Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1723–1726

TETRAHEDRON: *ASYMMETRY*

Synthesis of optically active β-benzyl-γ-butyrolactone through lipase-catalyzed kinetic resolution

Yolanda Caro, Christian F. Masaguer and Enrique Raviña*

Departamento de Química Orgánica, Laboratorio de Química Farmacéutica, Facultad de Farmacia, Universidad de Santiago de Compostela, E-15782 Santiago de Compostela, Spain

Received 21 May 2001; accepted 11 July 2001

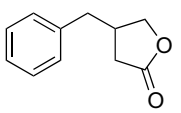
Abstract—The lipase-catalyzed kinetic resolution of the racemic γ-hydroxy ester **2**, coupled with subsequent acid-mediated cyclization, is an effective method for the synthesis of both enantiomers of β-benzyl-γ-butyrolactone **1**. This enzymatic process affords the product with high enantiomeric excess under mild reaction conditions and does not require optically active starting materials.

1. Introduction

β-Benzyl-γ-butyrolactone **1** is the core framework of a variety of the naturally occurring lignans which include some medicinally important compounds.[1,2] This compound is a key intermediate not only for preparing dibenzylbutyrolactone lignans, a class of natural compounds that can be found in many plants, but also for synthesizing other lignans which can be derived from dibenzylbutyrolactones themselves.[3]

β-Benzyl-γ-butyrolactone has also attracted attention because of its versatility as synthetic intermediate for other pharmacologically active compounds such as platelet aggregation inhibitors,[4] non-steroidal antiprogestins,[5] or central nervous system active compounds.[6,7] We are interested in these compounds as starting materials in the synthesis of optically active 3-aminomethyltetralones **3**, conformationally constrained butyrophenones, as potential antipsychotic compounds.[8] Therefore, in order to accomplish the asymmetric synthesis of a variety of compounds, enantiomerically pure (*R*)- and (*S*)-β-benzyl-γ-butyrolactone are used as the most versatile intermediates.

Although many synthetic methods to obtain both enantiomers have been developed, in general, multi-step, low yielding routes are reported.[9] In the cases when short synthetic routes are described, low enantiomeric excess are obtained.[10] Development of efficient synthetic methods producing optically pure benzylbutyrolactone is, therefore, very important. Herein, we report the synthesis of the optically active β-benzyl-γ-butyrolactone through the lipase-catalyzed kinetic resolution of the γ-hydroxy ester **2**.



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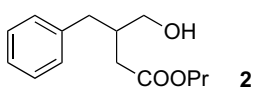

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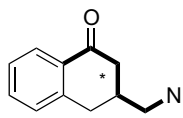

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2. Results and discussion

Our search was initially directed towards the enantioselective enzyme-catalyzed lactonization of the racemic β-benzyl-γ-hydroxy ester **2**, which was prepared in 81% yield from racemic β-benzyl-γ-butyrolactone **1**[11] by nucleophilic substitution of bromopropane with the potassium salt of the hydroxy acid in DMF solvent. The γ-hydroxy ester was subjected to enzyme screening for the biocatalytic cyclization using several commer-

* Corresponding author. Tel.: +34 981 594 628; fax: +34 981 594 912; e-mail: qofara@usc.es

