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Enantiocomplementary Synthesis of Functionalized Cycloalkenol Building Blocks Using Lipase

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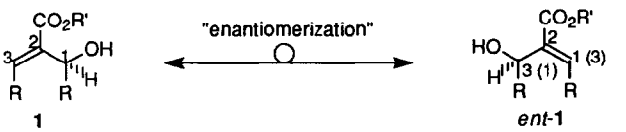
Abstract: Racemic 2-carbethoxy-2-cyclopenten-1-ol [(±)-**3a**] and racemic 2-carbethoxy-2-cyclohexen-1-ol [(±)-**3b**] afforded the corresponding (*R*)-acetates [(*R*)-**4a** and (*R*)-**4b**] leaving the corresponding (*S*)-alcohols [(*S*)-**3a** and (*S*)-**3b**] unchanged upon treatment with vinyl acetate in *tert*-butyl methyl ether in the presence of lipase PS, respectively, while the racemic acetates [(±)-**4a** and (±)-**4b**], derived from racemic precursors, (±)-**3a** and (±)-**3b**, on suspension with lipase in a phosphate buffer solution afforded the corresponding (*R*)-alcohols [(*R*)-**3a** and (*R*)-**3b**] leaving the corresponding (*S*)-acetates [(*S*)-**4a** and (*S*)-**4b**] unchanged, respectively.

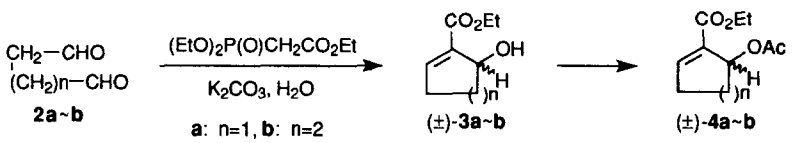
Owing to their chirality at allylic carbon center and functionality of ester group on the olefinic bond in the latent symmetric structure,[1] chiral unsaturated carbinols having the structural unit represented by **1** have a considerable synthetic potentiality as versatile chiral building blocks (**Scheme 1**). We report here an enantiocomplementary synthesis of two cyclic examples having this particular functional system employing lipase-mediated kinetic resolution.



1 *ent*-**1**

Scheme 1

The required substrates were prepared readily by following the reported method.[2] Thus, 2-carbethoxy-2-cyclopenten-1-ol [(±)-**3a**] was prepared from succinaldehyde and triethyl phosphonoacetate in aqueous potassium carbonate. Quite similarly, 2-carbethoxy-2-cyclohexen-1-ol [(±)-**3b**] was obtained from aqueous glutaraldehyde under the same conditions. Both compounds were treated with acetic anhydride in the presence of pyridine to give the corresponding racemic acetates [(±)-**4a** and (±)-**4b**], respectively (**Scheme 2**).



2a~b **a**: n=1, **b**: n=2 (±)-**3a~b** (±)-**4a~b**

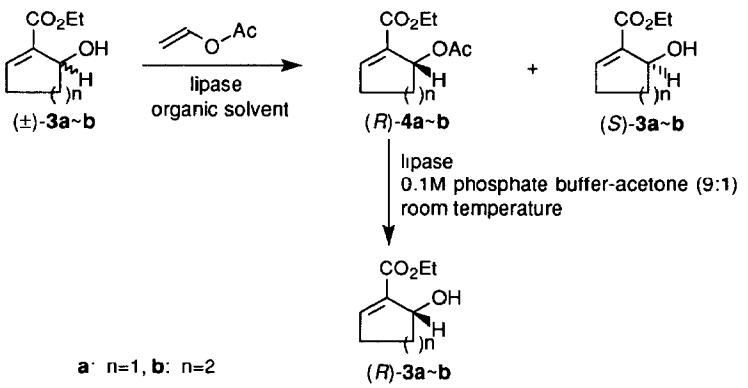
Scheme 2

The cyclopentenol [(±)-**3a**] was first treated with two equivalents of vinyl acetate in the presence of each of six lipases in each of three organic solvents at room temperature for 3 days.[1,3] Among lipases and the solvents used, a combination of lipase PS and *tert*-butyl methyl ether brought about an excellent enantiospecific esterification as shown in **Table 1a**. For a preparative purpose lipase PS [10 mg/mmol of (±)-**3a**] was used in

