 2**: Lipase Catalyzed Monoacetylation of Diol **4**[a]

diol **4** ⟶ monoacetate (+)-**1** + diacetate **3**

| entry | lipase[b] | weight ratio enzyme/4 | acyl donor[c] | solvent[c] | reaction time (h) | conversion[d] (%) | (+)-**1** (yield %) | ee[e] (%) |
|---|---|---|---|---|---|---|---|---|
| 1 | PPL | 1 | VA | VA | 8.5 | 58 | 83 | 92 |
| 2 | PPL | 1 | VA | VA | 30 | 73 | 53 | 95 |
| 3 | PPL | 1.5 | VA | VA | 15 | 64 | 63 | 94 |
| **4** | **PPL** | **1.5** | **VA** | **VA** | **23** | **74** | **52** | **>98**[f] |
| 5 | PPL | 1 | $Ac_2O$ | Toluene | 8 | 62 | 71 | 60 |
| 6 | PPL | 1 | AcOEt | AcOEt | 26 | 37 | 75 | 82 |
| 7 | PPL | 1 | AcOEt | AcOEt | 92 | 55 | 89 | 85 |
| 8 | SAM-II | 0.2 | VA | VA | 8 | 59 | 81 | 76 |
| 9 | SAM-II | 0.2 | VA | VA | 30 | 84 | 31 | 46 |
| 10 | CAL | 0.25 | VA | VA | 9.5 | 85 | 30[g] | 90[g] |
| 11 | CCL | 3 | VA | VA | 7 days | 48 | 70 | 30 |
| 12 | PPL on celite | 3.3 | VA | VA | 3 | 56 | 87 | 90 |
| 13 | PPL on celite | 3.3 | VA | VA | 10 | 74 | 52 | 94 |

a) All reactions were carried out on a 0.3 mmol scale using 3 ml of solvent, in the presence of 3 Å molecular sieves. When the acyl donor was not used as solvent, 5 eq. were employed. b) See note 9. c) VA = vinyl acetate. d) Conversion means the percentage of initial hydroxy groups which have been acetylated. e) Determined by formation of Mosher's esters and $^1$HNMR analysis of diastereoisomeric compositions. Major enantiomer was always (+)-**1** (absolute configuration R), except in entry 10. f) $[\alpha]_D$ = + 9.1 ($CHCl_3$, c = 1.1). g) Major enantiomer was (-)-**1** (absolute configuration S).

monoacetate of opposite configuration to that derived from hydrolysis of **3** was generally obtained. However, while with PPL, SAM-II and CCL the same prochiral hydroxymethyl was preferentially acetylated to give **(+)-1**, in the case of CAL (entry 10) the opposite enantiomer **(-)-1** was predominant. The absolute configuration R was assigned to monoacetate **(+)-1** by chemical correlation with (+)-(R)-3-hydroxymethylquinuclidine into which **(+)-1** was converted as described below. These facts indicate that, in the PPL catalyzed reactions of **3** and **4**, the *pro-R* $CH_2OR$ of the prochiral substrate (either diol and diacetate) reacts preferentially: this result is in agreement with the empirical model of the active site of PPL recently proposed by us.[4a]

It is noteworthy that pushing the conversion to higher degrees an improvement of enantioselectivity is generally observed. However, in the case of Lipase SAM-II (entry 8 and 9) an increase of conversion degree brings about a drastic loss of ee. According to the collected data the best combination of the various parameters seems to be the one described in entry 4: using crude PPL purchased from SIGMA, employing vinyl acetate both as acylating agent and solvent, and a 1.5 weight ratio enzyme/substrate, a chemical yield of 52% with an excellent ee > 98% was obtained when the reaction was stopped after 23 h at 74% conversion.

Having in our hands **(+)-1** in high optical purity, we could start to examine some synthetic applications of this new chiral building block. As a first exploitation we report here the preparation of both enantiomers of 3-hydroxymethylquinuclidine **2** (Scheme 1).

The synthesis of **(+)-2** was realized transforming **(+)-1** (ee > 98%, entry 4 in Table 2) into the corresponding mesylate **5** followed by hydrolysis of the acetate (LiOH in 2/1 $THF/H_2O$), hydrogenolysis of Cbz group and heating in acetonitrile in the presence of $Li_2CO_3$.

