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Synthesis and Kinetic Resolution of Furyl Substituted Secondary Carbinols by Porcine Pancreatic Lipase under Solvent Free Conditions

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Chiral furyl substituted carbinols were prepared from the related carbonyl compounds and their enzymatic kinetic resolution was studied by using porcine pancreatic lipase (PPL) in transesterification reaction under solvent free condition. This study revealed that carbinols having one less bulky group on the chiral center are good substrates for PPL and the resolution proceeds with higher ee's and less reaction time.

Keywords: Synthesis, Kinetic resolution, Porcine pancreatic lipase, Chiral furyl carbinols, Solvent free

INTRODUCTION

Lipases as versatile biocatalysts have been extensively employed in organic synthesis [1-3]. In particular, this class of enzyme is able to perform transesterification and hydrolytic reactions [4-7]. The enantioselective transesterification reaction of chiral and pro-chiral secondary alcohols with an acyl-donor in the presence of lipases is a simple and efficient route to optically active alcohols and esters. Among the enzymes used for this purpose, porcine pancreatic lipase (PPL) is well recognized and has been used as a valuable chiral catalyst in the asymmetric synthesis of organic compounds [8-11].

The hydroxyalkyl furans such as **1** and **2** are important building blocks for the synthesis of various natural products such as carbohydrates, macrollides and alkaloids [12-14]. Metz and co-workers provided an enantioselective method for the preparation of molluscicidal furanosesquiterpene lactones recciocarpin A and recciocarpin B by application of catalytic ring closing metathesis using (S)-**2** as the key precursor [12,15].

In continuation of our research interest in biotransformation reactions for the preparation of synthetically usefull chirons [16], in this work, the synthesis and resolution of a new class of furyl substituted secondary alcohols (**3-4**) by enzymatic methodology were studied. The substrate **3** was easily synthesized by the reduction of readily available furyl substituted α,β-saturated ketones from the condensation reaction of furfural and the related ketones. The substrste **4** was prepared by the reaction of allylbromide and zinc powder in saturated NH_4Cl in 86% yield.

EXPERIMENTAL

General

Chemicals were purchased from Merck and Fluka. Melting points were measured on an Electrothermal 9100 apparatus. Optical rotations were measured by Atago (Polax) polarimeter. IR spectra were determined on a Shimadzo IR-470 spectrometer. ^{1}H NMR spectra were recorded on a 500 MHz Bruker DRX-500 in $CDCl_3$ as solvent and TMS as internal standard. Preparative thin layer chromatography was prepared

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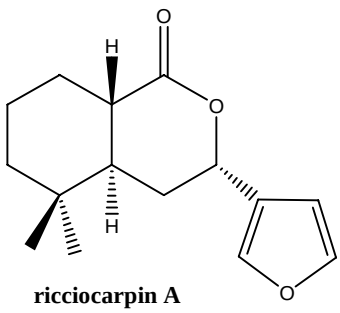

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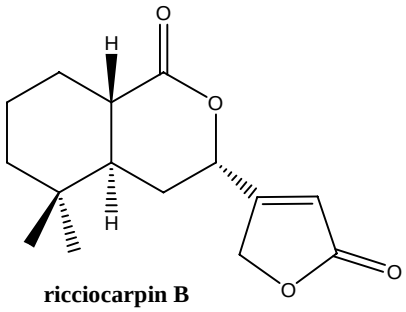

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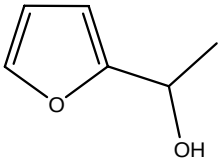

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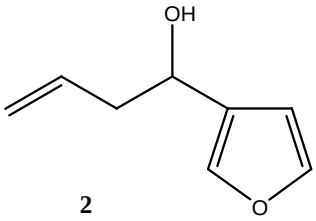

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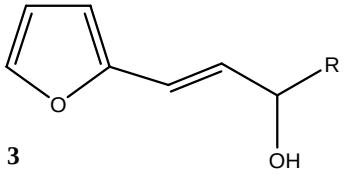

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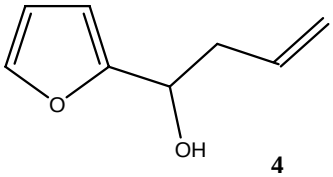
R= Me, Et, *m*-NO_2-C_6H_4, 2-furyl



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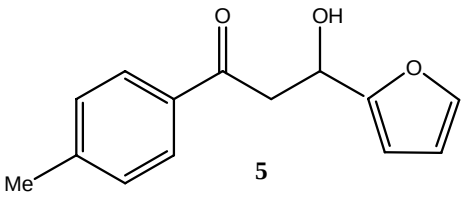

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from Merck (Kieselgel 60 H, F_{254}, Art No. 7730). GC was carried out using a Buck Scientific 910 instrument (capillary column, MXT-5, 15 m). All solvents used were dried and distilled according to standard procedures.