tert-butyl methyl ether [5~10 ml/mmol of (±)-**3a**] at 28~30 °C which gave rise to the (*R*)-acetate[4] [(*R*)-**4a**], $[\alpha]_D^{29}$ +2.6 (*c* 1.03, $CHCl_3$), in an excellent yield accompanied by the unchanged (*S*)-alcohol[4] [(*S*)-**3a**], $[\alpha]_D^{31}$ –34.5 (*c* 1.10, $CHCl_3$), in 48% yield, both in 100% ee[5] after 4 days.

On the other hand, the reaction of the cyclohexenol [(±)-3b] did not proceed in a clear-cut diastereoselective manner and failed to give both of the acetate and the alcohol in optically pure forms in a single operation in *tert*-butyl methyl ether. However, the (*R*)-acetate[6,7] [(*R*)-**4b**], $[\alpha]_D^{29}$ +132.1 (*c* 1.09, $CHCl_3$) (99% ee), and the (*S*)-alcohol[6,7] [(*S*)-**3b**], $[\alpha]_D^{31}$ –52.9 (*c* 1.60, $CHCl_3$) (95% ee), having high optical purity could be obtained in satisfactory yields in a single operation carrying out the reaction in vinyl acetate (**Table 1b**).

Chemical deacetylation of (*R*)-**4a** was found to be unexpectedly difficult. On conventional base or acid catalyzed alcoholysis (*R*)-**4a** gave a mixture of a minor amount of the alcohol (**3a**) and a major amount of an alkoxy olefin both in partially racemized forms the latter of which presumably was generated by solvolytic



Scheme 3

Table 1a: Lipase mediated acylation of racemic 2-carbethoxy-2-cyclopenten-1-ol [(±)-**3a**]

				(*R*)-**4a**		(*S*)-**3a**	
Entry	lipase[a)]	solvent	time (day)	yield (%)	e.e. (%)[d)]	yield (%)	e.e. (%)[d)]
1	PS[b)]	CH_2Cl_2	3	41.4	100	53.6	75.7
2	PS[b)]	benzene	3	49.5	95.8	45.2	100
3	PS[b)]	*tert*-BuOMe	3	53.6	86.7	44.7	100
4	PS[c)]	*tert*-BuOMe	4	49.9	100	48.2	100
5	OF[b)]	*tert*-BuOMe	3	10.8	77.7	85.7	9.9
6	AY[b)]	*tert*-BuOMe	3	4.5	98.5	90.7	11.3
7	AK[b)]	*tert*-BuOMe	3	51.5	95.9	44.3	100
8	MY[b)]	*tert*-BuOMe	3	3.8	88.3	88.7	6.2
9	PPL[b)]	*tert*-BuOMe	3	46.7	99.7	49.2	99.0

a) PS (*Pseudomonas sp.*, Amano); OF (*Candida cylindracea*, Meito); AY (*Candida rugosa*, Amano); AK (*Pseudomonas sp.*, Amamo); MY (*Candida cylindracea*, Meito); PPL (*Porcine Pancreas*, Wako): b) 100 mg/mmol of substrate: c) 10 mg/mmol of substrate: d) Determined by hplc using a chiral column, see, Ref. 5.

