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Enantiocomplementary Resolution of 4-Hydroxy-5-(4-methoxyphenoxy)-1-pentyne Using the Same Lipase

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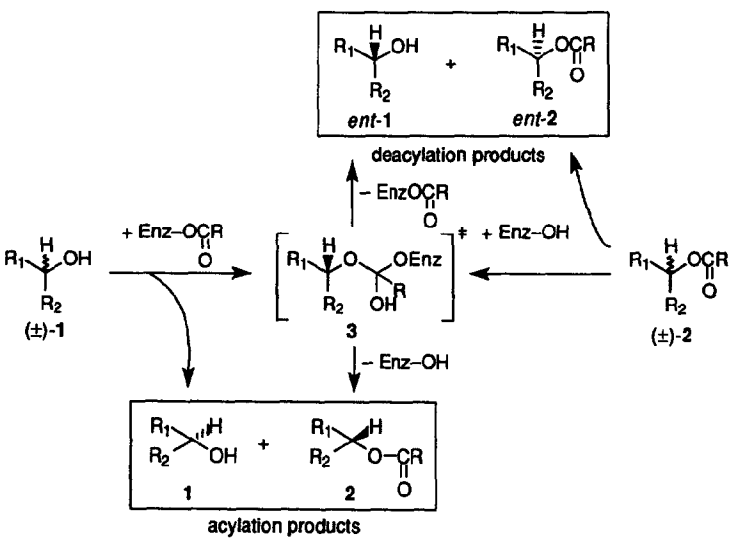
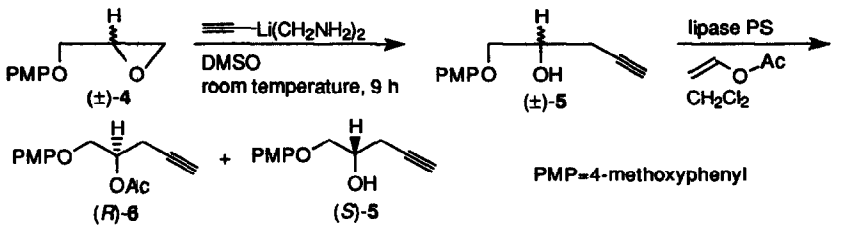
Abstract: Racemic 4-hydroxy-5-(4-methoxyphenoxy)-1-pentyne has been resolved in an enantiocomplementary way by kinetic acylation and deacylation reactions using the same lipase. The synthetic utility of the resolved products has been exemplified by transforming *S*-enantiomer into compactin lactone derivatives.

It has been well-established that lipases are able both to cleave and to form ester bonds depending on the conditions.[1] Since both processes are presumed to involve the common tetrahedral intermediate (**3**), it can be readily expected that each should give the same but antipodal mixture of an optically active alcohol and an optically active ester when a racemic substrate having chirality at the alkyl moiety is used as a substrate[2] (**Scheme 1**). The present report describes an example[3] by resolution of racemic 4-hydroxy-5-(4-methoxyphenoxy)-1-pentyne [(±)-**5**] using the same lipase (lipase PS, Amano) as an enantiospecific acylation and deacylation catalyst.



Scheme 1

We first examined the acylation of racemic alcohol [(±)-**5**] which was prepared in 95.5% by treating (±)-*O*-(4-methoxyphenyl)glycidol[4] [(±)-**4**] with lithium acetylide ethylenediamine complex in DMSO solution.[5] Treatment of (±)-**5** with 2 molar equiv. of vinyl acetate in a organic solvent in the presence of each of six lipases at 27-30 °C furnished the optically active ester (**6**) and the optically active alcohol (**5**) as shown in **Table 1**. Although it was revealed that stereospecificity and stereoselectivity were different with the lipases



Scheme 2

Table 1. Lipase-mediated Kinetic Acylation of the Racemic Alcohol [(±)-**5**] in Organic Solvent

