Pergamon

Tetrahedron: Asymmetry Vol. 6, No. 1, pp. 97-100, 1995
Elsevier Science Ltd
Printed in Great Britain
0957-4166/95 $9.50+0.00

0957-4166(94)00361-0

Enzymatic Synthesis of Optically Active (*S*)-(+)-2-Hydroxymethyl-3,4-dihydro-2*H*-pyran and (*S*)-(+)-2-Acetoxymethyl-3,4-dihydro-2*H*-pyran

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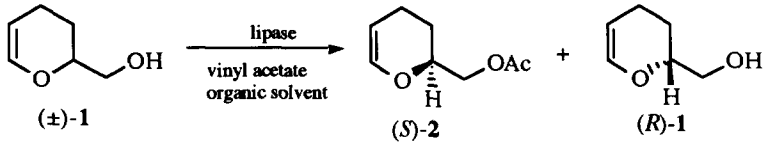
Abstract: *Porcine pancreas* lipase(PPL)-catalyzed acetylation of (±)-2-hydroxymethyl-3,4-dihydro-2*H*-pyran with vinyl acetate in organic solvent afforded (*S*)-(+)-2-acetoxymethyl-3,4-dihydro-2*H*-pyran. Alternatively, (±)-2-acetoxymethyl-3,4-dihydro-2*H*-pyran was resolved *via* hydrolysis catalyzed by PPL in acetone-phosphate buffer system to afford (*S*)-(+)-2-hydroxymethyl- 3,4-dihydro-2*H*-pyran with high enantiomeric purity.

Enzyme-catalyzed kinetic resolution of racemic substrates to prepare enantiomerically pure compounds has now become a very powerful tool in organic synthesis.[1] (±)-2-Hydroxymethyl-3,4-dihydro-2*H*-pyran (±)-**1** has been used as a versatile starting material in the synthesis of many biologically active compounds.[2] Optically active 2-hydroxymethyl-3,4-dihydro-2*H*-pyran would be desirable for the synthesis of homochiral target molecules. In the literature, (*S*)-(+)-2-hydroxymethyl-3,4-dihydro-2*H*-pyran (*S*)-**1**[3] has been prepared from levoglucosene in a multistep sequence and utilized in the synthesis of gentamicin C_{1a}. Alternatively, (*R*)-2-hydroxymethyl-3,4-dihydro-2*H*-pyran (*R*)-**1**[4] has been prepared by resolution from 3,4-dihydro-2*H*-pyran-2-carboxylic acid followed by esterfication and reduction. As part of our current program on the synthesis of new chiral building blocks and chiral insect pheromones, we wish to report here our results on the lipase-catalyzed preparation of (*S*)-(+)-2-hydroxymethyl-3,4-dihydro-2*H*-pyran (*S*)-**1** and (*S*)-(+)-2-acetoxymethyl-3,4-dihydro-2*H*-pyran (*S*)-**2** (Schemes 1 and 2).



Scheme 1

The results of the acetylation of (±)-**1** catalyzed by PPL are summarized in Scheme 1 and Table 1. As our screening test for searching for the required lipases, we employed PFL and PCL (entries 1 and 2), and CRL. The use of CRL(*Candida Rugosa* lipase) resulted in the optically inactive compounds. Of the lipases tested, PPL exhibited the highest enantioselectivity. A notable feature of this transformation is that the velocity and enantioselectivity are highly dependent on the amount of lipases and the nature of the solvent. Chloroform was the best choice of the solvent (entries 4-6). As shown in Table 1, the acetylated product (*S*)-**2** was obtained in as high as 90% e.e. (entry 6). Alternatively, the enantiomerically enriched (*R*)-**1** was obtained in 80% e.e.

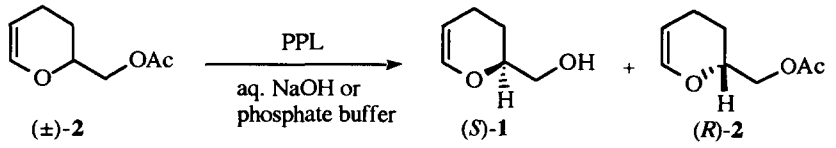
(entry 5). The typical enzymatic acylation procedure is as follows. To a solution of (±)-**1** (355 mg, 3.10 mmol) in $CHCl_3$(5 mL), was added PPL (20 mg) and vinyl acetate (880 mg, 10.3 mmol). The reaction mixture was shaken at 28°C in water bath shaker for 85 h and was monitored by GC.[5] After filtration, the filtrate was concentrated *in vacuo* and the resulting residue was chromatographed on Al_2O_3(neutral, pH 7.0) using ethyl acetate/hexanes (1 : 4) as eluent to afford (*S*)-**2** [97 mg, 20%, $[\alpha]^{25}_D$ +56.1(*c* 1.7, $CHCl_3$)] in 90% e.e. and unreacted (*R*)-**1** (220 mg, 62%) as colorless oils.