Typical Procedure for Substituted Ketones

3-(2-Furyl)-1-(3-nitrophenyl)-prop-2-ene-1-one (6c). Furfural (25.0 mmol) was added to a cooled (10 ºC) stirred solution of 3-nitroacetophenone (25.0 mmol) in water (20 ml). To this mixture 30% sodium hydroxide solution (2 ml) was added and the mixture was stirred at room temperature for 4 h. The resulting mixture was acidified by 10% sulfuric acid, organic phase was separated and extracted by ether (2 × 15 ml). The ethereal solution was dried ($MgSO_4$) and evaporated to give 3-(2-furyl)-1-(3-nitrophenyl)-prop-2-ene-1-one (7.8 mmol) in 88% yield, as a yellow solid, mp.: 102-104 ºC. IR (KBr): 1660, 1600, 1520, 1470, 1350, 965, 870, 800, 740, 700, 670 cm^{-1}; ^1H NMR ($CDCl_3$): 8.86 (s, 1H), 8.45 (dd, *J* = 0.88, 8.0 Hz, 1H), 8.37 (d, *J* = 7.72 Hz, 1H), 7.73 (t, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 15.2 Hz, 1H), 7.60 (s, 1H), 7.47 (d, *J* = 15.2, 1H), 6.82 (d, *J* = 3.3 Hz, 1H), 6.57 (m, 1H) ppm.

1-(2-Furyl)-pent-1-ene-3-one (6b). The reaction of furfural and 2-butanone by the procedure used for **6c** provided **6b** as a ~1:1 mixture with its isomer 1-(2-furyl)-2-methyl-1-butene-3-one in 79% yield. A pure sample of **6b** was separated by preparative TLC (*n*-hexane/EtOAc: 5/1) as yellow oil. IR (neat); 3100, 1650, 1610, 1450, 1380, 1240, 1010, 960, 740 cm^{-1}; ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): 7.54 (s, 1H), 7.3 (d, *J* = 15.8 Hz, 1H), 6.61 (d, *J* = 3.4 Hz, 1H), 6.60 (d, *J* = 15.8 Hz, 1H), 6.44 (dd, *J* = 1.5, 3.2 Hz, 1H), 2.6 (q, *J* = 7.35 Hz, 2H), 1.11 (t, *J* = 7.35 Hz, 3H) ppm.

1,3-di-(2-Furyl)-prop-2-ene-1-one (6d). Off yellow solid, mp.: 80-81.5 ºC, 4 h, 92% yield. IR (KBr): 1660, 1600, 1550, 1460, 1250, 1040, 1000, 970, 760 cm^{-1}; ^1H NMR ($CDCl_3$): 7.66 (s, 1H), 7.64 (d, *J* = 15.3 Hz, 1H), 7.54 (s, 1H), 7.34 (d, *J* = 15.5 Hz, 1H), 7.33 (d, *J* = 3.4 Hz, 1H), 6.74 (d, *J* = 3.3 Hz, 1H), 6.60 (dd, *J* = 1.7, 3.3 Hz, 1H), 6.53 (dd, *J* = 1.7, 3.3 Hz, 1H) ppm.

Typical Procedure for Substituted Alcohols

4-(2-Furyl)-3-buten-2-ol (3a). To a magnetically cold (0 ºC) solution of furfural acetone (3.0 g, 22.0 mmol) in methanol (20 ml) a solution of $NaBH_4$ (1.4 g) in 2 M NaOH (2 ml) was added. The progress of the reaction was monitored by TLC (*n*-hexane/EtOAc: 1/1). The reaction was completed after 1 h. Most of the methanol was removed under vacuum and the residue was diluted with water (20 ml) and extracted with diethylether (3 × 20 ml). The ethereal solution was dried ($MgSO_4$) and evaporated in a rotary evaporator to give 4-(2-furyl)-3-buten-2-ol (2.9 g, 21.0 mmol) as a colorless oil, in 95% yield. (IR neat): 3400, 1640, 1120, 1060, 960, 750 cm^{-1}; ^1H NMR ($CDCl_3$): 7.3 (d, *J* = 1.3 Hz, 1H), 6.33 (d, *J* = 16.0 Hz, 1H), 6.32 (dd, *J* = 3.4, 1.3 Hz, 1H), 6.19 (d, *J* = 16.0 Hz, 1H), 6.18 (d, *J* = 3.4 Hz, 1H), 4.4 (quintet, *J* = 16.0 Hz, 1H), 3.2 (s, br, 1H), 1.3 (d, *J* = 6.5 Hz, 3H) ppm.

