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Enzymatic Resolution of N-Hydroxymethyl γ-Butyrolactams. An Access to Optically Active γ-Butyrolactams

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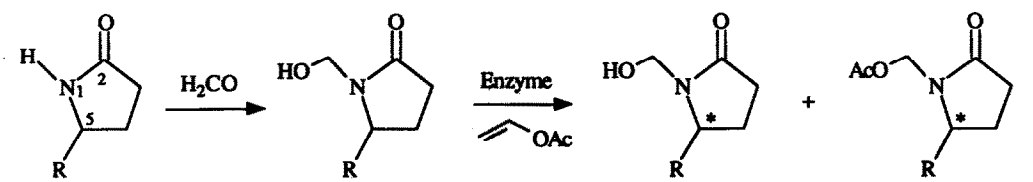
Abstract: *Enzymatic resolution of substituted pyrrolidinones was achieved using lipases by transesterification of their 1-hydroxymethyl derivatives in the presence of vinyl acetate.*

We recently reported that the enzymatic resolution of lactones can be conducted by hydrolysis in the presence of esterases or lipases.[1] Our present interest in the chemistry of lactams led us to examine in the same way their possible resolution using enzymes. Screening of the literature shows that their hydrolysis is only possible using not readily available enzymes.[2] Although chemical preparations of optically active γ-butyrolactams have been reported,[3] these methods lack versatility and seem applied only to simple compounds, usually bearing one substituent in position 5.

We decided to explore the enzymatic resolution of γ-butyrolactams, using a labile group fixed on the nitrogen atom: an hydroxymethyl appeared promising, owing to its facile fixation and removal.



(*R*, *S*)-**1** (*R*, *S*)-**2** (*R*) or (*S*)-**2** (*S*) or (*R*)-**3**

The desired N-hydroxymethyl γ-butyrolactams **2** were prepared in quantitative yields by treatment of the corresponding lactams with paraformaldehyde in the presence of catalytic amounts of potassium carbonate and water under sonication. The transesterification of lactam **2a** (R = Me) with vinyl acetate catalyzed by the lipase from Porcine Pancreas (PPL) or the lipase from *Pseudomonas cepacia* [4] (PL) was examined in various solvents.[5] The results are reported Table 1.

With PPL, moderate enantioselectivities were obtained and better results were observed with PL in THF. Similar results were obtained in acetone, *tert*-amyl alcohol or *tert*-butylmethyl ether (TBME). Addition of triethylamine, aimed to quench acetaldehyde, had no influence on the rate or the enantioselectivity of the

reaction. PL immobilized on Hyflo Super Cel ® 6 was more active than the free lipase since in the reactions reported Table 1 only a quarter of the amount of enzyme was used; besides the enantioselectivities[7] of the reactions were improved. Such E values (see Table 1) allow an easy preparation of either alcohol **2a** or either acetate **3a** with high enantiomeric purities.[8]

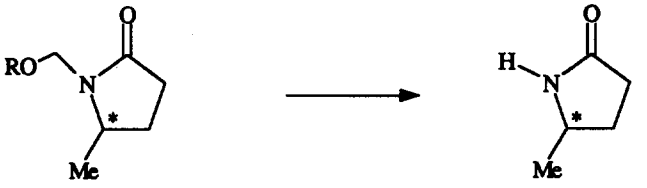
Table 1: *Transesterification of 1-hydroxymethyl-5-methyl-2-pyrrolidinone 2a*

Enzyme [a]	Solvent	Temperature (°C)	Time (h)	Conversion[b] (%)	Ee alcohol 2[7] (%)	Ee acetate 3[7] (%)	E [b]
PPL	*i*-Pr_2O	40	144	44	52	66	8
PPL	THF	45	96	38	40	64	7
PL	*i*-Pr_2O	20	14	50	74	74	15
PL	THF	20	28	52	88	82	28
PL-HSC	*i*-Pr_2O	20	5	52	88	84	28
PL-HSC	THF	20	28	50	87	87	41
PL-HSC	pentane	20	95	44	75	94	97

[a] PPL: lipase from Porcine Pancreas. PL: lipase from *Pseudomonas cepacia*. PL-HSC: PL immobilized on Hyflo Super Cel ®.

[b] Calculated according to reference 8.

