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

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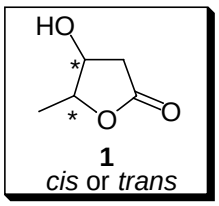
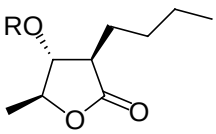
Abstract – A three-step sequence involving highly stereoselective deconjugation of ethyl (*E*)-2-pentenoate, osmylation, and resolution by lipase-catalyzed enzymatic acetylation allowed an extremely expeditious synthesis of (3*R*,4*S*)-3-hydroxy-4-methyl-γ-butyrolactone with 90% ee, from which (–)-blastmycinolactol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

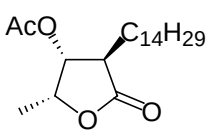
Both *cis*- and *trans*-3-hydroxy-4-methyl-γ-butyrolactones (**1**) are useful chiral building blocks for the synthesis of a series of γ-lactones such as (+)-blastmycinone (**3**), a hydrolysis product of antimycin A_3, and compound (**4**), a lipid metabolite produced by the Gorgonian coral *Plexaura flava*.[1] Recently Harcken and Brückner[2] reported an efficient route to chiral *cis*-4-alkyl-3-hydroxy-γ-butyrolactones which relies on Sharpless asymmetric dihydroxylation[3] 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 (≤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 acetylation[4] and its conversion to (–)-blastmycinolactol (**2**) and (+)-blastmycinone (**3**).



1
cis or *trans*



2: R = H
3: R = *i*-butyroyl



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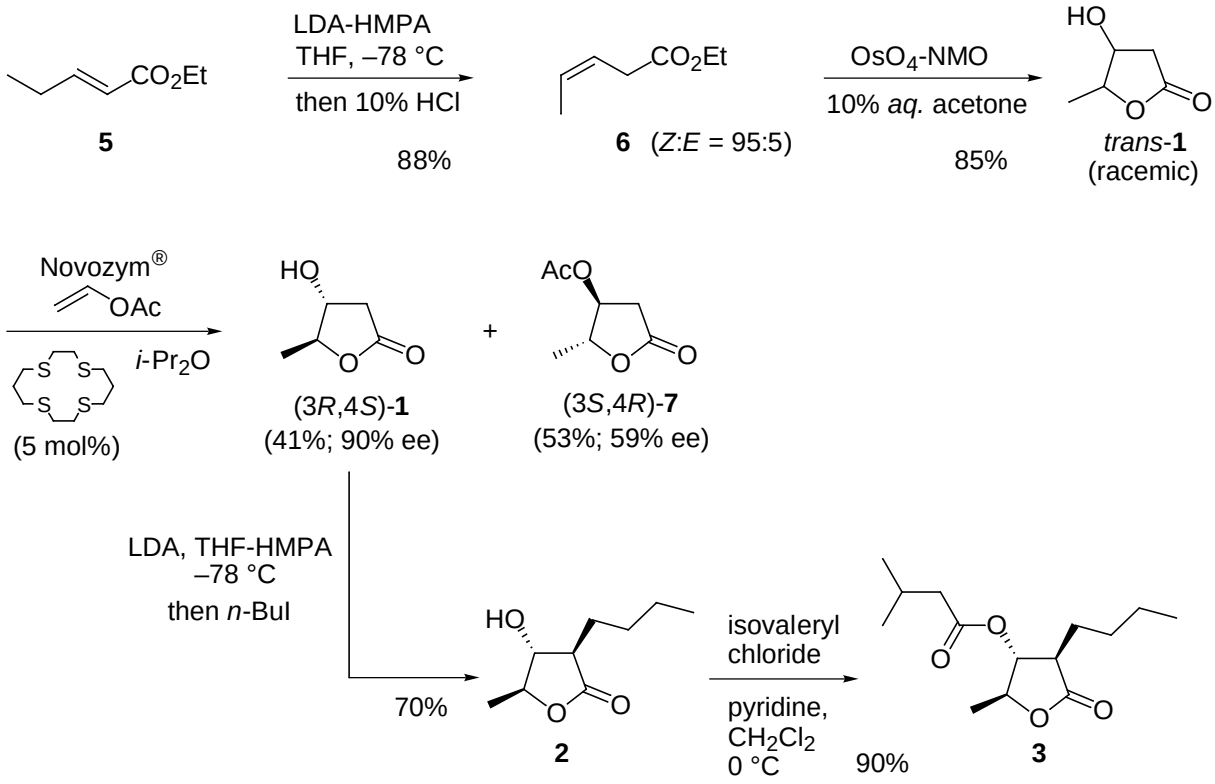
Dedicated to Professor Shô Itô on the occasion of his 77th birthday.

