

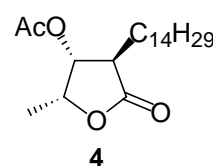
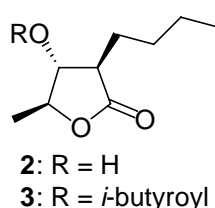
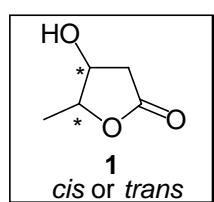
CONCISE SYNTHESIS OF (3*R*, 4*S*)-3-HYDROXY-4-METHYL- γ -BUTYROLACTONE

Takashi Nishiyama, Toshiko Nishioka, Tomoyuki Esumi, Yoshiharu Iwabuchi, and Susumi Hatakeyama*

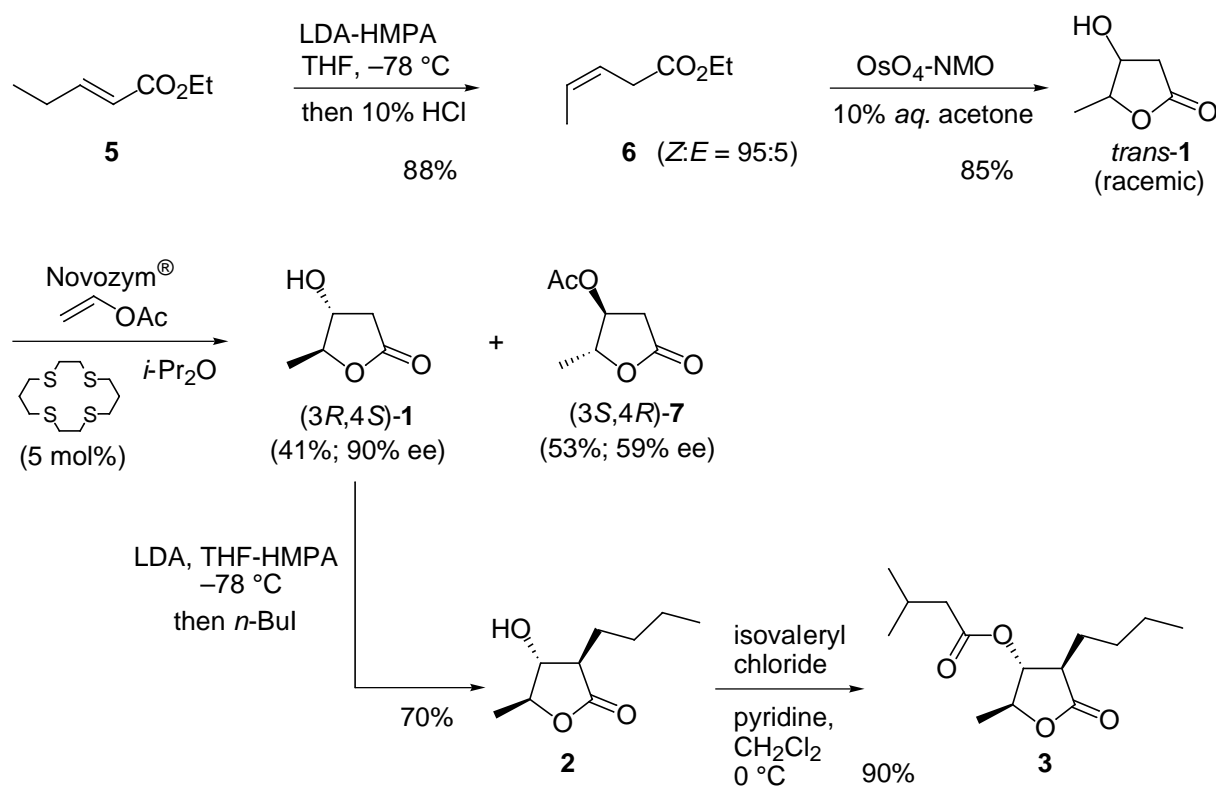
Faculty of Pharmaceutical Sciences, Nagasaki University, Nagasaki 852-8521, Japan

Abstract – A three-step sequence involving highly stereoselective deconjugation of ethyl (*E*)-2-pentenoate, osmylation, and resolution by lipase-catalyzed enzymatic acetylation allowed an extremely expeditious synthesis of (3*R*,4*S*)-3-hydroxy-4-methyl- γ -butyrolactone with 90% ee, from which (–)-blastmycinolactol and (+)-blastmycinone were synthesized.

Both *cis*- and *trans*-3-hydroxy-4-methyl- γ -butyrolactones (**1**) are useful chiral building blocks for the synthesis of a series of γ -lactones such as (+)-blastmycinone (**3**), a hydrolysis product of antimycin A₃, and compound (**4**), a lipid metabolite produced by the Gorgonian coral *Plexaura flava*.¹ Recently Harcken and Brückner² reported an efficient route to chiral *cis*-4-alkyl-3-hydroxy- γ -butyrolactones which relies on Sharpless asymmetric dihydroxylation³ of (*E*)- β,γ -unsaturated esters. In order to develop a simple and efficient method for the enantioselective synthesis of **1**, we have also examined asymmetric dihydroxylations of ethyl (*E*)- and (*Z*)-3-pentenoates. However, we found that this approach is not suitable for the synthesis of the *trans*-isomer because of low enantioselectivity of the dihydroxylation reaction ($\leq 25\%$ ee) although the *cis*-isomer is available with high enantiomeric excess (*ca.* 80% ee). Therefore, we needed to develop an alternative method which provides the *trans*-isomer with high optical purity. We describe herein an extremely concise synthesis of (3*R*,4*S*)-3-hydroxy-4-methyl- γ -butyrolactone *via* resolution of racemic *trans*-lactone (**1**) by lipase-catalyzed acetylation⁴ and its conversion to (–)-blastmycinolactol (**2**) and (+)-blastmycinone (**3**).



