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Lipase-catalyzed kinetic resolution of Baylis–Hillman products

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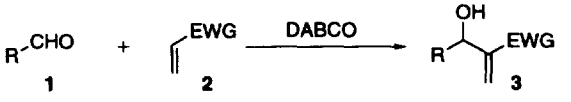
Abstract

Lipase-catalyzed kinetic resolution of the various Baylis–Hillman products, α-methylene-β-hydroxy compounds, were examined. When lipase PS was used as a biocatalyst in acetonitrile, transesterification of racemic ethyl 3-hydroxy-2-methylenebutanoate or 3-hydroxy-2-methylenepentanoate proceeded in a practical enantiomeric excess. The resolution by hydrolysis of the acetate derivatives was also tried. In contrast, in case of racemic ethyl 3-acetoxy-2-methylenepentanoate, under the conditions using lipase AK, the E value of the resolution was >321.

1. Introduction

Since, in 1972, Baylis and Hillman reported that α-methylene-β-hydroxy compounds **3** were readily prepared from aldehydes **1** and alkenes **2** with the electron withdrawing groups (Eq. 1),[1] much effort to obtain optically active Baylis–Hillman products has been made.[2] Of them, a kinetic resolution is one of the most useful and convenient methods.[3] In this paper, we describe the enzymatic kinetic resolution of the racemic Baylis–Hillman products with various side chains (R shown in Eq. 1) by the use of lipases from the point of both transesterification of the hydroxy forms and hydrolysis of the acetate derivatives.



(1)

EWG = electron withdrawing group

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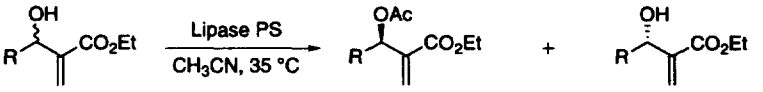
Table 1
Optical resolution of Baylis–Hillman products by transesterification[4]



(±)-4 (R)-5 (S)-4

entry	R	time (day)	acylating reagent	acetate yield (%)	acetate ee (%)	alcohol yield (%)	alcohol ee (%)	E value
1	Me [(±)-4a]	6	isopropenyl acetate	43 [(R)-5a[4]]	97	42 [(S)-4a]	> 99	> 349
2	Et [(±)-4b]	7	isopropenyl acetate	34 [(R)-5b]	90	53 [(S)-4b]	44	29
3	Et [(±)-4b]	7	vinyl aetate	37 [(R)-5b]	> 99	50 [(S)-4b]	70	> 424
4	Et [(±)-4b]	7	vinyl trifluoroacetate	—[a]	—	62 [(S)-4b]	13	—
5	n-C_5H_{11} [(±)-4c]	12 h	isopropenyl acetate	no reaction				
6	CCl_3 [(±)-4d]	3	vinyl aetate	no reaction				

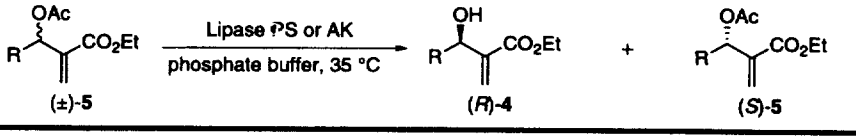
[a]The trifloroacetate could not be isolated, because of the lability.

2. Results and discussion

The results of the resolution by transesterification are shown in Table 1. First, isopropenyl acetate was used as an acylating reagent. The molecular recognition of lipase PS (*Pseudomonas* sp.) for the substrates of these reactions was extremely high. When the side chain was a methyl group (±)-**4a**,[1a] it is especially worthy to note that the enantiomeric purity of the recovered alcohol was also very high (entry 1).[5] However, alcohol (±)-**4b**[6] (R=Et) did not afford a satisfactory result (entry 2). Enantiomeric excess (ee) was determined by the ratio of the peak areas obtained by separation using a gas chromatograph equipped with a chiral column.[7] Next, in the case of using vinyl acetate as the acylating reagent, the enantiomeric purities of both acetate (*R*)-**5b** and the recovered (*S*)-**4b** were increased, and the E value[8] resulted in >424 (entry 3). In order to increase the reaction rate, vinyl trifluoroacetate, which is a more reactive acylating reagent, was used (entry 4). However, the reaction rate unexpectedly decreased to give the recovery of alcohol (*S*)-**4b** in 62% yield (13% ee). Due to the lability of the corresponding acetate, the reaction resulted in the formation of the complex mixture. Therefore, the trifluoroacetate could not be isolated. Transesterification of (±)-**4c**, which possesses the longer side chain (R=C_5H_{11}), did not proceed at all (entry 5). In the case of the compound (±)-**4d**[9] with halogen atoms in the side chain, the reaction did not proceed in the least (entry 6). As described earlier, transesterification of Baylis–Hillman products by lipase PS was a practical method for the compound whose side chain was a methyl or ethyl group.

