Lipase-catalyzed Transesterification of Methyl 2-Substituted 3-Hydroxy-4-pentenoates and its Synthetic Application to the Taxol Side Chain

Tadakatsu Mandai,* Tetsuta Oshitari, Masafumi Susowake

Department of Chemistry and Bioscience, Kurashiki University of Science and the Arts, 2640 Nishinoura, Tsurajima, Kurashiki 712-8505, Japan
Fax +81(86)4401062; E-mail: ted@chem.kusa.ac.jp

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Abstract: *Syn*-and *anti*-methyl 2-substituted 3-hydroxy-4-pentenoates were efficiently resolved in lipase-catalyzed transesterification. This protocol was successfully applied to the synthesis of the taxol side chain.

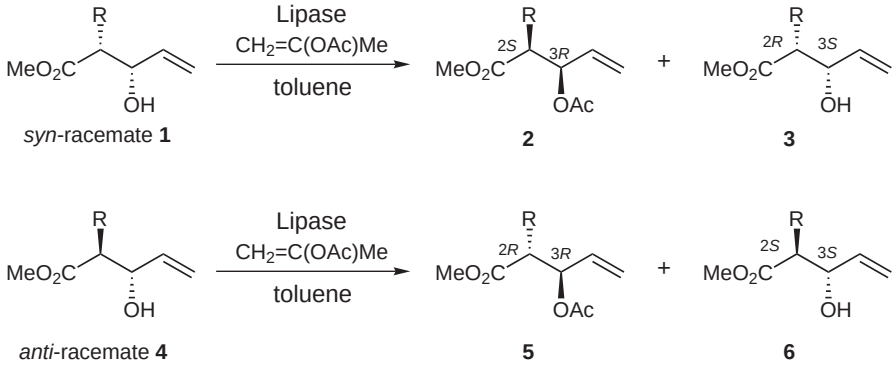
Key words: *syn*- and *anti*-methyl 2-substituted 3-hydroxy-4-pentenoates, lipase-catalyzed kinetic resolution, 1,2-amino alcohols, the taxol side chain

Acyclic 1,2-amino alcohols are not only important constituents of natural products such as sphingosine,[1] statine,[2] and phenylisoserine[3] as the taxol side chain, but also significant chiral auxiliaries for diverse asymmetric syntheses.[4] Among a number of synthetic methods for acyclic 1,2-amino alcohols reported hitherto, the sequence of Evans' asymmetric aldol reaction/the release of a 2-substituted 3-hydroxycarboxylic acid/Curtius rearrangement[5] has been well recognized as a useful method owing to the reliability of stereochemistry throughout the process. For these reasons we wanted to devise a more straightforward access to both *syn*- and *anti*-2-substituted 3-hydroxy esters with high optical purities that takes the place of Evans' asymmetric aldol reaction.[6]

To this end, we envisioned to utilize lipase-catalyzed transesterification[7] of 2-substituted 3-hydroxy esters. A very few related studies were reported so far on lipase-catalyzed transesterifications of 3-hydroxy esters such as *cis*-1-ethoxycarbonyl-2-hydroxycyclohexane,[8] *tert*-butyl 3-hydroxy-4-pentenoate,[9] 4-aryloxy-3-hydroxy esters,[10] and *syn*- and *anti*-2-substituted 3-hydroxy esters[11] whose substituents at the C-2 position were severely limited to Ph-, MeS-, and PhS- groups. To the best of our knowledge, there has not been reported to date a general and efficient lipase-catalyzed transesterification for acyclic 2-substituted 3-hydroxy esters.[12]

In this context, we designed *syn*- and *anti*- methyl 2-substituted 3-hydroxy-4-pentenoates **1**[13] and **4**[13] as enzymatically acceptable substrates of high synthetic flexibility, disclosing that (3*R*)-alcohols[14] for both isomers were acetylated with exceedingly high enantioselectivities in lipase-catalyzed transesterification as shown in Scheme 1.