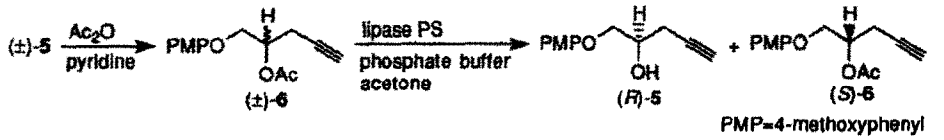
			acetate (**6**)			alcohol (**5**)			time
entry	lipase[a]	solvent	config.	yield	opt. purity (ee %)[b]	config.	yield	opt. purity (ee %)[b]	(day)
1	MY	*tert*-BuOMe	*S*	43.8	23.3	*R*	52.1	17.2	8
2	AY	*tert*-BuOMe	*S*	36.8	25.0	*R*	58.5	15.9	2
3	OF	*tert*-BuOMe	*R*	8.0	40.2	*S*	85.1	11.9	14
4	AK	*tert*-BuOMe	*R*	51.3	54.9	*S*	43.9	87.8	2
5	Wako	*tert*-BuOMe	*R*	trace	83.1[c]	*S*	95.4	2.8	14
6	PS	*tert*-BuOMe	*R*	56.4	62.0	*S*	41.3	98.0	2
7	PS	toluene	*R*	50.8	89.6[c]	*S*	45.1	94.0	1
8	PS	toluene	*R*	49.8	77.1[c]	*S*	44.8	>99	2.2
9	PS	CH_2Cl_2	*R*	47.5	>99	*S*	49.1	96.9	4

a) 100 mg/mmol of **5** was used. b) Optical purity was determined by hplc using a chiral column (**5**: CHIRALCEL OD, *i*-PrOH-hexane 1:9 v/v; **6**: CHIRALCEL OD, *i*-PrOH-hexane 1:99 v/v). c) Optically enriched **6** could be purified (~99% ee) by recrystallization from hexane.

used, lipase PS in dichloromethane produced the optically pure (*R*)-acetate[6] [(*R*)-**6**], mp 75-76 °C, $[\alpha]_D^{30}$ +10.11 (*c* 1.02, $CHCl_3$), in 47.5% (95.0% theoretical) accompanied by the unreacted (*S*)-alcohol [(*S*)-**5**] in 49.1% (98.2% theoretical) with optical purity of 96.9% ee (**Table 1**: entry 9). Optically pure (*S*)-alcohol [(*S*)-**5**], $[\alpha]_D^{30}$ +19.83 (*c* 1.01, $CHCl_3$), could be obtained in 44.8% yield (89.6% theoretical) when the reaction was carried out in toluene (**Table 1**: entry 8) (**Scheme 2**).

Having obtained satisfactory result in acylation reaction with lipase PS, we next examined the deacylation of the racemic acetate [(±)-**6**], obtained quantitatively from (±)-**5**, in a mixture of phosphate buffer and acetone in the presence of the same lipase. The reaction did really take place in an anticipated way though the optically pure alcohol [(*R*)-**5**] and ester [(*S*)-**6**] could not be obtained at the same time under the same conditions. Thus, the reaction in a 9:1 mixture of buffer-acetone furnished the optically pure antipodal acetate [(*S*)-**6**] in 42% (84% theoretical) yield (**Table 2**: entry 1), while the reaction in a 1:9 mixture of buffer-acetone furnished the antipodal alcohol [(*R*)-**5**] in 39.8% (79.6% theoretical) yield with 95% ee (**Table 2**: entry 3) (**Scheme 3**).

In order to demonstrate the synthetic potential of the resolved compounds as chiral synthons, we utilized (*S*)-alcohol [(*S*)-**5**] as a starting material for a β-hydroxy-δ-lactone constituting the essential structural unit associated with the HMG Co-A reductase inhibiting activity of compactin and mevinolin.[7]



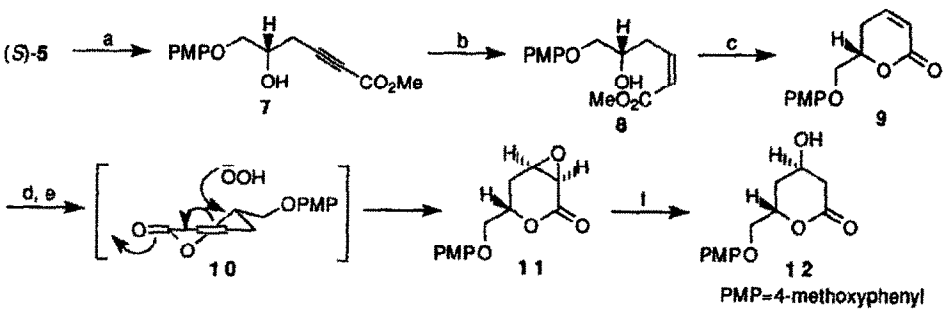
Scheme 3

Table 2. Lipase-mediated Kinetic Deacylation of the Racemic Acetate [(±)-**6**] by Lipase PS in Phosphate Buffer[a]

		alcohol (**5**)			acetate (**6**)			time
entry	buffer[b] : acetone	config.	yield	opt. purity (ee %)[c]	config.	yield	opt. purity (ee %)[c]	(day)
1	9 : 1	*R*	58.0	70.0	*S*	42.0	>99	2
2	1 : 9	*R*	38.8	96.2	*S*	56.5	67.4	3
3	1 : 9	*R*	39.8	95.0	*S*	54.8	82.3[d]	4
4[e]	1 : 9	*R*	53.2	98.1	*R*	23.8	38.8	2