The required racemic *trans*-lactone (**1**) was prepared from ethyl (*E*)-2-pentenoate (**5**) in 75% overall yield by stereoselective deconjugative protonation[5] 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 OsO_4 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

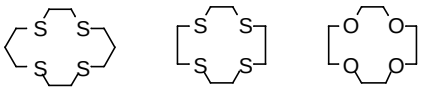
The following is the experimental procedure of the best result we have obtained (entry 10). To a stirred solution of recemic *trans*-lactone (**1**) (500 mg, 4.31 mmol) in *i*-Pr_2O (5 mL) were added Novozym® (250 mg), vinyl acetate (0.5 mL, 6.5 mmol) and 1,4,8,11-tetrathiacyclodecane (55.6 mg, 0.215 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 (SiO_2 30 g, 1:1 *n*-hexane-Et_2O) afforded (3*R*,4*S*)-**1** (203 mg, 41%), $[\alpha]^{29}_D$ –11.3° (*c* 1.03, $CHCl_3$), 90% ee, {lit.,[1a] $[\alpha]^{25}_D$ –10.8° (*c* 1.21, $CHCl_3$), >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 ℃, $[\alpha]^{23}_D$ –17.8° (*c* 0.78, MeOH) {lit.,[1d] mp49-50 ℃, $[\alpha]^{26}_D$ –18.1° (*c* 0.80, MeOH)}, and (+)-blastmycinone (**3**), $[\alpha]^{23}_D$ +9.0° (*c* 1.0, $CHCl_3$) {lit.,[1d] $[\alpha]^{26}_D$ +10.2° (*c* 1.2, $CHCl_3$)}, by the established procedure.[1c] Both **2** and **3** exhibited identical spectral properties (^1H and ^{13}C 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

					(3*R*,4*S*)-**1**		(3*S*,4*R*)-**7**	
entry	enzyme	solvent	crown ether[a] (5 mol%)	time (h)	yield (%)[b]	ee (%)[c]	yield (%)[b]	ee (%)[d]
1	PS	CH_2Cl_2	none	48	48	21	49	34
2		THF	none	23	33	51	60	37
3		Et_2O	none	9	47	39	29	44
4		*i*-Pr_2O	none	19	47	75	46	55
5		*i*-Pr_2O	**A**	9.5	36	82	55	42
6	Novozym®	CH_2Cl_2	none	2	45	83	52	45
7		THF	none	0.8	50	71	42	39
8		Et_2O	none	1.2	34	84	55	43
9		*i*-Pr_2O	none	1.3	45	85	51	67
10		*i*-Pr_2O	**A**	1	41	90	53	59
11		*i*-Pr_2O	**B**	0.5	32	80	64	40
12		*i*-Pr_2O	**C**	1	39	80	62	40

a) crown ether: 

A **B** **C**

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 phospate buffer-acetone).

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REFERENCES

1. For leading references, see: (a) H. Takahata, Y. Uchida, and T. Momose, *J. Org. Chem.*, 1994, **59**, 7201. (b) K. Nishide, A. Aramata, T. Kamanaka, T. Inoue, and M. Node, *Tetrahedron*, 1994, **50**, 8337. (c) M. B. M. de Azevedo and A. E. Greene, *J. Org. Chem.*, 1995, **60**, 4940. (d) P. A. Jacobi, and P. Herradura, *Tetrahedron Lett.*, 1997, **38**, 6621.
2. C. Harcken and R. Brückner, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 2750.
3. For a review on Sharpless asymmetric dihydroxylation, see: H. C. Kolb, M. S. VanNieuwenhze, and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
4. For reviews on lipase-catalyzed reactions, see: (a) C.-H. Wong and G. M. Whitesides, *Enzymes in Synthetic Organic Chemistry*; Pergamon Press, Oxford, 1994. (b) K. Nakamura and Y. Hirose, *J. Synth. Org. Chem. Jpn.*, 1995, **53**, 668.
5. (a) E. P. Krebs, *Helv. Chim. Acta*, 1981, **64**, 1023. (b) A. S. Kende and B. H. Toder, *J. Org. Chem.*, 1982, **47**, 163. (c) Y. Ikeda, N. Ukai, and H. Yamamoto, *Tetrahedron*, 1987, **43**, 743. (d) P. Galatsis, J. J. Manwell, and S. D. Millan, *Tetrahedron Lett.*, 1996, **37**, 5261.

6 Y. Takagi, J. Teramoto, H. Kihara, T. Itoh, and H. Tsukube, *Tetrahedron Lett.*, 1996, **37**, 4991.