The reaction with *syn*-racemates **1** was executed as follows. Stirring a solution of **1** (7~38 mmol) and 2-propenyl acetate (3 equiv) in toluene (1.5 mL per mmol of **1**) with Chirazyme® (*Candida antarctica*, fraction B, 0.5 g per g of **1**)[15] at room temperature ~70 °C for 40~72 hours resulted in the clean acetylation of one enantiomer to give (2*S*,3*R*)-acetates **2**.[16] The unsolved lipase was filtered off and the filtrate was concentrated and purified by column chromatography (SiO_2). Gratifyingly, both the enantioselectivity and the chemical yield of the unreacted (2*R*,3*S*)-alcohols **3**[16] were also found to be excellent. Similarly, the reaction with *anti*-racemates **4** proceeded quite efficiently under the same reaction conditions to afford both (2*R*,3*R*)-



Scheme 1

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acetates **5**[16] and the unreacted (2*S*,3*S*)-alcohols **6**[16] in a highly enantioselective manner, the results being summarized in Tables 1 and Table 2.

To determine the absolute configuration of alcohols **6**, **6a** (>99% ee, 4.76 mmol) was transformed into alcohol **9**, an aggregation pheromone of the smaller European elm bark beetle (*Scolytus multistriatus*),[18] as depicted in Scheme 2. Hydrogenation of the terminal olefin (HN=NH/MeOH,[19] 96%) provided saturated alcohol **7**. Protection of the hydroxyl group (CH_2=CHOEt, 93%) followed by reduction of the methyl ester ($LiAlH_4$, 98%) gave rise to alcohol **8**. Tosylation of **8** (*p*-TsCl, 91%), reduction ($LiAlH_4$, 92%) and deprotection (3 M HCl, 82%) afforded **9** {$[\alpha]_D^{24}$ –22.7 (*c* 1.00, hexane), Lit.[20] $[\alpha]_D^{19}$ –21.4 (c 1.02, hexane)} in 60% overall yield.

To demonstrate the synthetic utility of our method, we executed the synthesis of the taxol side chain. *Anti*-aldol isomer **10**[21] (1.26 g, 5.2 mmol) was subjected to the transesterification [Chirazyme® (0.6 g), 2-propenyl acetate (1.72 mL, 15.6 mmol), toluene (7.8 mL)], providing acetate **11** (44%, 98.5%ee) and unreacted alcohol **12** (49%, >99%ee) (Scheme 3).

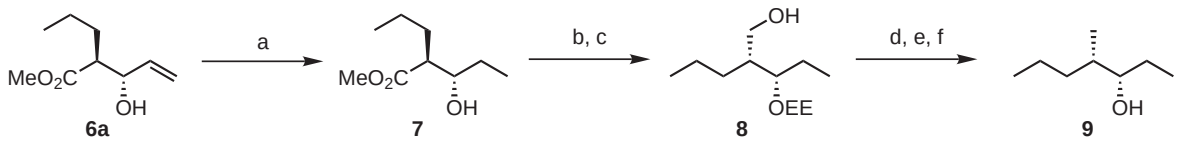
Compound **12** thus obtained was transformed into cyclic carbamate **13** in 80% yield via Curtius rearrangement of the free acid released by palladium-catalyzed hydrogenolysis[22] of the allyl ester. Protection of the nitrogen with $(Boc)_2O$ and oxidative cleavage (RuO_2/$NaIO_4$)[23] of the double bond furnished carboxylic acid **14** in 88% yield. Ring opening (2 M NaOH/MeOH, r.t., 2 h), deprotection of the Boc group, and ensuing benzoylation provided *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**15**) in 71%

Table 1 Lipase-catalyzed Kinetic Resolution of *syn*-Racemate **1**

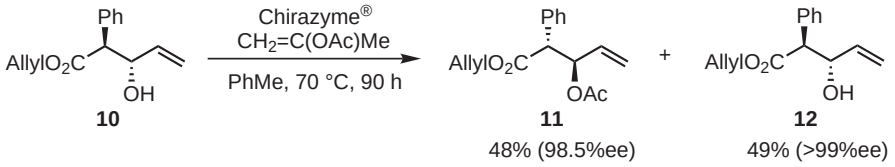
Entry	**1**: R-		Temp. (°C)/Time (h)	Yield (%ee)		
				Acetate **2**	Alcohol **3**	E value[17]
1	*n*-C_3H_7-	**1a**	70/72	40 (99): **2a**	47 (>99): **3a**	>1000
2	$(CH_3)_2CHCH_2$-	**1b**	70/72	41 (96): **2b**	45 (86): **3b**	136
3	*trans*-EtCH=CH-	**1c**	70/40	48 (99): **2c**	49 (99): **3c**	>1000
4	$(CH_3)_2C$=$CHCH_2$-	**1d**	70/72	49 (>99): **2d**	48 (>99): **3d**	>1000
5	CH_2=$CH(CH_2)_7$-	**1e**	70/72	43 (99): **2e**	51 (98): **3e**	922
6	$PhSCH_2CH_2$-	**1f**	50/40	48 (>99): **2f**	50 (>99): **3f**	>1000
7	CH_3-	**1g**	r.t./72	48 (89): **2g**	42 (>99): **3g**	90

