Pergamon

Tetrahedron: *Asymmetry* 13 (2002) 1219–1222

TETRAHEDRON: *ASYMMETRY*

Lipase-catalyzed kinetic resolution of (±)-*trans*-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzo[*b*]furan

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Received 21 May 2002; accepted 10 June 2002

Abstract—Kinetic resolution of the title compound (±)-**1** was effected through *Candida cylindracea* lipase- and *Rhizopus arrhizus* lipase-catalyzed transesterification with vinyl acetate in organic solvents. The influence of the enzyme and the solvent on the enantioselectivity was studied.

1. Introduction

During the last decade enzymes have been extensively used as catalysts for the synthesis of optically active compounds.[1–5] Of these enzymes, lipases are the most widely employed, not only because they are cheap and readily available from many different sources, but because they show high enantioselectivities in the transformation of a broad range of substrates and high stability in organic solvents. Lipases are used for both enantioselective hydrolysis of racemic esters of primary or secondary alcohols in aqueous media and enantioselective esterification of racemic primary or secondary alcohols in organic solvents.[6,7]

We recently published the enzyme-catalyzed kinetic resolution of 1,4-benzodioxanes and chromanes possessing a hydroxymethyl group at their stereogenic center.[7,8] In continuation of these investigations, we now report on an extension of this simple procedure to the enantioselective synthesis of (2*R*,3*S*)-(−)-2-(4-hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihidro benzo[*b*]furan, (−)-**1**, which can be used as a starting material for the total synthesis of its naturally occurring biologically active derivatives possessing different side chains at C-5 [9–13] following the procedure we described[14] most recently.

The enzyme-catalyzed acylation of (±)-**1** (Scheme 1) was carried out by stirring a suspension of the substrates in the presence of vinyl acetate (VA) as irreversible acyl donor at room temperature in different solvents. The progress of the reaction was monitored by TLC and the reaction was terminated by filtration of the enzyme. The optically active alcohols and their enantiomeric acetates were separated using preparative TLC.

The conversion rates were calculated from the yields of recovered alcohols and the enantiomer ratios of the alcohols were determined by HPLC using a Chiral-AGP column as the stationary phase.

Pseudomonas fluorescens lipase (PFL) was used successfully for the kinetic resolution of 1,4-benzodioxanes and chromanes possessing a hydroxymethyl group at their stereogenic center.[7,8] Therefore, this enzyme was also used as the catalyst for the kinetic resolution of (±)-**1**. Surprisingly, however, no transformation of (±)-**1** could be detected either in dioxane or VA.

It is also well documented in the literature[15,16] that *Pseudomonas cepacia* lipase (PCL) shows high enantioselectivity towards a wide range of sterically hindered primary alcohols. The performance of this enzyme was, therefore, examined in different solvents. The results are summarized in Table 1.

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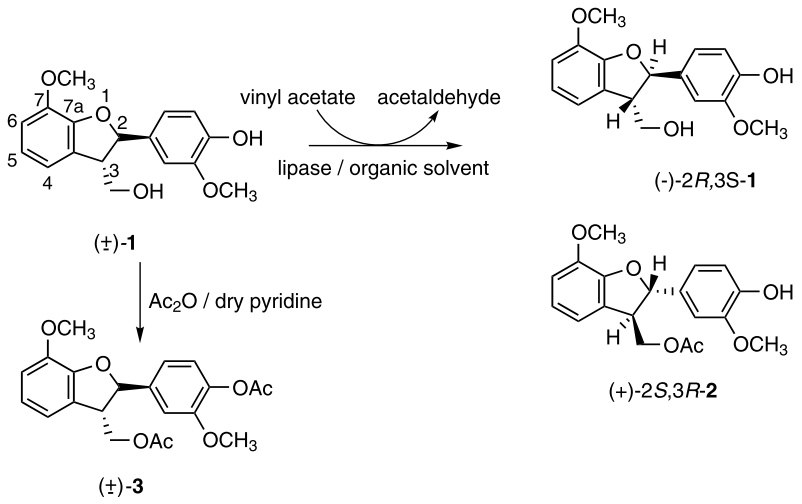
0957-4166/02/$ - see front matter
PII: S0957-4166(02)00314-2



Scheme 1.

Table 1. Results of the PCL lipase-catalyzed acetylation of (±)-**1**

Entry	Solvent[a]	Time (days)	Conversion (%)[b]	Enantiomer ratio of (−)-**1**[c]	Enantiomer ratio of (+)-**2**[c]	E[d]
1	Diisopropyl ether	7	–	–	–	–
2	Dichloromethane	7	–	–	–	–
3	Vinyl acetate	4	54	76:24	36:64	2.8
4	Dioxane	5	50	56:44	45:55	1.4

[a] All the solvents were anhydrous.
[b] Degree of conversion was calculated from the yield of recovered alcohol [(−)-**1**].
[c] Enantiomer ratio was determined by chiral HPLC.
[d] $E=\ln[(1-C)(1-ee)]/\ln[(1-C)\ (1+ee)]$; calculated according to Ref. 17.