In addition, the enzymatic kinetic resolution of the acetate derivatives was carried out. Some acetate derivatives were prepared from the corresponding alcohols. The results are shown in Table 2. Independent of the side chains' length, the chemical yields of hydrolysis were low, and the reaction rate was very slow on the whole. Although the combination of (±)-**5b** and lipase PS revealed a faster reaction rate, the enantiomeric excess was low (entry 1). When lipase AK was used for hydrolysis of (±)-**5b**, in spite of only a 17% yield of alcohol (*R*)-**4b**, the enantiomeric excess was >99%. Suprisingly, the E value was >321 (entry 2). The substrate (±)-**5e** with a longer side chain did not afford satisfactory results (entries 3,

Table 2
Optical resolution of Baylis–Hillman products by hydrolysis



(±)-5 (*R*)-4 (*S*)-5

entry	R	Lipase[a]	time (day)	alcohol		acetate		E value
				yield (%)	ee (%)	yield (%)	ee (%)	
1	Et [(±)-5b]	PS	5	20 [(*R*)-4b]	75	49 [(*S*)-5c]	12	8
2	Et [(±)-5b]	AK	13	17 [(*R*)-4b]	> 99	33 [(*S*)-5c]	46	> 321
3	n-C_7H_{15} [(±)-5e]	PS	11	17 [(*R*)-4e]	85	61 [(*S*)-5e]	27	16
4	n-C_7H_{15} [(±)-5e]	AK	14	14 [(*R*)-4e]	92	76 [(*S*)-5e]	1	26
5	n-C_7H_{15} [(±)-5e]	AK[a]	11	20 [(*R*)-4e]	93	58 [(*S*)-5e]	41	41

[a]Lipase AK was used three times as much as that of lipase in entry 4.

4, and 5). When the quantity of the biocatalyst was increased, the reaction rate was naturally accelerated (entries 4 and 5).

In conclusion, we succeeded in the preparation of the optically active Baylis–Hillman products **3** with exceedingly high enantiomeric excess by means of enzymatic kinetic resolution. When lipase PS was used in acetonitrile, transesterification of racemic ethyl 3-hydroxy-2-methylenebutanoate (±)-**4a** and ethyl 3-hydroxy-2-methylenepentanoate (±)-**4b** proceeded with high E values in good chemical yield and enantiomeric excess. However, hydrolysis of the acetate derivative, ethyl 3-acetoxy-2-methylenepentanoate (±)-**5b** with lipase AK, gave enantiomerically pure alcohol (*R*)-**4b** with the E value >321. It is expected that these compounds will be applied to syntheses of natural products as chiral building blooks.

3. Experimental

Solvents and reagents were dried and distilled before use. Normal reagent-grade solvents were used for flash chromatography. Lipases PS and AK were supplied by Amano Pharmaceutical Co., Ltd.

All reactions were monitored by thin-layer chromatography with silica gel (SiO_2) plates (Merk, silica gel 60 F254 1.05715). Gas chromatography (GC) was run on a GC-380 GL Sciences. A chiral column (Chirasil-DEX CB, 0.25 mm×25 m) was used for GC.

The NMR spectra were recorded on Varian model Gemini-200 spectrometers in chloroform-d_1 ($CDCl_3$). Chemical shifts (δ) are reported with chloroform (δ=7.26 ppm) as an internal standard. Splitting patterns are designated as 's, d, t, q, and m'; these symbols indicate 'singlet, doublet, triplet, quartet, and multiplet', respectively. Infrared (IR) spectra were obtained on a JASCO model FT/IR-5000 in the neat state. Optical rotations were recorded on HORIBA model SEPA-300 using $CHCl_3$ as a solvent. Elemental analyses were run with Yanaco model MT-3.

3.1. Transesterification of ethyl 3-hydroxy-2-methylenebutanoate (±)-4a

To a solution of (±)-**4a** (2.00 g, 13.9 mmol) in acetonitrile (30 ml) were added isopropenyl acetate (4.17 g, 41.6 mmol) and lipase PS (3.00 g). After stirring at 35°C for 6 days, Celite was added. The reaction mixture was filtered through a glass filter. The filtrate was washed with satd aq. sodium hydrogen carbonate ($NaHCO_3$), dried over anhydrous magnesium sulfate ($MgSO_4$,) and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 15:1–5:1) to give acetate (*R*)-**5a** (1.12 g, 43%) and alcohol (*S*)-**4a** (0.853 g, 42%). (*R*)-**5a**; $[\alpha]_D^{21}$ +20.1 (c 3.44, $CHCl_3$). (*S*)-**4a**; R_f=0.15 (SiO_2, hexane:EtOAc, 4:1); $[\alpha]_D^{21}$ −18.2 (c 7.19, $CHCl_3$).