0957-4166/01/$ - see front matter
PII: S0957-4166(01)00317-2

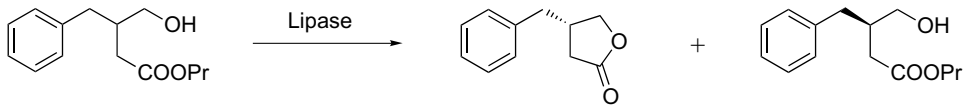
cially available lipases (Amano's *Pseudomonas* lipases AK, AH and PS, *Candida* lipase AYS, and *Aspergillus* lipase AS; and Novo Nordisk's Lipozime IM® and Novozym® 435): lipases were checked in a *tert*-butyl methyl ether solution of (±)-**2**, stirred for 24 h and then analyzed by TLC. A low conversion, as judged visually, had taken place with Amano AK, PS, AYS and AS lipases, while a high-yielding transformation appeared in the Lipozime IM® lipase (immobilized lipase from *Rhizomucor miehei*) and Novozym® 435 lipase (immobilized lipase from *Candida antarctica*) reactions. These reactions were repeated in *tert*-butyl methyl ether, THF, dioxane, benzene or hexane as solvents at either room temperature or 50°C, and reaction times of 12–24 h (Table 1). With Novozym® 435 lipase no enantiodifferentiation was observed, and racemic lactone **1** was always obtained. When the reaction was carried out in the presence of Lipozime IM® enantiomeric excesses (e.e.s) were obtained in all cases, the best result being an e.e. of 64%[12] for the (*S*)-(−)-**1** lactone (entry 3) ($[\alpha]_D^{25}$ −5.0 (*c* 1, $CHCl_3$)) after 14 h in hexane solvent at room temperature, and 12% e.e.[13] for the residual ester (*R*)-(−)-**2** ($[\alpha]_D^{20}$ −1.0 (*c* 1, $CHCl_3$)).

Since the enzymatic lactonization of (±)-**2** proved to be ineffective for the preparation of enantiomerically pure β-benzyl-γ-butyrolactone, an alternative route was explored. This consisted of the lipase-catalyzed kinetic resolution of hydroxy ester (±)-**2** (Scheme 1) and subsequent acid-mediated cyclization.

In the enzyme-catalyzed acetylation of the hydroxy ester (±)-**2**, the seven above-mentioned tested enzymes were checked under acylating conditions. A solution of (±)-**2** (10 mg) and the lipase (5 mg) in anhydrous vinyl acetate (1 mL) used as solvent and acyl donor was stirred at room temperature for 24 h. The acetylation was analyzed by TLC and NMR, and the Amano lipases from *Pseudomonas cepacia* (AH and PS) showed the best results for the acetylation. These reactions were repeated on a higher scale using (±)-**2** (100 mg), the lipase (50 mg) and vinyl acetate (5 mL). With lipase AH, the acetate (+)-**4** was obtained in 46% yield with an e.e. of 38%,[15] and the residual hydroxy ester (+)-**2** was returned in 48% yield and 12% e.e. The enantioselectivity of the reaction was rather poor ($E=2.5$). Thus, the enantiodiscrimination in kinetic resolution of (±)-**2** using lipase AH as catalyst was not satisfactory. However, when the lipase-catalyzed transesterification was carried out using lipase PS, good kinetic resolution was achieved, which furnished the hydroxy ester (+)-**2** in good yield with e.e. of 94%, and the acetate (+)-**4** with 69% e.e., $E=20$ (Scheme 2).

Since acetate (+)-**4** could not be obtained in satisfactory e.e. in the transesterification, we carried out the enantioselective lipase-catalyzed hydrolysis of the acetate group. Good results were obtained when lipase PS was added to a solution of acetate (+)-**4** ($[\alpha]_D^{20}$ +5.5 (*c* 1, MeOH), 69% e.e.) in *tert*-BuOH:phosphate buffer (1:6), and stirred at room temperature for 8 h (Scheme 2). Hydroxy ester (*R*)-(−)-**2** was obtained in 71% yield (39% from (±)-**2**) with 96% e.e., $[\alpha]_D^{20}$ −8.0 (*c* 1, MeOH). Cyclization of the optically active hydroxy esters (+)-**2** and (−)-**2** with *p*-TsOH in benzene afforded the lactones (*S*)-(−)-**1** ($[\alpha]_D^{24}$ −7.3 (*c* 1, $CHCl_3$), 94% e.e.), and