Table 1. Results of the Lipase Catalyzed Acetylation of (±)-**1**[a]

Entry	Lipase[b] (mg/mmol of substrate)	Temp (°C)	Solvent	Time (h)	Conv[c] (%)	Acetate,(*S*)-(+)-**2** % e.e.[d] (% y) $[\alpha]^{25}_D$[e]	Alcohol,(*R*)-(-)-**1** % e.e.[d] (% y) $[\alpha]^{25}_D$[e]	E[f]
1	PFL(8.19)	25	THF	5	56	47 (30) +30.2	62 (49) -41.8	4. 9
2	PCL(4.83)	4	$CHCl_3$	3	30	45 (30) +29.9	26 (59) -17.2	3. 4
3	PPL(99.8)	25	*t*BuOMe	1	49	57 (32) +37.5	55 (53) -37.0	6. 2
4	PPL(13.1)	28	$CHCl_3$	38	48	78 (63) +49.3	72 (22) -47.2	17. 3
5	PPL(11.1)	28	$CHCl_3$	46	59	56 (58) +36.9	80 (32) -53.7	8. 2
6	PPL(6.43)	28	$CHCl_3$	85	9	90 (20) +56.1	9 (62) -5.8	21.1

[a]As acylating agent, vinyl acetate was used. [b]The enzyme *Pseudomonas fluorescences* lipase (PFL) used was purchased from Fluka. The specific activity was 31.5 U/mg. The enzyme *Pseudomonas cepacia* lipaes (PCL) used was supplied by Amano Pharmaceutical Co., Ltd. *Porcine pancreas* lipase (PPL) was purchased from Sigma. The specific activity is 17.5 U/mg. [c]The conversion degree was calculated by the expression $c = ee_s/(ee_s + ee_p)$ (ref. 6) [d] % e.e. was determined by ^{1}H NMR spectra of (+)-**2** and the acetate of (+)- or (-)-**1** in the presence of 0.30 mol equiv of Eu(hfc)$_3$ and compared with the acetate of (±)-**2**. (*S*)-**2** showed at δ 3.17 for the methyl group of the acetate while (*R*)-**2** showed at δ 3.15 in 200 MHz ^{1}H NMR in the presence of Eu(hfc)$_3$. [e]The values in $CHCl_3$ at 25 °C. [f]Ref. 6.

Subsequently, we have examined the enzymatic hydrolysis of (±)-**2** in water using 0.013 M NaOH solution as titrant and acetone-phosphate buffer system for enhancing the enantioselectivity (Scheme 2).



(±)-**2** (*S*)-**1** (*R*)-**2**

Scheme 2

The results of the hydrolysis of (±)-**2** catalyzed by PPL are summarized in Table 2. Of the lipase employed for screening, PPL was again the best choice. At first, we have chosen a water system by adding 0.013 M NaOH solution to maintain pH 7 which gave (*S*)-**1** with higher enantioselectivity (entry 1). Among the systems tested, 0.01 M acetone-phosphate buffer system was most effective for enhancing the enantioselectivity. The enantiomer (*S*)-**1** of >99% e.e. was obtained with high E value[6] (entry 2). On the other hand, the reaction did not proceed in 0.1 M acetone-phosphate buffer. The phosphate buffer in the presence of 3% v/v of acetone was more effective for high enantiomeric exess than phosphate buffer without acetone (entries 2 and 3). It is notable that the reactions can be carried out on gram scales conveniently. The typical enzymatic hydrolysis using the acetone-phosphate buffer is as follows. To a solution of (±)-**2** (845 mg, 5.42 mmol) in acetone (10 mL) at 19 °C was added 0.01 M phosphate buffer (pH 7.4, 300 mL)[7] followed by PPL(82 mg). The reaction mixture was shaken at 19 °C for 12 h in water bath shaker and was monitored by GC.[5] The reaction mixture was extracted with ethyl acetate (100 mL) for four times and then evaporated in vacuo. Separation by Al_2O_3(neutral, pH 7.0) column chromatography using ethyl acetate/hexanes (1 : 4) as eluent to afford (*S*)-**1** (130

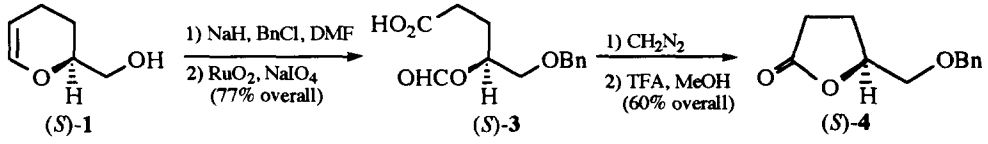
mg, 21%) in >99% e.e. and unreacted (*R*)-**2** (550 mg, 65%) in 48% e.e. The specific rotation of (*S*)-**1** was $[\alpha]^{25}_D$ +65.7 (*c* 0.25, $CHCl_3$) [lit.[3] $[\alpha]^{25}_D$ +77 (*c* 1, $CHCl_3$)].