a) 100 mg/mmol of **6** was used. b) 0.1 M Phosphate buffer solution was used. c) Optical purity was determined by hplc using a chiral column (**5**: CHIRALCEL OD, *i*-PrOH-hexane 1:9 v/v; **6**: CHIRALCEL OD, *i*-PrOH-hexane 1:99 v/v). d) Optically enriched **6** could be purified (~99% ee) by recrystallization from hexane. e) Optically enriched **6** (70% ee) was used.

Suspension of (*S*)-**5**, $[\alpha]_D^{29}$ +19.82 (*c* 1.06, $CHCl_3$), palladium(II) chloride (6 mol %), copper(II) chloride (2 equiv.), and sodium acetate (2 equiv.) in methanol was stirred for overnight under the atmosphere of carbon monoxide (1 atm)[8,9] to furnish the methyl ester (**7**), $[\alpha]_D^{29}$ +22.6 (*c* 1.05, $CHCl_3$), in 78% yield. Partial hydrogenation using Lindlar catalyst followed by treating the resulting *cis*-olefin (**8**) with methanolic hydrochloric acid afforded the α,β-unsaturated δ-lactone (**9**), mp 92 °C, $[\alpha]_D^{28}$ −109.0 (*c* 1.19, $CHCl_3$), in 74.4% overall yield. Exposure of **9** to alkaline hydrogen peroxide in methanol[9,10] followed by treating the crude product containing some methanolysis product with pyridinium *p*-toluenesulfonate in hot benzene gave the epoxide (**11**), mp 84-85 °C, $[\alpha]_D^{30}$ +45.5 (*c* 1.05, $CHCl_3$), in 73.1% yield as a single epimer whose stereo-

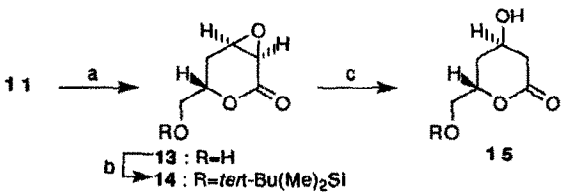


Scheme 4

Reagents and conditions: a) $PdCl_2$ (cat.), $CuCl_2$, NaOAc, CO, MeOH, room temperature, 12 h; b) H_2, Lindlar catalyst, benzene, room temperature, 3 h; c) conc. HCl-MeOH (1:3), 12 h; d) 30% H_2O_2, 6N-NaOH, MeOH, room temperature, 1 h; e) PPTS (cat.), benzene, reflux, 30 min; f) diphenyl diselenide, $NaBH_4$, AcOH (cat.), THF, 0 °C, 10 min.

chemical outcome clearly indicated that the introduction of the hydroperoxide occurred in a stereoelectronically favored way[11] as shown (**10**). On treatment with the complex,[12] generated in the same flask from diphenyl diselenide and sodium borohydride in THF[13] containing catalytic amount of acetic acid, **11** furnished the desired lactone (**12**), mp 87-88 °C, $[\alpha]_D^{30}$ +19.4 (*c* 1.01, $CHCl_3$), in 84.3% yield as a single regio-isomer (**Scheme 4**).

On the other hand, the β-hydroxy-δ-lactone (**15**) having another protecting group could also be prepared from the same epoxide (**11**). Thus, exposure of **11** to 2.2 equiv. of ceric ammonium nitrate (CAN) in aqueous acetonitrile[14] allowed oxidative removal of the *p*-methoxyphenyl protective group to afford the primary alcohol (**13**) which then was transformed into the silyl ether (**14**), $[\alpha]_D^{29}$ +34.8 (*c* 1.18, $CHCl_3$), in 71% overall yield. On the same selenolate mediated reduction in ethanol,[12] **14** gave the TBS-protected compactin lactone (**15**), $[\alpha]_D^{28}$ –1.90 (*c* 1.00, $CHCl_3$), in 72.6% yield as a single regio-isomer (**Scheme 5**).



Scheme 5

Reagents and conditions: a) $Ce(NH_4)_2(NO_3)_6$, MeCN-H_2O (4:1), room temperature, 10 min; b) *tert*-$Bu(Me)_2SiCl$, imidazole, 4-dimethylaminopyridine, DMF, room temperature, 12 h; c) diphenyl diselenide, $NaBH_4$, AcOH (cat.), EtOH, room temperature, 10 min.

References and Notes

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