1-(2-Furyl)-pent-1-ene-3-ol (3b). Colorless oil, 1 h, 79% yield; IR (neat): 3350, 1645, 1550, 1480, 1450, 1365, 1065, 1010, 740 cm^{-1}; ^1H NMR ($CDCl_3$): 7.39 (s, 1H), 6.42 (dd, *J* = 1.9, 3.1 Hz, 1H), 6.35 (s, 1H), 6.28 (d, *J* = 3.1 Hz, 1H), 1.99 (s, 3H), 1.34 (d, *J* = 6.4 Hz, 3H) ppm.

3-(2-Furyl)-1-(3-nitrophenyl)-prop-2-ene-1-ol (3c). Light brown oil, 1 h, 97% yield; IR (neat): 3400, 1610, 1590, 1540, 1450, 1370, 1140, 1005, 960 cm^{-1}, ^1H NMR ($CDCl_3$): 8.31 (s, 1H), 8.16 (dd, *J* = 1.3, 8.1 Hz, 1H), 7.77 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 8.1 Hz, 1H), 7.37 (s, 1H), 6.55 (d, *J* = 15.7 Hz, 1H), 6.40 (dd, *J* = 1.85, 3.2 Hz, 1H), 6.32 (d, *J* = 3.2 Hz, 1H), 6.28 (dd, *J* = 6.8, 15.7 Hz, 1H), 5.46 (d, *J* = 6.8 Hz, 1H), 2.45 (s, br, 1H) ppm.

1,3-di-(2-Furyl)-prop-2-ene-1-ol (3d). Colorless oil, 1 h, 95% yield, IR (neat): 3400, 2940, 2900, 2850, 1640, 1520, 1480, 1440, 1140, 1080, 1000, 960 cm^{-1}. ^1H NMR ($CDCl_3$): 7.43 (m, 1H), 7.40 (s, 1H), 6.57 (d, *J* = 15.8 Hz, 1H), 6.41 (dd, *J* = 6.0, 15.8 Hz, 1H), 6.39 (m, 1H), 6.36 (m, 1H), 6.32 (d, *J* = 3.16 Hz, 1H), 6.30 (d, *J* = 3.1 Hz, 1H), 5.38 (d, *J* = 6.0 Hz, 1H), 2.41 (s, br, 1H) ppm.

3-(2-Furyl)-3-hydroxy-1-(*p*-toluyl) propane-1-one (5). The procedure used for the preparation of **6c** was employed which provided **5** as sole product. Yellow solid, mp.: 68-70 ºC, 4 h, 76% yield, IR (KBr): 3500, 1660, 1600, 1220, 1020, 970, 830, 800, 730, 720 cm^{-1}; ^1H NMR ($CDCl_3$): 7.90 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 0.72 Hz, 1H), 7.29 (d, *J* = 8.1 Hz, 2H), 6.37 (m, 1H), 6.35 (d, *J* = 3.1 Hz, 1H), 5.37 (dd, *J* = 3.0, 8.9 Hz, 1H), 3.60 (s, br, 1H), 3.58 (dd, *J* = 8.9, 17.8 Hz, 1H), 3.47 (dd, *J* = 3.0, 17.8 Hz, 1H) ppm.

1-(2-Furyl)-3-butene-1-ol (4). To a magnetically stirred solution of ammonium chloride (15 ml) and THF (3 ml), zinc powder (2 g, 30.6 mmol), furan-2-carbaldehyde (1.6 g, 16.65 mmol) and 3-bromopropene (4.1 g, 33.3 mmol) were added. The reaction mixture was stirred at room temperature for 2 h and then extracted by diethyl ether (3 × 10 ml). The organic layer was dried ($MgSO_4$) and evaporated in a rotary evaporator to provide 1-(2-furyl)-3-butene-1-ol (1.4 g, 10.1 mmol) in 86% yield as colorless oil. (IR neat): 3450, 1620, 1500, 1120, 1995, 920 cm^{-1}; ^1H NMR ($CDCl_3$): 7.39 (m, 1H), 6.34 (dd, *J* = 1.8, 3.25 Hz, 1H), 6.26 (m, 1H), 5.81 (m, 1H), 5.19 (td, *J* = 1.9, 10.2 Hz, 1H), 5.16 (td, *J* = 1.9, 17.2 Hz, 1H), 4.76 (dd, *J* = 5.84, 5.95 Hz, 1H), 2.64 (m, 1H), 1.71 (s, br, 1H) ppm.