TLC monitoring of the reactions clearly showed that PCL (on Toyonite®, Ammano) catalyzed the transesterification of (±)-**1** neither in dry dichloromethane nor in diisopropyl ether. In contrast, the ca. 50% conversion of **1** could be detected in dry dioxane or in pure VA after a few days. TLC analysis also clearly indicated that the acetylation of (±)-**1** took place regioselectively [(±)-**1** to (+)-**2**] in these cases. The product formed in this process was different from the diacetate (±)-**3** prepared by simple acetylation of (±)-**1**. The most convincing evidence for the structure of monoacetate **2** was the downfield shift by ca. 0.5 ppm of 3-CH_2 in the ^{1}H NMR spectrum, as shown in Table 2.

Table 2. Selected ^{1}H NMR data of compounds (±)-**1**, (+)-**2**, (±)-**3**

Compound	Chemical shifts (ppm)		
	7-OCH_3	3′-OCH_3	3-CH_2-OR
(±)-**1**	3.89	3.86	3.93
(+)-**2**	3.89	3.86	4.39
(±)-**3**	3.91	3.81	4.39

However, HPLC analysis of (−)-**1** and (+)-**2** showed that the acetylation took place only with moderate enantioselectivity in both solvents. In order to improve enantioselectivity of this transformation [(±)-**1** to (−)-**1**+(+)-**2**] a number of further lipases in different solvents (dichloromethane, diisopropyl ether, neat VA) were tried.

In the case of lipase from *Aspergillus niger*, *Mucor miehei*, *Rhizopus niveus* and Hog pancreas no transformation could be detected, but lipases from *Candida antarctica* (CAL), *Candida cylindracea* (CCL) and *Rhizopus arrhizus* (RAL) were effective. The results of these experiments are summarized in Table 3.

As shown in entry 1, CAL catalyzed the transesterification of (±)-**1** without any enantioselectivity. Fortunately, significantly higher enantioselectivity was observed using CCL and RAL (entries 2 and 3) than was found for PCL. Moreover, PCL and CCL showed the opposite enantioselectivity with respect to RAL.

The absolute configuration of (−)-**1** and (+)-**2** were determined by CD spectroscopy using the helicity rule described recently for the 7-methoxy-2,3-dihydrobenzo[*b*]furan chromophore.[18]

Since a negative Cotton effect ($\Delta\varepsilon=-0.05$) for the ^1L_b-band CD ($\lambda=292$ nm) was observed for (−)-**1**, its heterocyclic ring adopts a preferred envelope conformation of *M*-helicity according to the above mentioned rule (*P*/*M*-helicity of the heterocyclic ring leads to a

Table 3. Enzymatic esterification of (±)-**1**

Entry	Enzyme	Solvent[a]	Time (h)	Conversion (%)[b]	Enantiomer ratio of (−)-**1**[c]	Enantiomer ratio of (+)-**2**[c]	E[d]
1	CAL	Vinyl acetate	100	43	50:50	50:50	0
2	CCL	Diisopropyl ether	100	52	92:8	8:92	36
3	RAL	Vinyl acetate	100	56	15:85	77:23	6.8

[a] All the solvents were anhydrous.
[b] Degree of conversion was calculated from the yield of recovered alcohol [(−)-**1**].
[c] Enantiomer ratio was determined by chiral HPLC.
[d] $E=\ln[(1-C)(1-ee)]/\ln[(1-C)\ (1+ee)]$; calculated according to Ref. 17.

positive/*negative* ^1L_b CD band, respectively, and the terms of *P*/*M*-helicity are defined by the positive and negative sign of torsion angle of the C(7a)–O–C(2)–C-3 bonds respectively). The substituents attached to the hetero-ring at C-2 and C-3 are equatorially oriented as determined by X-ray crystallography in the case of (±)-**1**.[19] Therefore, the (2*R*,3*S*)-absolute configuration could be attributed to (−)-**1**. Since (+)-**2** shows a mirror image CD spectrum to that of (−)-**1**, it possesses (2*S*,3*R*)-absolute configuration.

In summary, we have shown that by careful selection of the solvent in the CCL- or RAL-catalyzed acetylation of (±)-**1** using VA as the acylating agent, (2*R*,3*S*)-(−)-**1** and (2*S*,3*R*)-(+)-**1**, respectively, can be obtained in good chemical yields (84 and 88%) and high enantiomeric purity (ee = 84 and 70%) The compounds can be used as versatile building blocks for the synthesis of a variety of naturally occurring 2,3-dihydrobenzo-[*b*]furan-type neolignans with interesting biological activities.