Table 2 Lipase-catalyzed Kinetic Resolution of *anti*-Racemate **4**

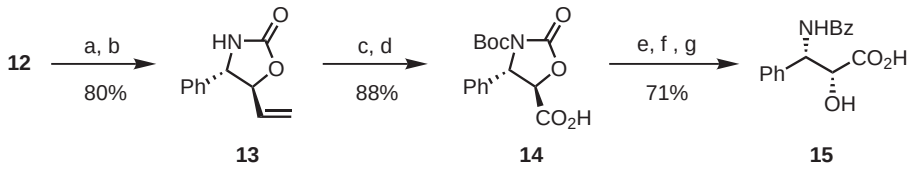
Entry	**4**: R-		Temp. (°C)/Time (h)	Yield (%ee)		
				Acetate **5**	Alcohol **6**	E value[17]
1	*n*-C_3H_7-	**4a**	70/72	45 (94): **5a**	46 (>99): **6a**	170
2	$(CH_3)_2CHCH_2$-	**4b**	70/72	43 (96): **5b**	45 (>99): **6b**	259
3	*trans*-EtCH=CH-	**4c**	70/40	48 (96): **5c**	46 (97): **6c**	207
4	$(CH_3)_2C$=$CHCH_2$-	**4d**	70/72	48 (93): **5d**	46 (>96): **6d**	145
5	CH_2=$CH(CH_2)_7$-	**4e**	70/72	49 (>99): **5e**	48 (>99): **6e**	>1000
6	$PhSCH_2CH_2$-	**4f**	50/40	50 (98): **5f**	50 (>99): **6f**	525
7	CH_3-	**4g**	r.t./72	46 (96): **5g**	44 (>99): **6g**	259



Scheme 2 (a) KO_2CN=NCO_2K/HOAc/MeOH, 0 °C to r.t., 12 h, 96%; (b) CH_2=CHOEt/cat. PPTS/CH_2Cl_2, r.t., 6 h, 93%; (c) $LiAlH_4$/THF, 0 °C, 0.5 h, 98%; (d) *p*-TsCl/cat. DMAP/pyridine, r.t., 20 h, 91% (e) $LiAlH_4$/THF, 0 °C to r.t., 12 h, 92%; (f) 3 M HCl/EtOH, r.t., 4 h, 82%



Scheme 3



Scheme 4 (a) $Pd(OAc)_2/PPh_3$, HCO_2H/Et_3N/THF, r.t., 10 h; (b) DPPA/Et_3N/toluene, r.t., 40 min, then 80 °C, 1.5 h; (c) $(Boc)_2O/Et_3N$/DMAP/THF, r.t., 2 h; (d) $RuO_2/NaIO_4$, CCl_4/MeCN/H_2O = 2:2:3, r.t., 15 h; (e) 2 M NaOH/MeOH, r.t., 1 h; (f) TFA, r.t., 2 h; (g) BzCl/aq $NaHCO_3$, r.t., 6 h

yield {$[\alpha]_D^{25}$ –35.3 (*c* 1.03, EtOH), mp 173.5–176 °C, Lit.[24] $[\alpha]_D^{20}$ –35.5 (*c* 1.07, EtOH), mp 175.5–177 °C} as outlined in Scheme 4.

In summary, we have established a practical method for obtaining *syn*- and *anti*-methyl 2-substituted 3-hydroxy-4-pentenoates with high optical purities by means of the lipase-catalyzed transesterification, which would offer access to other synthetically useful intermediates involving 1,2-amino alcohols less available from natural amino acids.

