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Chemoenzymatic synthesis of enantiomerically enriched kavalactones

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Abstract—Lipase-mediated kinetic resolution of methyl-3-hydroxy-5-phenylpentanoate and (6*E*)-ethyl 5-hydroxy-3-oxo-7-phenylhept-6-enoate is described in high enantiomeric excess and good yields. The effect of different lipases in different solvents has been screened using different acylating agents. This protocol has been extended for the preparation of enantiomerically pure biologically important kavalactones.

Kavalactones are a class of α-pyrones and 5,6-dihydropyrones isolated from the kava plant *Piper methysticum* (Piperaceae), which grows widely in the South Pacific islands[1] including Fiji and Hawaii. The extracts of its root and stem are used as a folk medicine or as a ceremonial drink in this region. Various structurally related analogues such as kavain (**1c**), methylstian (**1d**) and dihydrokavain-5-ol (**1e**) possess significant biological activities including anticonvulsive,[2a] muscle-relaxing,[2b] sedative,[2c] analgesic and antithrombotic,[2d] and have attracted attention in both the pharmaceutical and chemical research sectors. Some clinical studies indicate that the kavalactones have demonstrable anxiety-reducing effects. However, the FDA and CDC have issued warnings about the severe cause of liver injury probably associated with the use of kava-containing dietary supplements. These findings suggest the need for detailed investigations on the individual kavalactones as well as their structurally related analogues.

There are several reports on the synthesis of kavain, and its analogues, in particular, those involving asymmetric reduction.[3] However, in this investigation a chemoenzymatic synthetic strategy for kavalactones has been developed. In continuation of our earlier efforts towards the preparation of biologically important compounds or their intermediates by the application of enzymes,[4] we herein report an efficient and facile synthesis of optically pure (+)- and (−)-dihydrokavain (**1a**, **1b**) and (*R*)-(+)-kavain (**1c**) using a lipase catalyzed protocol (Fig. 1).

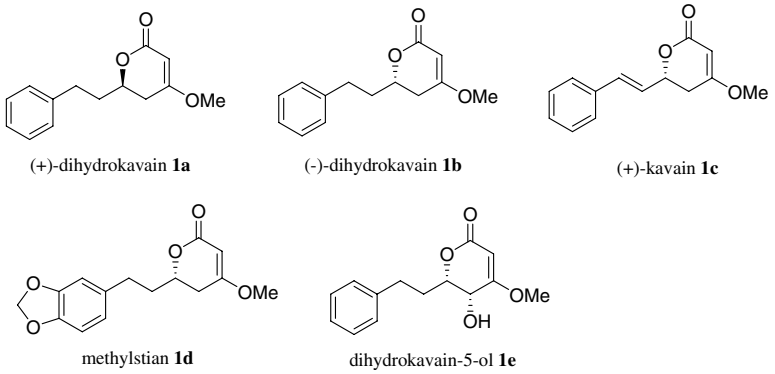

Figure 1. Kavain based compounds.

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Enantiopure dihydrokavain has been synthesized by employing β-keto ester **4** as the starting material. β-Keto ester **4** has previously been prepared[5,3g] by the alkylation of the dianion of methylacetoacetate **3** with benzyl bromide **2**. Reduction to β-hydroxy ester **5** was achieved using sodium borohydride in methanol. The racemic β-hydroxy ester **5** was resolved enzymatically using different lipases. Amongst all the lipases screened, *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS–C) gave good yields and high enantiomeric excess (Table 1). The effect of different solvents was also examined employing lipase PS–C. Among the solvents investigated, diisopropyl ether and hexane provided good conversions with high enantiomeric excess (Table 2). During the course of this study a report on the enzymatic resolution of β-hydroxy esters appeared,[6] however, there are no reports on the lipase-mediated resolution of substrate **5**.

The resolution of **5** gave (*S*)-acetate (*S*)-**5** and (*R*)-alcohol (*R*)-**5**. These two products were separated by column chromatography (EtOAc–hexane, 8:2). After separation alcohol (*R*)-**5** was treated with lithium diisopropylamide (LDA) and following addition of *t*-butyl acetate, hydroxy β-keto ester (*R*)-**6** was obtained. This was lactonized with TFA to give (*R*)-**7** which upon treatment with dimethyl sulfate in acetone in the presence of potassium carbonate afforded (*R*)-(+)-dihydrokavain (*R*)-**1a** $[\alpha]_D^{24}$ −26.6 (*c* 4.5, $CHCl_3$); [Ref. 7 $[\alpha]_D^{25}$ −28 (*c* 1.92, EtOH)]. (*S*)-(−)-Dihydrokavain (*S*)-**1b** was obtained using the same procedure after hydrolysis of acetate (*S*)-**5** using potassium carbonate in methanol (Scheme 1) $[\alpha]_D^{24}$ +28.0 (*c* 1.5, $CHCl_3$); [Ref. 7 $[\alpha]_D^{10}$ +30 (*c* 1, EtOH)].