Table 2. Results of the Lipase Catalyzed Hydrolysis of (±)-**2**[a]

Entry	Lipase[b] (mg/mmol of substrate)	Temp (°C)	Solvent	Time (h)	Conv[c] (%)	Alcohol,(*S*)-(+)-**1** % e.e.[d] (% y) $[\alpha]^{25}_D$[e]	Acetate,(*R*)-(-)-**2** % e.e.[d] (% y) $[\alpha]^{25}_D$[e]	E[f]
1	PPL(1.56)	25	distilled water	9.5	40	92(28) +61.7	61(58) -38.3	45
2	PPL(18.5)	19	acetone-phosphate buffer	12	33	>99(21) +65.7	48(65) -30.3	>100
3	PPL(15.2)	19	acetone-phosphate buffer	11	44	92(33) +61.6	72(46) -45.1	52

[a] (±)- **2** was obtained by acetylation with Ac_2O in pyridine. [b-f] The footnotes are the same as those in Table 1.

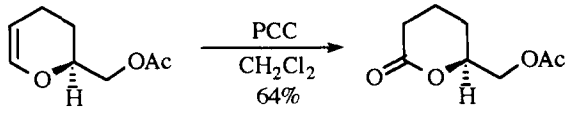
The enantiomerically enriched (*S*)-**1** and (*S*)-**2** thus obtained were transformed to the chiral synthons in the synthesis of optically active natural products (Schemes 3 and 4).



(*S*)-**1** (*S*)-**3** (*S*)-**4**

Scheme 3

Protection of alcohol moiety of the optically active (*S*)-**1** with benzyl chloride followed by oxidative cleavage[8] of the enolic olefin with RuO_2 afforded γ-formyloxy acid (*S*)-**3**[9] in 77% overall yield. Esterfication with diazomethane followed by lactonization yielded (*S*)-(+)-γ-benzyloxymethyl-γ-butyrolactone (*S*)-**4**[9,10] in 60% overall yield (Scheme 3). The specific rotation of (*S*)-**4** was $[\alpha]^{25}_D$ +20.7 (*c* 0.39, EtOH), [lit.[10] $[\alpha]^{25}_D$ +18.1 (*c* 2.70, EtOH)]. Alternatively, the compound (*S*)-**2** was readily oxidized[11] with PCC in CH_2Cl_2 to afford the lactone (*S*)-**5**[9,12], $[\alpha]^{25}_D$ +29.4 (*c* 0.48, $CHCl_3$), [lit.[12] $[\alpha]^{25}_D$ +30 (*c* 0.98, CCl_4)], in 64% yield (Scheme 4).



(*S*)-**2** (*S*)-**5**

Scheme 4

Acknowledgment. Generous financial support by Minisry of Education(BSRI-94-3420) and in part by Non Directed Research Fund of the Korea Research Foundation(1993) is gratefully acknowledged. We thank Amano Pharmaceutical Co., Ltd. for generous gift of PCL and CRL.

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5. The reaction was monitored using Varian 3700 gas chromatography equipped with a 5% OV-101 (Chrom G-HP, 100/120 50 cm x 1/8") GC conditions : injector temp 70 °C, detector temp 130 °C; flow rate of carrier N_2 gas : 25 psi. The column temperature was maintained at 40 °C for 5 min, increased at a rate of 10 °C/min to 110 °C. The retention time of the alcohol was 4.34 min and the acetate was 9.39 min.
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9. The spectral and physical data of all the compounds are in agreement with assigned structure. Selected data are as follows. (*S*)-**3**: TLC; SiO_2, EtOAc/hexanes 1 : 3, R_f = 0.35. $[\alpha]^{25}_D$ -7.5 (*c* 0.28, $CHCl_3$). ^{1}H NMR (300 MHz,$CDCl_3$) δ 1.90-2.10 (m, 2H), 2.45-2.50 (m, 2H), 3.50 (s, 2H), 4.50 (q, J = 7.9 Hz, 2H), 5.10-5.20 (m, 1H), 7.20 (s, 5H), 8.10 (s, 1H), 9.70 (s, 1H). IR (film); 3560 - 2640, 1726, 1710, 1650, 1500, 1470 cm^{-1}. (*S*)-**4**: TLC; SiO_2, EtOAc/hexanes 1 : 1, R_f = 0.83. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.90-2.20 (m, 2H), 2.50-2.80 (m, 2H), 3.40-3.60 (m, 2H), 4.20-4.30 (m, 1H), 4.55 (s, 2H), 7.25 (s, 5H). IR(film); 1780, 1450, 1220, 1170 cm^{-1}. (*S*)-**5**: TLC; TLC; SiO_2, EtOAc/hexanes 1 : 1, R_f= 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.70 - 1.90 (m, 4H), 2.10 (s, 3H), 2.35-2.50 (m, 1H), 2.50-2.60 (m, 1H), 4.10-4.20 (m, 2H), 4.50-4.55 (m, 1H). IR (film);1751, 1734, 1513, 1414, 1046 cm^{-1}.
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(*Received in Japan* 21 *October* 1994)