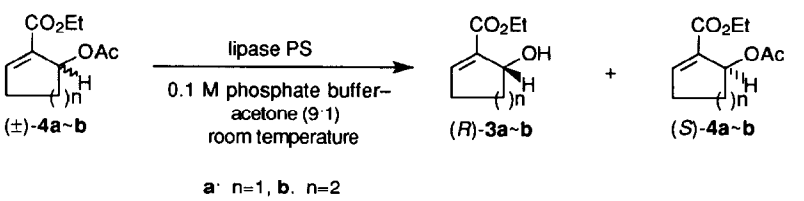
Table 1b: Lipase mediated acylation of racemic 2-carbethoxy-2-cyclohexen-1-ol [(±)-**3b**]

				(*R*)-**4b**		(*S*)-**3b**	
Entry	lipase	solvent	time (day)	yield (%)	e.e. (%)	yield (%)	e.e. (%)
1	PS[a)]	*tert*-BuOMe	11	21.9	100	64.8	35.4
2	PS[b)]	*tert*-BuOMe	2	48.0	90.8	46.0	94.7
3	PS[b)]	vinyl acetate	7	40.0	98.8	53.2	94.6

a) 10 mg/mmol of substrate: b) 100 mg/mmol of substrate: c) Determined by hplc using a chiral column, see, Ref. 7.

addition-elimination sequence. Although the optically pure (*R*)-**3a** could eventually be obtained in a satisfactory yield by careful hydrolysis of (*R*)-**4a** with diluted aqueous potassium carbonate, it could be obtained much more cleanly and in a much simpler way using lipase in a phosphate buffer-acetone solution.[8] Lipase PS was again superior to other lipases and hydrolyzed the (*R*)-acetate [(*R*)-**4a**] into the (*R*)-alcohol [(*R*)-**3a**], $[\alpha]_D^{31}$ +34.4 (*c* 1.04, $CHCl_3$), in 92% yield without causing any racemization in a phosphate buffer-acetone solution [9:1 v/v, 5 ml/mmol of (*R*)-**4a**] after 12 h at room temperature. Similarly, the homologous (*R*)-**4b** afforded the (*R*)-alcohol [(*R*)-**3b**], $[\alpha]_D^{27}$+57.9 (*c* 0.99, $CHCl_3$), in 92.5% yield without causing racemization under the same conditions though it took much longer reaction time (~100 h) (**Scheme 3**).

We next examined the lipase mediated hydrolysis of the racemic acetates [(±)-**4a** and **b**] in a phosphate buffer-acetone solution (9:1 v/v). Lipase PS again showed an excellent selectivity in which the (*R*)-alcohols [(*R*)-**3a** and **b**] were generated selectively remaining the (*S*)-acetates [(*S*)-**4a** and **b**] unchanged. Thus, (±)-**4a** in a solution of 0.1 M phosphate buffer and acetone [9:1 v/v, 5 ml/mmol of (±)-**4**] suspending lipase PS



Scheme 4

Table 2a: Lipase mediated hydrolysis of racemic 3-acetoxy-2-carbethoxycyclopentene [(±)-**4a**]

			(*R*)-**3a**		(*R*)-**4a**	
Entry	lipase	time (day)	yield (%)	e.e. (%)[d)]	yield (%)	e.e. (%)[d)]
1	PS[a)]	0.4	46.8	100	46.2	83.3
2	PS[b)]	0.5	38.8	100	49.9	79.2
3	PS[b)]	1	42.4	100	46.1	93.4
4	PS[c)]	1	43.6	99	44.8	100
5	PPL[c)]	1	28.8	74.9	18.6	73.4
6	PLE[c)]	0.4	27.2	93.3	60.6	41.3

a) 200 mg/mmol of substrate: b) 20 mg/mmol of substrate: c) 100 mg/mmol of substrate: d) Determined by hplc using a chiral column, see Ref. 5.