Racemic **10** was obtained as a pale yellow liquid by reaction of cinnamaldehyde **8** with the dianion of ethyl acetoacetate **9**. Racemic **10** was resolved using lipases PS–C and PS–D with different acylating agents. Amongst the acylating agents examined, vinyl acetate gave low yields as well as low conversion rates. However, isopropenyl acetate and vinyl chloroacetate gave good yields and high enantiomeric excess. Amongst the solvents em-

Table 1. Transesterification of methyl 3-hydroxy-5-phenylpentanoate **5** and (6*E*)-ethyl 5-hydroxy-3-oxo-7-phenylhept-6-enoate **10** with various lipases in diisopropyl ether

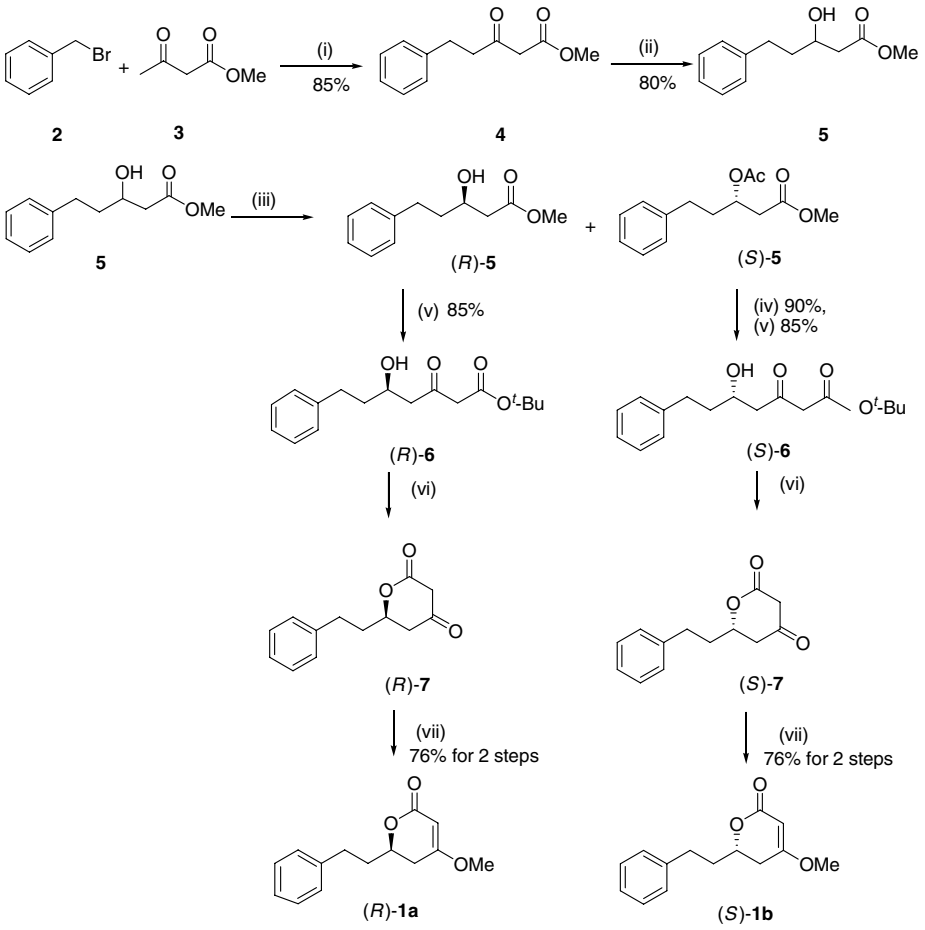
Entry	Ester	Lipase[a]	Acylating agent[b]	Time (h)	Alcohol		Acetate		*E*
					Yield[c] (%)	Ee[d] (%)	Yield[c] (%)	Ee[d] (%)	
1	**5**	PS–C	A	18	46	>99	46	>99	1055
2	**5**	PS–D	A	24	45	>99	45	>99	1055
3	**5**	PS	A	240	35	30.4	33	>99	339
4	**5**	CRL	A	240	98		—	—	—
5	**5**	AYS	A	240	90		—	—	—
6	**10**	PS–C	B	20	42	>99	42	>99	1055
7	**10**	PS–D	B	30	40	96	40	>99	751
8	**10**	PS–C	C	30	42	>99	43	>99	1055
9	**10**	PS–D	C	35	40	94	40	>99	646
10	**10**	PS	C		60	80.2	20	>99	501
11	**10**	PS–C	A	24	35	82	30	90	48.6
12	**10**	PS–D	A	30	32	80	30	79.5	21

[a] *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS–C), *Pseudomonas cepacia* lipase immobilized on diatomite (PS–D), *Pseudomonas cepacia* (PS) from (Amano Pharmaceutical company, Japan), *Candida rugosa* lipase (AYS) *Candida rugosa* lipase (CRL) from Sigma.
[b] A = vinyl acetate, B = vinyl chloroacetate, C = isopropenyl acetate.
[c] Isolated yields.
[d] Determined by chiral HPLC (chiral column AS–H; Diacel) employing hexane–isopropanol (90:10) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).