The absolute configuration of alcohol **2a** ($[\alpha]_D$ -9 (c 0.475; THF), ee >98% [7]) was determined after thermal conversion (200° C/10-15 mmHg, 30 min) into (*R*)-5-methyl-2-pyrrolidinone **1a** ($[\alpha]_D$ +16.5° (c 1.35; EtOH)) previously reported in the literature ($[\alpha]_D$ +18 (c 1.0; EtOH)).[9] After hydrolysis into alcohol (EtOH, H_2O, KOH; 80% yield) and heating, the acetate **3a** ($[\alpha]_D$ -61 (c 0.625; THF), ee>98% [7]) was similarly converted into (*S*)-5-methyl-2-pyrrolidinone.



(*R*)-**2a** R=H 200° C (*R*)-**1a**

(*S*)-**3a** R=$COCH_3$ KOH/MeOH then 200° C (*S*)-**1a**

Transesterification of 5-alkyl-1-hydroxymethyl-2-pyrrolidinones **2b-2f** was conducted using the conditions reported above with PL immobilized on Hyflo Super Cel ®. In pentane, compare with lactam **2a** lower ee's were obtained. Studies with other solvents are reported Table 2. Excellent results were observed in *tert*-butylmethyl ether (E: 45 to 78) (Yields: 90-95%). The (*R*) absolute configuration of alcohols **2b, 2d, 2e** and of acetate **3f** as well as the (*S*) absolute configuration of alcohol **2f** and of acetates **3b, 3d, 3e** were determined after transformation into (*R*)- or (*S*)-5-alkyl-2-pyrrolidinones **1** and comparison of their chiroptical properties with those published.[10] The signs of the optical rotation of lactam **2c** and lactam **3c** being identical

respectively to those of lactams **2b, 2d, 2e** and lactams **3b, 3d, 3e**, we reasonably attributed to these two compounds the (*R*) and (*S*) absolute configurations respectively.[11]

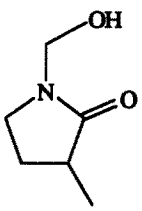
Table 2: ***Transesterification of 5-alkyl-1-hydroxymethyl-2-pyrrolidinones 2b-2f***

R	N°	Solvent [b]	Time (h)	Conversion [a] (%)	Ee alcohol 2[7] (%)	Ee acetate 3[7] (%)	E [a]
Ethyl	**2b**	TBME	7	53	98	88	75
Ethyl	**2b**	THF	47	51	92	88	52
n-Propyl	**2c**	TBME	7	46	81	93	70
n-Propyl	**2c**	THF	49	45	74	90	43
n-Butyl	**2d**	TBME	7	37	56	95	71
n-Butyl	**2d**	THF	49	41	60	88	27
n-Pentyl	**2e**	TBME	7	48	86	93	78
n-Pentyl	**2e**	THF	49	46	74	86	30
i-propyl	**2f**	TBME	7	51	96 [c]	86 [c]	52

[a] Calculated according to reference 8. [b] TBME: *tert*-butylmethyl ether [c] The absolute configurations of the products were the opposite of those obtained from lactams **2b-2e**.

Resolution of 1-hydroxymethyl-3-methyl-2-pyrrolidinone **4** was also attempted in the conditions used above (PL-HSC, pentane or TBME). A low enzymatic recognition was observed; after 50% conversion the acetate and the remaining alcohol were isolated with ee's [7] of 42 (TBME) or 44% (pentane) (E: 3-4). This result can be explain by the fact that the chiral center is more far of the alcohol function compared with 5-substituted pyrrolidinones **2**. However we emphasize that optically active 3-methyl-2-pyrrolidinone [12] has to our knowledge never been reported.

This methodology is not limited to monocyclic butyrolactams. Excellent results have been also obtained with the bicyclic compound **5**, bearing three chiral centers.[13] With TBME in the presence of vinyl acetate, PL-HSC catalyzed transesterification gave after 77h (47% conversion) the acetate and the remaining alcohol with ee's of respectively 90 and 80% [7,12] (E = 48), (overall yield: 92%). To our knowledge this is the first straighforward method which allows the preparation of a bicyclic lactam with such a high ee.