From the same (R)-monoacetate **(+)-1** we synthesized **(-)-(S)-2**[10] cyclizing **6**, obtained by protection of the hydroxyl group of **1** as THP, followed by hydrolysis of the acetate, mesylation of OH and removal of THP and Cbz groups. Of course this enantiomer could be obtained more directly from **(-)-1** using the same process (route 1) just described for achieving **(+)-2** from **(+)-1**. However, since **(-)-1** was obtained with lower ee,[11] we preferred to follow the two steps longer route 2.

Formation of Mosher's esters from the products **(+)-** and **(-)-2** and $^1$HNMR analysis of their diastereoisomeric compositions allowed to establish that, while the route 1 is completely enantiospecific (**(+)-2** could be obtained with ee > 98%), in the case of route 2 a slight racemization occurred at the level of THP protection so that **(-)-2** could be obtained from **(+)-1** with ee up to 93%.

Other synthetic applications of this new chiral building block are now in progress in our laboratories.

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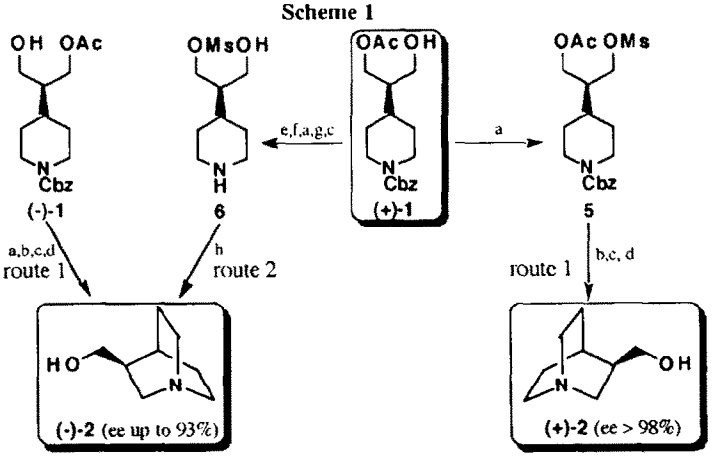
**Scheme 1**




Reagents and conditions a) MsCl, $Et_3N$, $CH_2Cl_2$, -30°C, 5', b) LiOH, $THF/H_2O$ 2/1, r. t., 6 h, c) $H_2$, Pd/C 10%, EtOH/AcOH, r. t.; d) $Li_2CO_3$, $CH_3CN$, reflux, 2 h, 63% (4 steps); e) 3,4-dihydro-2*H*-pyran, *p*-TSA, $CH_2Cl_2$, 0°C, 5', f) LiOH, $THF/H_2O$ 2/1, r. t., 8 h, 95% (2 steps), g) *p*-TSA, MeOH, r. t., overnight; h) $Li_2CO_3$, $CH_3CN$, reflux, 2 h, 60% (4 steps).

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6. All new compounds showed satisfactory spectral ($^1$H, $^{13}$CNMR, IR) and analytical data.

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8. Preparation of **3** from the commercially available 1-benzyl-4-piperidone: **a)** 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid), pyridine, r. t., 48 h, 89%; **b)** $H_2$, Pd/C 10%, MeOH, r. t., overnight, 92%; **c)** HCl/MeOH, reflux, 1 h; **d)** BzlOCOCl, NaOH, $H_2O$, 0°C, 95% (2 steps); **e)** $NaBH_4$, LiCl, EtOH/THF, r. t., 83% **f)** $Ac_2O$, $Et_3N$, DMAP, $CH_2Cl_2$, r. t., 30', 90%.

9 Crude PPL (50 U/mg of powder, measured using olive oil as standard) and CCL (from *Candida cilyindracea*, 500 U/mg of powder) were purchased from Sigma. Lipase SAM-II (from *Pseudomonas fluorescens*, 42 U/mg) was purchased from Fluka. Lipases Amano AY (from *Candida*, 30 U/mg) and Amano PS (from *Pseudomonas cepacia*; 30 U/mg) were kindly provided to us by Mitsubishi Italia. CAL (lipase Novozym 435, from *Candida antarctica*; 7 U/mg) was kindly provided to us by Novo Nordisk. PPL on celite was prepared simply liophylising a mixture of crude PPL and celite in pH 7 phosphate buffer, according to the procedure reported in ref. 5b.

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11. We are still working in order to improve this result.


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