Table 2. Effect of solvents on the transesterification of methyl 3-hydroxy-5-phenylpentanoate (**5**) and (6*E*)-ethyl 5-hydroxy-3-oxo-7-phenylhept-6-enoate (**10**) using lipase PS–C[a]

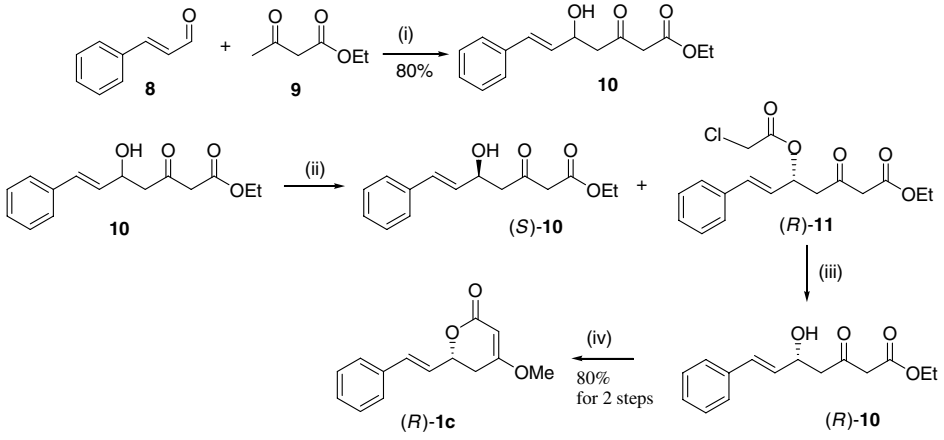
Entry	Ester	Solvent	Log *P*	Acylating agent[b]	Time (h)	Alcohol		Acetate		*E*
						Yield[c] (%)	Ee[d] (%)	Yield[c] (%)	Ee[d] (%)	
1	**5**	Hexane	3.5	A	20	45	>99	45	>99	1055
2	**5**	Diisopropyl ether	1.9	A	18	46	>99	46	>99	1055
3	**5**	*t*-Butyl methyl ether	NA	A	24	31	59.2		>99	358
4	**5**	Toluene	2.5	A	48	41	>96	38	>99	1055
5	**5**	Diethyl ether	0.85	A	48	44	>99	44	>99	1055
6	**10**	Diisopropyl ether	1.9	B	20	42	96	40	>99	751
7	**10**	Hexane	3.5	B	30	40	94.4	39	>99	646
8	**10**	Hexane	3.5	C	28	42	>99	43	>99	1055
9	**10**	Diisopropyl ether	1.9	C	34	40	94	40	98.4	356

[a] *Pseudomonas cepacia* lipase immobilized on modified ceramic particles (PS–C) (Amano Pharmaceutical company).
[b] A = vinyl acetate, B = vinyl chloroacetate, C = isopropenyl acetate.
[c] Isolated yields.
[d] Determined by chiral HPLC (chiral column AS–H; Diacel) employing hexane–isopropanol (90:10) as mobile phase at 0.5 mL/min and monitored by UV (254 nm).



Scheme 1. Reagents and conditions: (i) NaH, *n*-BuLi, THF, 0 °C; (ii) $NaBH_4$, MeOH, 0 °C–rt; (iii) Lipase PS–C, vinyl acetate (6 equiv), diisopropyl ether; (iv) K_2CO_3, MeOH; (v) $MeCO_2Bu^t$, LDA (3 equiv), THF, −78 °C; (vi) TFA, CH_2Cl_2, 10 h; (vii) K_2CO_3, acetone, $(MeO)_2SO_2$.

ployed, diisopropyl ether led to good results compared with hexane. The acetate obtained after enzymatic resolution with vinyl acetate and isopropenyl acetate could not be hydrolyzed. Therefore, vinyl chloroacetate was used as the acylating agent in this enzymatic resolution. Chloroester (*R*)-**11** obtained after enzymatic resolution was readily hydrolyzed to δ-hydroxy β-ketoester (*R*)-**10** using 25% aq ammonia in methanol. The δ-hydroxy β-ketoester (*R*)-**10** was lactonized using potassium carbonate in methanol and the solvent was evaporated. The residue was dissolved in acetone and dimethylsulfate and stirred for 10 h at room temperature to afford (*R*)-(+)-kavain **1c** as a white crystalline solid following purification by column chromatography (Scheme 2). The structure elucidation of (*R*)-kavain **1c** was carried out by spectral and physical methods (^{1}H NMR, melting



Scheme 2. Reagents and conditions: (i) NaH, *n*-BuLi, THF, 0 °C; (ii) lipase, vinyl chloroacetate (10 equiv), diisopropyl ether, 20 h; (iii) aq NH_3 (25%), MeOH; (iv) (a) K_2CO_3, MeOH, rt., 3 h; (b) acetone, $(MeO)_2SO_2$, rt, 10 h.

point) and also by comparison of the optical rotation values of previously reported results[8,7] with those of the natural product.

In conclusion, we have developed a simple and efficient approach for the enantiopure preparation of both forms of dihydrokavain and (*R*)-(+)-kavain employing a lipase mediated resolution process.

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