3.2. Transesterification of ethyl 3-hydroxy-2-methylenepentanoate (±)-4b with isopropenyl acetate

To a solution of (±)-**4b** (0.202 g, 1.28 mmol) in acetonitrile (30 ml) were added isopropenyl acetate (0.640 g, 6.39 mmol) and lipase PS (1.50 g). After stirring at 35°C for 7 days, Celite was added. The reaction mixture was filtered through a glass filter. The filtrate was washed with satd aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 15:1–5:1) to give acetate (*R*)-**5b** (0.088 g, 34%) and alcohol (*S*)-**4b** (0.107 g, 53%). (*R*)-**5b**; R_f=0.40 (SiO_2, hexane:EtOAc, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$), 6.29 (1H, s), 5.74 (1H, d, *J*=1.3 Hz), 5.56 (1H, m), 4.22 (2H, q, *J*=7.2 Hz), 2.08 (3H, s), 1.60–1.90 (2H, m), 1.30 (3H, t, *J*=6.3 Hz), 0.89 (3H, t, *J*=7.2 Hz); IR (neat), 2976, 1744, and 1632 cm^{-1}; $[\alpha]_D^{21}$ +11.5 (c 1.91, $CHCl_3$). Anal. calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C, 60.05; H, 8.02. (*S*)-**4b**; $[\alpha]_D^{21}$ −6.14 (c 2.93, $CHCl_3$).

3.3. Transesterification of ethyl 3-hydroxy-2-methylenepentanoate (±)-4b with vinyl acetate

To a solution of (±)-**4b** (0.204 g, 1.29 mmol) in acetonitrile (30 ml) were added vinyl acetate (0.562 g, 6.53 mmol) and lipase PS (1.50 g). After stirring at 35°C for 7 days, Celite was added. The reaction mixture was filtered through a glass filter. The filtrate was washed with satd aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 15:1–5:1) to give acetate (*R*)-**5b** (0.095 g, 37%) and alcohol (*S*)-**4b** (0.102 g, 50%). (*R*)-**5b**; $[\alpha]_D^{21}$ +10.1 (c 2.96, $CHCl_3$). (*S*)-**4b**; $[\alpha]_D^{28}$ −12.4 (c 1.93, $CHCl_3$).

3.4. Ethyl 3-acetoxy-2-methylenepentanoate (±)-5b

The mixture of (±)-**4b** (0.568 g, 3.59 mmol) and acetic anhydride (5 ml) was heated at reflux for 2.5 h, cooled, and diluted with ethyl acetate. The ethyl acetate solution was washed with satd aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 20:1) to give acetate (±)-**5b** (0.464 g, 65%).

3.5. Ethyl 3-acetoxy-2-methylenedecanoate (±)-5e

The mixture of ethyl 3-hydroxy-2-methylenedecanoate (0.390 g, 1.71 mmol) and acetic anhydride (5 ml) was heated at reflux for 3 h, cooled, and diluted with ethyl acetate. The ethyl acetate solution was washed with satd aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 30:1) to give acetate (±)-**5e** (0.437 g, 71%). (±)-**5e**; R_f=0.45 (SiO_2, hexane:EtOAc, 4:1); ^{1}H NMR (200 MHz, $CDCl_3$), 6.26 (1H, s), 5.72 (1H, d, *J*=1.0 Hz), 5.60 (1H, m), 4.21 (2H, q, *J*=7.2 Hz), 2.07 (3H, s), 1.20–1.30 (15H, m), 0.80–0.90 (3H, m); IR (neat),

2932, 1750, 1721 and 1634 cm^{-1}. Anal. calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.28; H, 10.04.

3.6. Hydrolysis of ethyl 3-acetoxy-2-methylenepentanoate (±)-5b by lipase PS

To a solution of (±)-**5b** (0.151 g, 0.754 mmol) in 0.1 M phosphate buffer (7.5 ml) was added lipase PS (0.075 g). After stirring at 35°C for 5 days, Celite was added. The reaction mixture was filtered through a glass filter, and satd aq. $NaHCO_3$ was added to the filtrate. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 15:1) to give acetate (*R*)-**4b** (0.074 g, 49%) and alcohol (*S*)-**5c** (0.023 g, 20%). (*R*)-**4b**; $[\alpha]_D^{24}$ −5.54 (c 2.80, $CHCl_3$). (*S*)-**5c**; $[\alpha]_D^{24}$ +10.5 (c 1.05, $CHCl_3$).