Table 2b: Lipase mediated hydrolysis of racemic 1-acetoxy-2-carbethoxy-2-cyclohexen-1-ol [(±)-**4b**]

			(*R*)-**3b**		(*S*)-**4b**	
entry	lipase	time (day)	yield (%)	e.e. (%)[c]	yield (%)	e.e. (%)[c]
1	PS[a]	0.5	22.9	100	71.0	32.4
2	PS[b]	1	30.1	100	68.1	48.6
3	PS[a]	2	40.8	100	54.0	78.8
4	PS[a]	3	42.6	100	52.0	91.1
5	PLE[b]	0.3	26.0	60.3	49.3	36.7
6	PPL[b]	10	10.5	~1	77.7	~0

a) 200 mg/mmol of substrate: b) 100 mg/mmol of substrate: c) Determined by hplc using a chiral column, see Ref. 7.

afforded both (*R*)-**3a**, $[\alpha]_D^{30}$ +34.2 (*c* 0.85, $CHCl_3$), and (*S*)-**4a**, $[\alpha]_D^{29}$ –2.6 (*c* 1.08, $CHCl_3$), in excellent yields and in optically pure states after 24 h at ambient temperature (**Scheme 4**; **Table 2a**). The same treatment of (±)-**4b** gave the optically pure (*R*)-**3b**, $[\alpha]_D^{28}$ +57.6 (*c* 0.59, $CHCl_3$) (100% ee), and the optically enriched (*S*)-**4b**, $[\alpha]_D^{30}$ –125.7 (*c* 1.24, $CHCl_3$) (91% ee), in excellent yields after 3 days at ambient temperature (**Scheme 4**; **Table 2b**).

In conclusion it is in particular noteworthy that the enantiomeric alcohols (**3a** and **b**) and the acetates (**4a** and **b**) can be obtained in optically pure or highly optically enriched forms by the lipase-mediated acylation and deacylation approaches shown which may be utilized complementarily depending on the chirality of target molecules. The present synthesis, therefore, may be termed enantiocomplementary.

References and Notes

1. Some examples intending to utilize the functionality of an allylic system having latent symmetry, see: Takano, S.; Inomata, K.; Takahashi, M.; Ogasawara, K. *Synlett* **1991**, 636 and references cited therein.
2. Graff, M.; AlDilaimi, A.; Seguineau, P.; Rambaud, M.; Villieras, J. *Tetrahedron Lett.* **1986**, *27*, 1577; Villieras, J.; Rambaud, M.; Graff, M. *Synth. Commun.* **1986**, *16*, 149; Amri, H.; Rambaud, M.; Villieras, J. *Tetrahedron* **1990**, *46*, 3535.
3. cf. Klibanov, A. M. *Acc. Chem. Res.* **1990**, *23*, 114.
4. Absolute configuration has been determined unambiguously by conversion into the known vitamin D_3 intermediate, see: Takano, S.; Yamane, T.; Takahashi, M.; Ogasawara, K. *Synlett* **1992**, 410.
5. Optical purities were determined by hplc using a column packed with CHIRALCEL OD for both **3a** and **4b** (10% v/v *i*-PrOH-hexane).
6. Absolute configuration has not been determined rigorously yet. However, the observed enzymatic and chromatographic behaviors correspond well to those of the five-membered analogue. Furthermore, the prediction by the empirical rule based on ^{1}H-nmr (500 MHz) spectroscopy of the MTPA esters (*R*- and *S*-) supported its stereochemistry as shown: cf. Takano, S.; Takahashi, M.; Yanase, M.; Sekiguchi, Y.; Iwabuchi, Y.; Ogasawara, K. *Chemistry Lett.* **1988**, 1827 and Kusumi, T.; Otani, I.; Inouye, Y.; Kakisawa, H. *Tetrahedron Lett.* **1988**, *29*, 4731.
7. Optical purity was determined by hplc using a chiral column: CHIRALCEL OD (1% v/v *i*-PrOH-hexane) for **4b** and CHIRALCEL OB (1% v/v *i*-PrOH-hexane) for **3b**.
8. cf. Itoh, T.; Ohta, T. *Chemistry Lett.* **1991**, 217.