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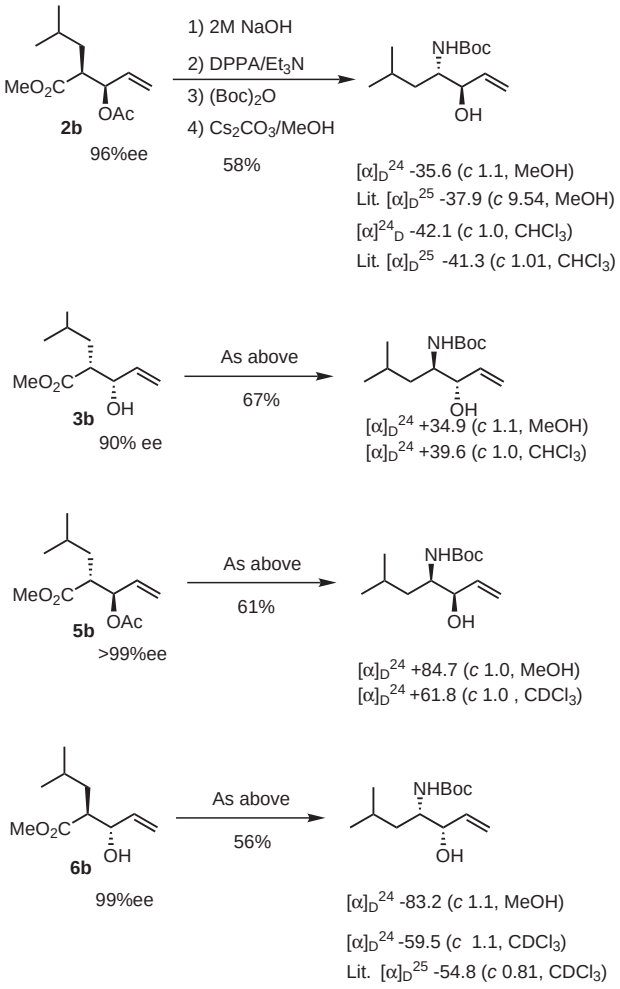
(13) For instance, compounds **1b** and **4b** were prepared as follows. A solution of methyl 4-methylvalerate (7.48 g, 57.5 mmol) in THF (20 mL) was added dropwise to a solution of LDA (60.3 mmol) in hexane (38.7 mL)/THF (50 mL) at –78 °C and the mixture was stirred for 1 h. Then, acrolein (4.61 mL, 68.9 mmol) was added and the mixture was stirred at –78 °C for 2 min. After usual workup, the oil obtained was purified by medium-pressure column chromatography (Yamazen, Ultra Pack™, ∅ 50 × 300 mm, hexane/ethyl acetate = 6:1~4:1 as eluent) to afford the less polar *syn*-racemate **1b** (5.03 g, 27.0 mmol, 47% yield) and the more polar *anti*-racemate **4b** (4.70 g, 25.2 mmol, 44% yield). Each compound can easily be discriminated by the chemical shifts of methine protons at 2- and 3-positions in ^{1}H NMR spectra ($CDCl_3$, 500 MHz) : δ 2.62–2.68 (m, 1 H, C*H*COO) and 4.28–4.33 (m, 1 H, C*H*OH) for **1b**, and δ 2.58–2.63 (m, 1 H, C*H*COO) and 4.14–4.20 (m, 1 H, C*H*OH) for **4b**. The chemical shifts of the methine protons at 2- and 3-positions of **1** are generally observed in the down field compared with those of **4**. Additionally, *syn*-racemates **1** are generally less polar than *anti*-racemates **4** on TLC analysis (hexane/ethyl acetate = 5:1~3:1).
(14) Lipase-catalyzed enantioselective acylation of 1-alkene-3-ols has been well examined, see: (a) Ito, T.; Akasaki, E.; Kudo, K.; Shirakami, S. *Chem. Lett.* **2001**, 262. (b) Ito, T.; Kudo, K.; Tanaka, N.; Sakabe, K.; Takagi, Y.; Kihara, H. *Tetrahedron Lett.* **2000**, *41*, 4591.

(15) The quantity of the lipase was not optimized. The lipase collected was washed with ether, dried in air for 5 min and stored below 5 °C. The lipase retains full activity and can be reused at least three times.