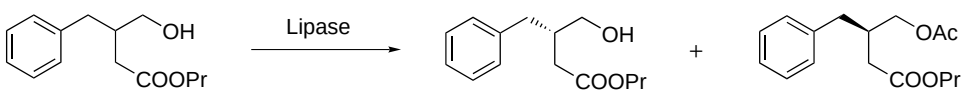
Table 1. Lipase-catalyzed lactonization of γ-hydroxyester **2**



(−)-**2** (*S*)-(-)-**1** (*R*)-(-)-**2**

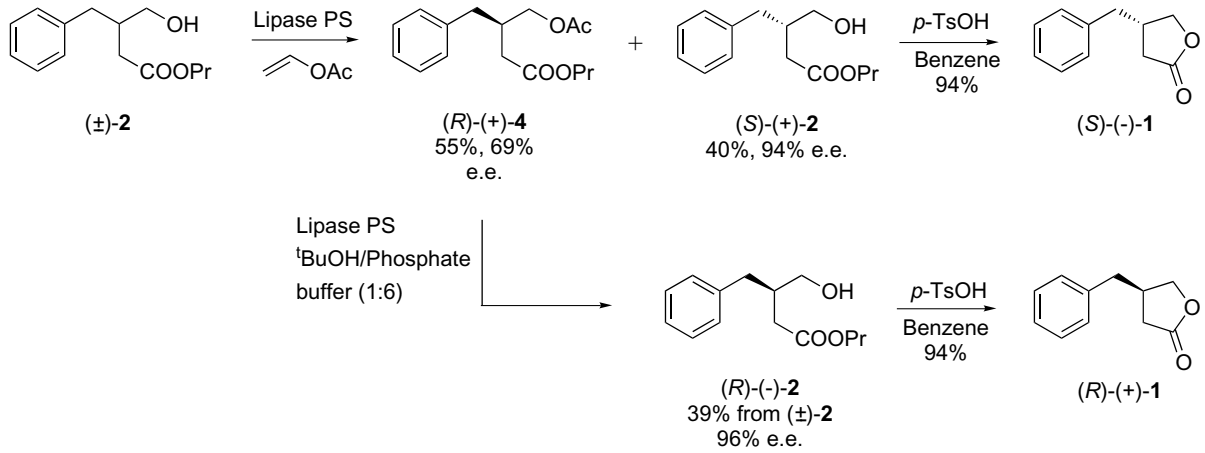
Entry	Lipase[a]	Solvent	Temp. (°C)	Time (h)	Lactone (*S*)-(−)-**1**		Alcohol (*R*)-(−)-**2**		*E*-value[b]
					Yield (%)	% e.e.	Yield (%)	% e.e.	
1	N. 435	^{t}BuOMe	rt	30	61	0	20	0	–
2	N. 435	Hexane	rt	13	37	5	45	ND	–
3	L. IM	Hexane	rt	14	17	64	62	12	5
4	L. IM	Benzene	rt	50	11	45	70	2	2
5	L. IM	Toluene	rt	50	11	22	65	2	2
6	L. IM	Cyclohexane	rt	50	28	38	55	14	2
7	L. IM	THF	50	60			No reaction		
8	L. IM	Dioxane	50	60			No reaction		

[a] N. 435, Novozym® 435; L. IM, Lipozime IM®
[b] Enantioselectivity was calculated from the formula $E=\ln[1-c(1-\text{e.e.}_s)]/\ln[1-c(1+\text{e.e.}_s)]$.[14]



(±)-**2** (*S*)-(+)-**2** (*R*)-(+)-**4**

Scheme 1.



Scheme 2.

(*R*)-(+)-**1** ($[\alpha]_D^{24}$ +7.5 (*c* 1, $CHCl_3$), 96% e.e.), respectively, in excellent yields.

The absolute configurations of the (+)-**2** hydroxy ester as (*S*) and the acetate (+)-**4** as (*R*) were assigned based on the literature values of (*S*)-(−)-**1** lactone[10a] ($[\alpha]_D^{23}$ −6.4 (*c* 2, $CHCl_3$), 82% e.e.).