3.7. Hydrolysis of ethyl 3-acetoxy-2-methylenepentanoate (±)-5b by lipase AK

To a solution of (±)-**5b** (0.151 g, 0.754 mmol) in 0.1 M phosphate buffer (7.5 ml) was added lipase AK (0.075 g). After stirring at 35°C for 13 days, Celite was added. The reaction mixture was filtered through a glass filter and satd aq. $NaHCO_3$ was added to the filtrate. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 15:1) to give acetate (*R*)-**4b** (0.050 g, 33%) and alcohol (*S*)-**5c** (0.021 g, 17%). (*R*)-**4b**; $[\alpha]_D^{23}$ −23 (c 0.30, $CHCl_3$). (*S*)-**5c**; $[\alpha]_D^{23}$ +18 (c 0.50, $CHCl_3$).

3.8. Hydrolysis of ethyl 3-acetoxy-2-methylenedecanoate (±)-5e by lipase PS

To a solution of (±)-**5e** (0.149 g, 0.615 mmol) in 0.1 M phosphate buffer (7.5 ml) was added lipase PS (0.075 g). After stirring at 35°C for 11 days, Celite was added. The reaction mixture was filtered through a glass filter and satd aq. $NaHCO_3$ was added to the filtrate. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 15:1) to give acetate (*R*)-**4e** (0.091 g, 61%) and alcohol (*S*)-**5e** (0.024 g, 17%). (*R*)-**4e**; $[\alpha]_D^{30}$ −1.60 (c 1.88, $CHCl_3$). (*S*)-**5e**; $[\alpha]_D^{28}$ +3.51 (c 1.14, $CHCl_3$).

3.9. Hydrolysis of ethyl 3-acetoxy-2-methylenedecanoate (±)-5e by lipase AK

To a solution of (±)-**5e** (0.249 g, 0.914 mmol) in 0.1 M phosphate buffer (12.5 ml) was added lipase AK (0.125 g). After stirring at 35°C for 14 days, Celite was added. The reaction mixture was filtered through a glass filter and satd aq. $NaHCO_3$ was added to the filtrate. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 30:1–2:1) to give acetate (*R*)-**4e** (0.190 g, 76%) and alcohol (*S*)-**5e** (0.030 g, 14%). (*R*)-**4e**; $[\alpha]_D^{25}$ −2.99 (c 1.88, $CHCl_3$). (*S*)-**5e**; $[\alpha]_D^{30}$ +17 (c 0.77, $CHCl_3$).

3.10. Hydrolysis of ethyl 3-acetoxy-2-methylenedecanoate (±)-5e by lipase AK

To a solution of (±)-**5e** (0.149 g, 0.615 mmol) in 0.1 M phosphate buffer (7.5 ml) was added lipase AK (0.225 g). After stirring at 35°C for 11 days, Celite was added. The reaction mixture was filtered through a glass filter and satd aq. $NaHCO_3$ was added to the filtrate. The mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, hexane:EtOAc, 30:1–2:1) to give acetate (*R*)-**4e** (0.087 g, 58%) and alcohol (*S*)-**5e** (0.028 g, 20%). (*R*)-**4e**; $[\alpha]_D^{29}$ −6.79 (c 1.62, $CHCl_3$). (*S*)-**5e**; $[\alpha]_D^{28}$ +2.71 (c 1.29, $CHCl_3$).

3.11. Hydrolysis of ethyl 3-acetoxy-2-methylenepentanoate (R)-5b

To a solution of (*R*)-**5b** (0.022 g, 0.11 mmol) in acetone (1 ml) was added aq. 19% HCl (1 ml). After stirring at 25°C for 2 days, satd aq. $NaHCO_3$ was added. The mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and concentrated in vacuo to give alcohol (0.012 g, 73%).

3.12. Hydrolysis of ethyl 3-acetoxy-2-methylenedecanoate (S)-5e

To a solution of (*S*)-**5e** (0.070 g, 0.26 mmol) in acetone (3 ml) was added aq. 19% HCl (1 ml). After stirring at 25°C for 3 days, satd aq. $NaHCO_3$ was added. The mixture was extracted with ethyl acetate. The extract was dried over $MgSO_4$ and concentrated in vacuo to give alcohol (0.065 g, 93%).

Acknowledgements

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7. The enantiomers of the alcohols were perfectly separated on the chiral column. On the other hand, those of acetates did not separate at all, except for **4a**. Accordingly, the enantiomeric purities of the inseparable acetates were determined after hydrolyzing to the corresponding alcohols with aq. 19% HCl in acetone.
8. E value was calculated from $E=\ln[(1-c)(1-ee_s)]/\ln[(1-c)(1+ee_s)]$ where $c=ee_s/(ee_s+ee_p)$. The ee_s and ee_p represent the enantiomeric excesses of substrate and product, respectively. See Chen, C. S.; Fujimoto, K.; Girdaukas, K.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294.
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