(16) The enantiomeric purity of alcohols **3** and **6** were determined by Chiralcel OD-H (hexane–2-propanol, 230 nm or 254 nm). Acetates **2** and **5** were also analyzed by Chiralcel OD-H (hexane/2-propanol, 230 nm or 254 nm) after having been converted to the corresponding alcohols via methanolysis (K_2CO_3/MeOH, r.t., 1 h). Some of them were transformed into known 1,2-amino alcohols to confirm their absolute configuration. For instance, acetates **2b** (96% ee), **3b** (90% ee after resubjection to the lipase-catalyzed transesterification), **5b** (>99% ee), and **6b** (99% ee) were converted to N-protected amino alcohols in 58%, 67%, 61%, and 56% overall yields, respectively via sequential alkaline hydrolysis (2 M NaOH/MeOH, r.t., 2 h), Curtius rearrangement (DPPA/Et_3N/toluene, r.t., 4 h and 80 °C, 1 h), N-protection [$(Boc)_2O$/Et_3N/cat. DMAP/THF, r.t., 2 h], and ring opening (0.4 equiv. of Cs_2CO_3/MeOH, r.t., 11 h),[25] the results being summarized below (Scheme 5). The optical rotation values were compared with those of reported in the literatures. See: (a) Leanna, M. R.; DeMattei, J. A.; Li, W.; Nichols, P. J.; Rasmussen, M.; Morton, H. E. *Org. Lett.* **2000**, *2*, 3627. (b) DeMattei, J. A.; Leanna, M. R.; Li, W.; Nichols, P. J.; Rasmussen, M. W.; Morton, H. E. *J. Org. Chem.* **2001**, *66*, 3330.



Scheme 5

(17) (a) Chen, C.-S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294. (b) Chen, C.-S.; Wu, S.-H.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1987**, *109*, 2812.

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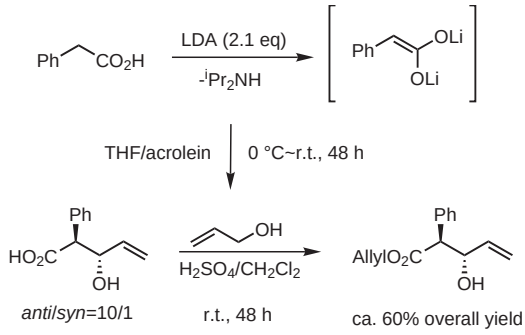
(21) (a) The attempted alkaline hydrolysis of the corresponding methyl ester of **10** failed entirely due to the intensive retro-aldol reaction. Thus we adopted the allyl ester **10** cleanly convertible to the free carboxylic acid by the palladium-catalyzed hydrogenolysis under a neutral condition. The compound **10** was prepared according to the Mulzer's protocol: Mulzer, J.; Segner, J.; Brüntrup, G. *Tetrahedron Lett.* **1977**, 4651. (b) A solution of phenylacetic acid (13.6 g, 100 mmol) in THF (40 mL) was added dropwise to a stirred solution of LDA (210 mmol) in THF–hexane (140 mL/135 mL) at 0 °C and the reaction mixture was stirred at 0 °C for 45 min and at r.t. for 2 h. The solvent was removed under reduced pressure and the residual viscous material was dried in vacuo at 70 °C for 2 h to give pale yellow solids. The lithium enolate thus obtained was dispersed in THF (100 mL) and acrolein (8.02 mL, 120 mmol) was added dropwise at 0 °C. After being stirred at r.t. for 48 h, the solvent was evaporated and ice-cold 3 N HCl (120 mL) was added to the residue. Extraction with $CHCl_3$ gave 2-phenyl-3-hydroxy-4-pentenoic acid (*anti*/*syn* = ca. 10:1) as a viscous oil (17.4 g) which without purification was esterified with allyl alcohol (14.9 mL, 220 mmol) in methanol-free CH_2Cl_2 (150 mL) in the presence of concd H_2SO_4 (2 mL) at r.t. for 48 h to give a diastereomeric mixture of allyl esters. The *anti*-ester **10** was isolated in 60% overall yield (Scheme 6) by medium-pressure column chromatography (SiO_2, toluene–EtOAc = 10:1~5:1).



Scheme 6

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