3. Conclusion

In conclusion, the lipase-catalyzed kinetic resolution of racemic γ-hydroxy ester (±)-**2**, coupled with subsequent acid-mediated cyclization, is an effective method for the synthesis of both enantiomers of β-benzyl-γ-butyrolactone **1**. This enzymatic process affords high e.e.s under mild reaction conditions and does not require optically active starting materials. Utilization of optically active butyrolactone **1** for the stereoselective synthesis of new central nervous system agents is currently under investigation.

4. Experimental

4.1. General

Melting points were determined with a Kofler hot stage instrument or a Gallenkamp capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Perkin–Elmer 1600 FTIR spectrophotometer; the main bands are given in cm^{-1}. ^1H NMR spectra were recorded with a Bruker WM AMX (300 MHz); chemical shifts are recorded in parts per million (δ) downfield from tetramethylsilane (TMS). Mass spectra were performed on a Hewlett–Packard HP5988A mass spectrometer by electron impact (EI). Optical rotations at the sodium D-line were determined using a Perkin–Elmer 241 polarimeter. Flash column chromatography was performed using Kieselgel 60 (60–200 mesh, E. Merck AG, Darmstadt, Germany). Reactions were monitored by thin-layer chromatography (TLC) on Merck 60 GF_{254} chromatogram sheets using iodine vapor and/or UV light for detection. The commercially available lipase samples were obtained as gifts from Amano Pharmaceutical Co., Ltd. (Nagoya, Japan) and Novo Nordisk Bioindustrial, S.A. (Madrid, Spain), and used as received.

4.2. Preparation of propyl 3-benzyl-4-hydroxybutanoate (±)-2

Lactone (±)-**1** (5 g, 28.4 mmol) was dissolved in a solution of KOH in methanol (5%, 65 mL) and stirred at rt for 8 h. The solvent was evaporated in vacuo and the residue suspended in anhydrous DMF (15 mL). 1-Bromopropane (5.2 mL, 56.8 mmol) was added, the mixture was stirred for 24 h, and more 1-bromopropane (5.2 mL, 56.8 mmol) was added and stirring continued for a further 16 h at rt. Water (20 mL) was added and the solution was extracted with Et_2O (3×30 mL). The organic extracts were concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, CH_2Cl_2) to give propyl 3-benzyl-4-hydroxybutanoate (±)-**2** as a yellowish oil (5.4 g, 81%). IR (film): *v* 3446, 2966, 1732, 1496 cm^{-1}; ^1H NMR: δ 0.93 (t, $J=7.4$ Hz, 3H, CH_3), 1.57–1.71 (m, 2H, CH_2-CH_3), 2.32–2.44 (m, 3H, CH-CH_2COO), 2.61, 2.73 (ABX, $J_{AB}=13.6$, $J_{AX}=6.8$, $J_{BX}=6.5$ Hz, 2H, CH_2Ph), 3.51, 3.64 (ABX, $J_{AB}=10.8$, $J_{AX}=5.3$, $J_{BX}=3.8$ Hz, 2H, CH_2OH), 4.02 (t, $J=6.7$ Hz, OCH_2), 7.17–7.32 (m, 5H, Ph); MS (EI) m/z 237 $(M+H)^+$.

4.3. General procedure for the lipase-catalyzed lactonization

The lipase (Lipozime IM® or Novozym® 435, 50 mg) was added to a solution of (±)-**2** (100 mg, 0.42 mmol) in the solvent of choice (5 mL, Table 1), stirred at rt or 50°C (Table 1) for several hours (Table 1). After filtration through Celite, the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (silica gel, CH_2Cl_2) gave the lactone (*S*)-(−)-**1** and the hydroxyester (*R*)-(−)-**2**.