2. Experimental

The analytical and preparative TLC was done on silca gel 60 F_{254} plates (Fa. Merck). The reagents were purchased from Sigma-Aldrich. For work-up the solutions were dried ($MgSO_4$) and concentrated in vacuo. ^{1}H NMR spectra were recorded on a Bruker WP-200 spectrometer with TMS as internal standard in $CDCl_3$. The chemical shifts (δ) are given in ppm and the spin–spin coupling constants (J) in Hz. Optical rotations were measured on a Perkin–Elmer 341 polarimeter (l = 10 cm) at room temperature. CD spectra were recorded on a Jasco J-715 spectropolarimeter at room temperature in online mode with LCCD-311 HPLC flow cell unit.

Experimental details of the HPLC analysis are reported for all compounds in the form: column (mobile phase), enantiomeric excess, retention time (t_R) in min. HRMS were recorded in FAB mode (glycerol) on a VG 70HS MS spectrometer. Lipases were purchased from Fluka except lipase from *P. cepacia* on Toyonite® which was a gift from Ammano Pharmaceutical Co., Ltd. (±)-**1** was prepared according to the literature.[20]

2.1. General procedure for enzyme-catalyzed kinetic resolution

To the stirred solution of racemic substrate (60 mg) in solvent (30 mL), VA (60 μL) and lipase (60 mg) were added. The suspension was stirred at room temperature and monitored by TLC. The reaction was stopped by filtration of the enzyme, the filtrate was evaporated to dryness at reduced pressure and the residue was separated by preparative TLC (toluene–ethyl acetate = 4:1).

2.2. (2*R*,3*S*)-(−)-2-(4-Hydroxy-3-methoxyphenyl)-3-hydroxymethyl-7-methoxy-2,3-dihydrobenzo[b]furan, (−)-1

Prepared using CCL in diisopropyl ether to give (−)-**1** as a colorless oil (25.2 mg, 84%). ^{1}H NMR: δ 3.69 (1H, m, H_β), 3.86 (3H, s, OMe), 3.89 (3H, s, OMe), 3.93 (2H, m, H_γ), 5.85 (1H, d, J = 7.25 Hz, H_α), 6.8–7.0 (6H, m, aromatic protons). $[\alpha]_D = -10.6$ (c 0.1, CH_2Cl_2). CD: λ ($\Delta\varepsilon$): 292 nm (−0.05), 241 nm (0.14). HPLC: Chiral-AGP (0.01 M phosphate buffer–*i*PrOH = 95:5), 84%, 3.2 and 5.9 min. HRMS m/z 302.1149 (calcd for $C_{17}H_{18}O_5$, 302.1154).

2.3. (2*S*,3*R*)-(+)-2-(4-Hydroxy-3-methoxyphenyl)-3-acetoxymethyl-7-methoxy-2,3-dihydrobenzo[b]furan, (+)-2

Prepared using CCL in diisopropyl ether to give (+)-**2** as a colorless oil (28.4 mg, 78%). ^{1}H NMR: δ 2.05 (3H, s, OAc), 3.78 (1H, m, H_β), 3.91 (3H, s, OMe), 3.94 (3H, s, OMe), 4.30 (1H, dd, J = 5.2 Hz, J = 10.5 Hz, H_γ), 4.45 (1H, dd, J = 5.2 Hz, J = 10.5 Hz, $H_{\gamma'}$), 5.45 (1H, d, J = 6.71 Hz, H_α), 6.78–7.05 (6H, m, aromatic protons). $[\alpha]_D = +17.92$ (c 0.1, CH_2Cl_2). CD: λ ($\Delta\varepsilon$): 298 nm (+0.08), 242 nm (−0.09). HPLC: Chiral-AGP (0.01 M phosphate buffer–*i*PrOH = 9:1), 84%, 3.2 and 17.7 min. HRMS m/z 344.1261 (calcd for $C_{19}H_{20}O_6$, 344.1259).

2.4. (2*R**,3*S**)-2-(4-Acetoxy-3-methoxyphenyl)-3-acetoxymethyl-7-methoxy-2,3-dihydrobenzo[b]furan, (±)-3

Acetylation of (±)-**1** (694.2 mg, 2.29 mmol) with acetic anhydride (3 mL) in dry pyridine (10 mL) at room temperature gave **3** (683 mg, 77%) as a colorless oil. ^{1}H NMR: δ 2.05 (3H, s, OAc), 2.29 (3H, s, OAc), 3.78 (3H, s, OMe), 3.8 (1H, m, H_β), 3.88 (3H, s, OMe), 4.30 (1H, dd, J = 5.2 Hz, J = 10.5 Hz, H_γ), 4.45 (1H, dd,

$J=5.2$ Hz, $J=10.5$ Hz, $H_{\gamma'}$), 5.52 (1H, d, $J=6.71$ Hz, H_{α}), 6.78–7.05 (6H, m, aromatic protons). HRMS m/z 386.1362 (calcd for $C_{21}H_{22}O_7$, 386.1365).

Acknowledgements

The authors thank the National Science Foundation (OTKA T-034250 and T-033109) for valuable financial support.

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