Typical Procedure for PPL-Catalyzed Kinetic Resolution of (±)-1-(2-Furyl) ethanol

A mixture of racemic alcohols (±)-1 (10.0 mmol), vinyl acetate (12.0 mmol), solvent (5 ml) and lipase PPL (0.70 g) was stirred vigorously at 38 ºC and the progress of the reaction was monitored by TLC (acetone/*n*-hexane: 1/3) and GC. At ~50% conversion (see Table 1) the enzyme was filtered off, washed with dichloromethane (3 × 7 ml) and the volatile material was removed under vacuum. The residue was chromatoghraphed on silica gel (acetone/*n*-hexane: 1/3) to provide (-)-1 and (+)-1 (Table 1). The structures of products were confirmed by spectroscopic analysis (IR, ^1H NMR) and the enantiomeric excesses of the known products were established by comparison of their $[\alpha]_D$ with those reported in the literature. The same procedure was carried out for the solvent free reaction omitting only the solvent.

(+)-4-(2-Furyl)-3-buten-2-yl acetate (7a). Colorless oil, 16 h, 37% yield, $[\alpha]_D^{20} = +44^o$ (c = 2.5, $CHCl_3$); IR (neat): 3100, 2950, 1730, 1645, 1480, 1440, 1360, 1230, 1040, 950,

Table 1. Evaluation of Solvent Effects on the Kinetic Resolution of 1-(2-Furyl) Ethanol

Solvent	Reaction time (h)	Conversion (%)	(-)-1		(+)-1	
			Yield (%)[a]	Ee (%)[b]	Yield (%)	Ee (%)
THF	24	46	45	35	34	99
Hexane	24	35	44	12	25	76
CH_2Cl_2	24	40	40	15	32	98
Solvent free	16	50	45	98	35	95

[a]Isolated yields. [b]Ee's were established by comparison of $[\alpha]_D$ of the products with those reported in the literature [17].

750 cm^{-1}; ^1H NMR ($CDCl_3$): 7.37 (s, 1H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.39 (dd, *J* = 1.8, 3.2 Hz, 1H), 6.28 (d, *J* = 3.2 Hz, 1H), 6.14 (dd, *J* = 6.6, 16.0 Hz, 1H), 5.5 (quint., *J* = 6.6 Hz, 1H), 2.1 (s, 3H), 1.41 (d, *J* = 6.5 Hz, 3H) ppm.

(+)-1-(2-Furyl)-pent-1-ene-3-yl acetate (7b). Colorless oil, 18 h, 38% yield, $[\alpha]_D^{20}$ = +31° (c = 2.5, $CHCl_3$); IR (neat): 3090, 2945, 1735, 1640, 1442, 1365, 1240, 950, 748; ^1H NMR ($CDCl_3$): 7.38 (s, 1H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.36 (dd, 1.8, 3.1 Hz, 1H), 6.24 (d, *J* = 3.1 Hz, 1H), 6.20 (dd, *J* = 6.5, 16.0 Hz), 4.16 (q, *J* = 6.5 Hz, 1H), 2.05 (s, 3H), 1.62 (m, 2H), 0.98 (t, *J* = 7.2 Hz) ppm.

1-(2-Furyl)-3-butene-1-yl acetate. A sample of racemic 1-(2-Furyl)-3-butene-1-ol (**4**) was resolved by using the procedure employed in the resolution of (±)-1-(2-furyl) ethanol. The related acetate product was obtained as colorless oil, yield 10%, $[\alpha]_D^{20}$ = ~0 (c = 2.0, $CHCl_3$); IR (neat): 3100, 2900, 1730, 1640, 1500, 1430, 1380, 1240, 1160, 930 cm^{-1}; ^1H NMR ($CDCl_3$): 7.39 (dd, *J* = 1.5, 2.6 Hz, 1H), 6.33 (m, 2H), 5.89 (t, *J* = 7.15 Hz, 1H), 5.70 (tdd, *J* = 7.0, 10.2, 17.0 Hz, 1H), 5.08 (dd, *J* = 5.1, 10.2 Hz, 1H), 5.15 (dd, *J* = 5.1, 17.0 Hz, 1H), 2.71 (m, 2H), 2.07 (s, 3H) ppm.