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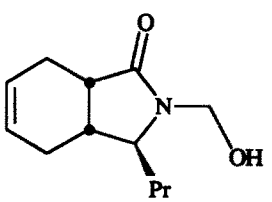

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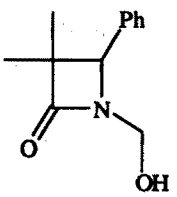

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This methodology was also applied to the β-lactam **6**.[14] Resolution in the conditions described above gave the remaining alcohol and the acetate with ee's ≥ 98% [7] (overall yield: 94%) (E > 200). Application of this reaction to the preparation of bicyclic β-lactams, such as antibiotics, seems very promising. This

example shows also that this reaction is not limited to γ-butyrolactams and should be applied to larger ring compounds such as δ-valerolactams and ε-caprolactams. Work is in progress to test this hypothesis.

References and Notes

1. Blanco, L.; Guibé-Jampel, E.; Rousseau, G. *Tetrahedron Lett.* **1988**, *29*, 1915. Fouque, E.; Rousseau, G. *Synthesis* **1989**, 661. Guibé-Jampel, E.; Rousseau, G.; Blanco, L. *Tetrahedron Lett.* **1989**, *30*, 67.
2. Evans, C.; McCague, R.; Roberts, S.M.; Sutherland, A.G. *J. Chem. Soc., Perkin Trans 1* **1991**, 656. Evans, C.; McCague, R.; Roberts, S.M.; Sutherland, A.G.; Wisdom, R. *J. Chem. Soc., Perkin Trans 1* **1991**, 2276. Formation of optically active lactams by lipase cyclization of aminoesters has been reported to be unsuccessful: Gutman, A.L.; Meyer, E.; Yue, X.; Abell, C. *Tetrahedron Lett.* **1992**, *33*, 3943.
3. (a) Amstutz, R.; Ringdahl, B.; Karlin, B.; Roch, M.; Jenden, D.J. *J. Med. Chem.* **1985**, *28*, 1760. (b) Burgess, L.E.; Meyers, A.I. *J. Org. Chem.* **1992**, *57*, 1656 and references cited therein.
4. PPL was purchased from Sigma and PL from Amano.
5. Enzymatic hydrolysis of acetate **2a** was not possible owing to its instability in water (pH 7). Representative procedure for the transesterification: the alcohol **1a** (121 mg, 1 mmol) was dissolved in THF (10 mL). PL (120 mg) or PL-HSC 6 was added (150 mg) followed by vinyl acetate (177 mg, 2.2 eq) and the mixture was stirred at the desired temperature. When the conversion ratios reported Table 1 and 2 were reached, the enzyme was filtered off and washed with ether. Column chromatography (SiO_2) gave the products (yields: 90-95%).
6. Bovara, R.; Carrea, G.; Ferrara, L.; Riva, S. *Tetrahedron : Asymmetry* **1991**, *2*, 931.
7. The enantiomeric excesses of the acetate **3** and of the alcohol **2** (after its conversion into acetate: acetic anhydride, DMAP, CH_2Cl_2, yields: 95%), were measured by ^1H NMR spectroscopy in the presence of $Eu(hfc)_3$.
8. Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C.J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
9. Andruszkiewicz, R.; Silverman, R.B. *J. Biol. Chem.* **1990**, *265*, 22288.
10. 5-Ethyl-2-pyrrolidinone: Marco, J.L. *J. Heterocyclic Chem.* **1986**, *23*, 287.
    5-Butyl-2-pyrrolidinone: Saliou, C.; Fleurant, A.; Célérier, J.P.; Lhommet, G. *Tetrahedron Lett.* **1991**, *32*, 3365.
    5-Pentyl-2-pyrrolidinone: Winkler, J.D.; Hershberger, P.M. *J. Am. Chem. Soc.* **1989**, *111*, 4852.
    5-Isopropyl-2-pyrrolidinone: Tseng, C.C.; Terashima, S.; Yamada, S.I. *Chem. Pharm. Bull.* **1977**, *25*, 29.
11. After removal of the hydroxymethyl group the (*R*) and (*S*) 5-propyl-2-pyrrolidinones were obtained. (*S*): $[\alpha]_D$ -8 (c 1.17; THF) ee: 91% 7.
12. The absolute configuration of the product is not known. Work is in progress to determine it.
13. This compound was prepared in three steps from *cis*-1,2,3,6-tetrahydrophthalimide by $NaBH_4$ reduction followed by reaction with propylmagnesium bromide and hydroxymethylation.
14. Preparation of 3,3-dimethyl-4-phenyl-2-azetidinone: Colvin, E.W.; Mc Garry, D.; Nugent, M.J. *Tetrahedron* **1988**, *44*, 4157.

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