The required racemic *trans*-lactone (**1**) was prepared from ethyl (*E*)-2-pentenoate (**5**) in 75% overall yield by stereoselective deconjugative protonation⁵ of the lithium dienolate derived from **5** followed by treatment of the resulting β,γ -unsaturated ester (**6**) (95:5 *Z/E*-mixture) with a catalytic amount of OsO₄ in the presence of *N*-methylmorpholine *N*-oxide. Lipase catalyzed acetylation of racemic *trans*-lactone (**1**) with vinyl acetate was examined under various conditions using lipase-PS, lipase-AK, lipase-AY, and Novozym[®]. As a result, lipase-AK and lipase-AY did not bring about effective kinetic resolution of **1**. Table 1 summarizes lipase-PS and Novozym[®] catalyzed acetylations, some of which show successful results. Novozyme[®] was found to be more effective than lipase-PS in this particular transformation. It is important to note that addition of 1,4,8,11-tetrathiacyclotetradecane (5 mol%) markedly improved the enantioselectivity as reported by Takagi and co-workers.⁶ Furthermore, we also examined lipase-catalyzed hydrolysis of the acetate of racemic *trans*-lactone (**1**) using lipase-PS, lipase-AK, lipase-AY, and Novozym[®] in 0.1 M phosphate buffer-acetone (10:1). In these cases, however, the level of enantioselectivity was disappointing. For example, Novozym[®]-catalyzed hydrolysis gave (3*S*,4*R*)-**1** (62% ee, 43%) and (3*R*,4*S*)-acetate (**7**) (77% ee, 39%) and this was the best result obtained by this method.



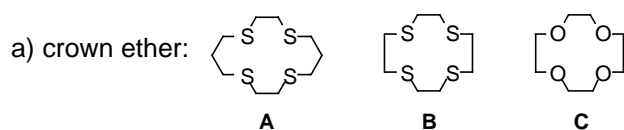
Scheme 1

The following is the experimental procedure of the best result we have obtained (entry 10). To a stirred solution of racemic *trans*-lactone (**1**) (500 mg, 4.31 mmol) in *i*-Pr₂O (5 mL) were added Novozym[®] (250 mg), vinyl acetate (0.5 mL, 6.5 mmol) and 1,4,8,11-tetrathiacyclodecane (55.6 mg, 0.215 mmol). After

stirring at room temperature for 1 h, the reaction mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. Purification of the residue by column chromatography (SiO₂ 30 g, 1:1 *n*-hexane-Et₂O) afforded (3*R*,4*S*)-**1** (203 mg, 41%), [α]²⁹_D -11.3° (*c* 1.03, CHCl₃), 90% ee, {lit.,^{1a} [α]²⁵_D -10.8° (*c* 1.21, CHCl₃), >99% ee}, and (3*S*,4*R*)-**7** (358 mg, 53%). The chiral lactone (**1**) thus obtained was converted into (-)-blastmycinolactol (**2**), mp 47-49 °C, [α]²³_D -17.8° (*c* 0.78, MeOH) {lit.,^{1d} mp49-50 °C, [α]²⁶_D -18.1° (*c* 0.80, MeOH)}, and (+)-blastmycinone (**3**), [α]²³_D +9.0° (*c* 1.0, CHCl₃) {lit.,^{1d} [α]²⁶_D +10.2° (*c* 1.2, CHCl₃)}, by the established procedure.^{1c} Both **2** and **3** exhibited identical spectral properties (¹H and ¹³C NMR, IR, HRMS) with those reported.^{1a-c} In conclusion, the present work enables us to secure large quantities of (3*R*,4*S*)-3-hydroxy-4-methyl- γ -butyrolactone with high optical purity (90% ee).

Table 1. Resolution of racemic *trans*-lactone1** by lipase-catalyzed acetylation**

entry	enzyme	solvent	crown ether ^a (5 mol%)	time (h)	(3 <i>R</i> ,4 <i>S</i>)- 1		(3 <i>S</i> ,4 <i>R</i>)- 7	
					yield (%) ^b	ee (%) ^c	yield (%) ^b	ee (%) ^d
1	PS	CH ₂ Cl ₂	none	48	48	21	49	34
2		THF	none	23	33	51	60	37
3		Et ₂ O	none	9	47	39	29	44
4		<i>i</i> -Pr ₂ O	none	19	47	75	46	55
5		<i>i</i> -Pr ₂ O	A	9.5	36	82	55	42
6	Novozym [®]	CH ₂ Cl ₂	none	2	45	83	52	45
7		THF	none	0.8	50	71	42	39
8		Et ₂ O	none	1.2	34	84	55	43
9		<i>i</i> -Pr ₂ O	none	1.3	45	85	51	67
10		<i>i</i> -Pr ₂ O	A	1	41	90	53	59
11		<i>i</i> -Pr ₂ O	B	0.5	32	80	64	40
12		<i>i</i> -Pr ₂ O	C	1	39	80	62	40



b) isolated yield.

c) determined by ¹H NMR (500 MHz) analysis of the corresponding (*R*)- and (*S*)-MTPA esters.

d) determined by ¹H NMR (500 MHz) analysis of the corresponding (*R*)- and (*S*)-MTPA esters after deacetylation (lipase-PS, 0.1 M phosphate buffer-acetone).

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