RESULTS AND DISCUSSION

At the outset of this study the solvent effect was evaluated on the kinetic resolution of 1-(2-furyl) ethanol (**1**) (prepared in 96% yield, according to the procedure used for **6c**) by PPL and the results are summarized in Table 1. These results revealed that the reaction under solvent free condition proceeds at lower reaction time and the ee% of the acetate product and the remaining alcohol is very high.

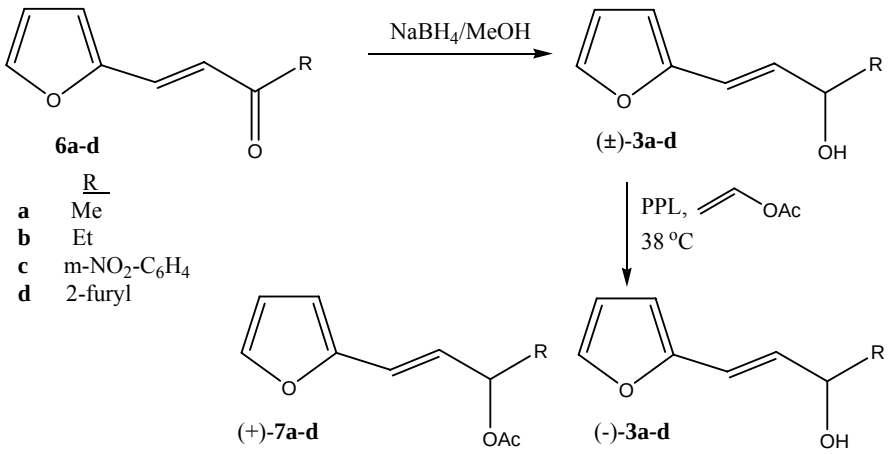
A simmilar assessment was carried out with the substrarte **3a** which on the basis of the reaction time and specific rotation $[\alpha]_D^{20}$ led to the same results (Table 2). Therefore the kinetic resolution of the substrates **3b** was conducted only under solvent free condition (Table 2).

Substrates **3c**, **3d** and **5** were prepared and subjected to PPL catalyzed kinetic resolution, both in solvent (THF, hexane and CH_2Cl_2) and under solvent free condition, using the same experimental procedure employed as in **1,** but no sign of the transesterification reaction could be detected. Substrate **4** was prepared from allylbromide and subjected to enzymatic resolution. In the presence of the solvent (THF, hexane and CH_2Cl_2) after 96 h GC examination revealed that only a trace of the acetate ester was formed. Under solvent free condition a very slow reaction was occurred and after 96 h at ~15% conversion, acetate ester was isolated in 10% yield without optical activity (Table 2).

In conclusion this study revealed that enzymatic kinetic resolution of 1-(2-furyl)ethanol (**1**) under solvent free condition comparing with the reactions in solvent proceeds more efficiently with excellent ee's for both acetate ester product and the remaining alcohol (Table 1). Secondary alcohols of type **3** (Scheme 1) having only one bulky group on the chiral center (**3a** and **3b**) are also good substrates for PPL under solvent free condition (Table 2). In contrast, substrates with bulky groups on both side of the chiral center (**3c**, **3d**, **4** and **5**) do not fit in the cavity of the enzyme and therefore are not suitable substrates for this enzyme. The research in this respect is on the way.

Table 2. Kinetic Resolution of Furyl Alcohols **3a**, **3b** and **4**

Entry	Solvent	Reaction time (h)	Conversion (%)	(-)-Alcohol		(+)-Acetate	
				Yield (%)[a]	$[\alpha]^{20}_D$	Yield (%)[a]	$[\alpha]^{20}_D$
3a	Solvent free	16	50	43	-35	37	+44
3a	THF	24	45	42	-25	34	+32
3a	Hexane	24	25	45	-20	24	+33
3a	CH_2Cl_2	24	35	43	-25	32	+32
3b	Solvent free	18	50	40	-20	38	+31
4	Solvent free	96	15	78	~0	10	~0



Scheme 1

ACKNOWLEDGMENTS

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