4.4. Procedure for the lipase-catalyzed acylation of the hydroxy ester (±)-2

To a solution of the hydroxy ester (±)-**2** (500 mg, 2.1 mmol) in vinyl acetate (20 mL), lipase PS (250 mg) was added. The mixture was stirred for 12 h at rt, filtered through Celite and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2) to give propyl (*R*)-4-acetoxy-3-benzylbutanoate (+)-**4** (327 mg, 55%) and propyl (*S*)-3-benzyl-4-hydroxybutanoate (+)-**2** (200 mg, 40%).

Propyl (*S*)-3-benzyl-4-hydroxybutanoate (+)-**2**: $[\alpha]_D^{20}$ +7.80 (*c* 1.0, CH_3OH), 94% e.e.

Propyl (*R*)-4-acetoxy-3-benzylbutanoate (+)-**4**: $[\alpha]_D^{20}$ +5.50 (*c* 1.0, CH_3OH), 69% e.e.; IR (film): *v* 2670, 1732, 1361 cm^{-1}; ^1H NMR: δ 0.94 (t, $J=7.4$ Hz, 3H, CH_3), 1.60–1.70 (m, 2H, CH_2-CH_3), 2.05 (s, 3H, CH_3COO), 2.34 (d, $J=3.6$ Hz, 1H, $CHCOO$), 2.37 (d, $J=3.0$ Hz, 1H, $CHCOO$), 2.42–2.53 (m, 1H, $CH(CH_2)_3$), 2.67–2.70 (m, 2H, CH_2Ph), 3.91–4.09 (m, 2H, CH_2OAc), 4.02 (t, $J=6.7$ Hz, 2H, O-CH_2-), 7.15–7.32 (m, 5H, Ph); MS (EI) *m*/*z* 278 M^+.

4.5. Procedure for the lipase-catalyzed hydrolysis of the acetate (+)-4

Lipase PS (60 mg) was added to a solution of acetate (+)-**4** (100 mg, 0.36 mmol) ($[\alpha]_D^{20}$ +5.5 (*c* 1, MeOH), 69% e.e.) in *tert*-BuOH:phosphate buffer (1:6 v/v, 10 mL), and stirred at rt for 8 h. After filtration through a Celite pad, the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (CH_2Cl_2) gave the hydroxy ester (*R*)-(−)-**2** (60.5 mg, 71%, 96% e.e.), $[\alpha]_D^{20}$ −8.0 (*c* 1, CH_3OH).

4.6. Procedure for the acid-catalyzed lactonization of the hydroxy esters 2

A solution of the hydroxy ester **2** (100 mg, 0.42 mmol) and *p*-TsOH (catalytic) in benzene (10 mL) was heated under reflux under argon for 3 h. The mixture was cooled to rt and then washed with saturated aqueous $NaHCO_3$ and water. The aqueous layers were extracted with ethyl acetate, and the combined organic phases dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, CH_2Cl_2) to afford the corresponding lactone (*S*)-(−)-**1** (70 mg, 94%). ($[\alpha]_D^{24}$ −7.3 (*c* 1, $CHCl_3$), 94% e.e.), or (*R*)-(+)-**1** ($[\alpha]_D^{24}$ +7.5 (*c* 1, $CHCl_3$), 96% e.e.).

Acknowledgements

This work was supported by Spanish Comisión Interministerial de Ciencia y Tecnología (CICYT) under Grant SAF98-0148-C04-03. We would like to thank Amano Pharmaceutical Co. Ltd (Nagoya, Japan) and Novo Nordisk Bioindustrial, S.A. (Madrid, Spain) for their generous gifts of lipases.

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12. The e.e. was determined from the ratio of the observed and literature[10a] specific rotations.
13. Determined by comparison with literature[9d] values after transformation into (*R*)-(+)-lactone.
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15. The acetate (*S*)-(−)-**4** ($[\alpha]_D^{20}$ −6.7 (*c* 1, MeOH), 84% e.e.), which was required as reference sample, was synthesized quantitatively by acetylation of the hydroxy ester (*S*)-(+)-**2** ($[\alpha]_D^{20}$ +7.0 (*c* 1, MeOH), 84% e.e.) with acetic anhydride in pyridine.