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EFFICIENT ENZYMATIC PREPARATION OF (+)- AND (–)-COREY LACTONE DERIVATIVES

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Two pairs of Corey lactone derivatives, (+)-**1**, (–)-**2** and (+)-**3**, (–)-**4** have been efficiently prepared in high optical purity by enzymatic esterification and enzymatic hydrolysis catalyzed by lipases from *Pseudomonas sp.*

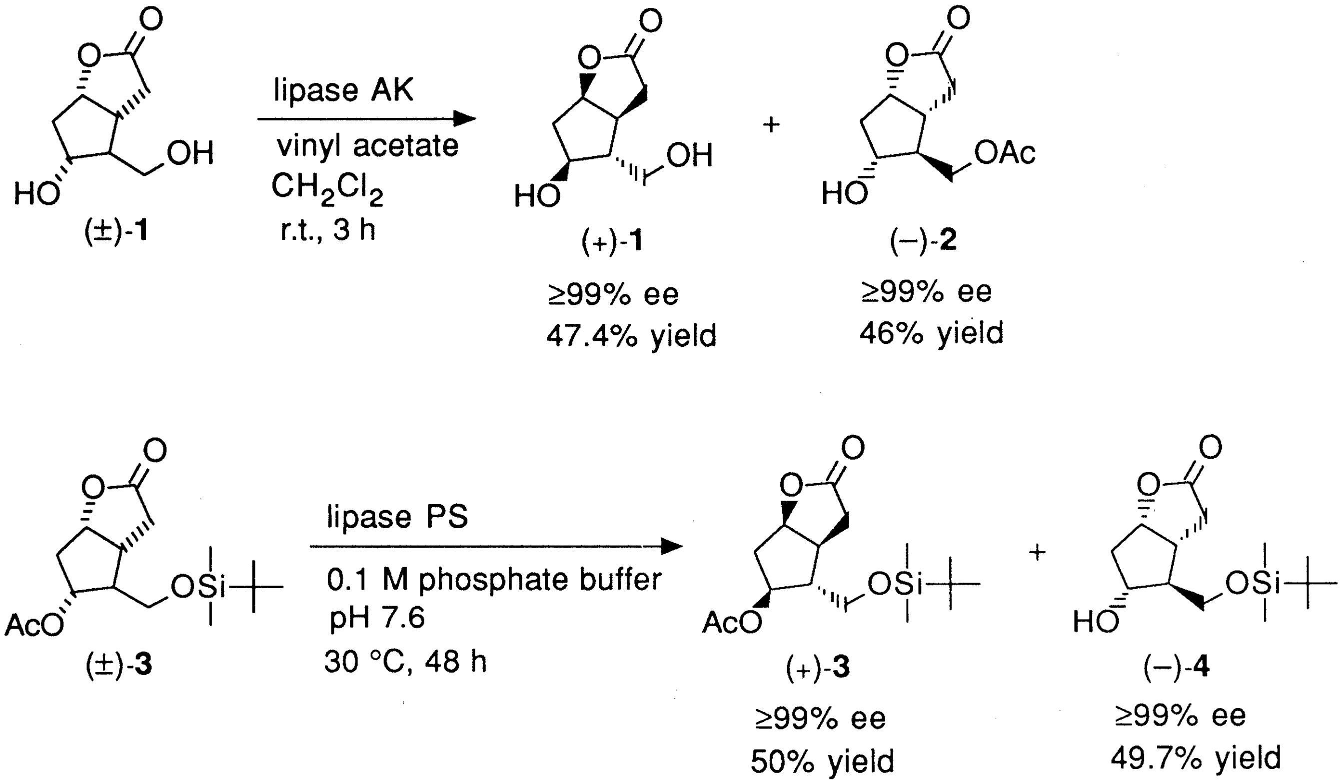
KEYWORDS Corey lactone; lipase PS; lipase AK; enzymatic transesterification; enzymatic hydrolysis

Prostaglandins and prostacyclins are important biologically active compounds and a number of synthetic methods of preparing them are reported.[1,2] The (–)-Corey lactone derivative is one of the most important key intermediates in the synthesis of prostaglandins, prostacyclins and their derivatives. (–)-Corey lactone derivatives are mode by numerous methods such as the optical resolution method, the asymmetric Diels-Alder method, and so on, but there are some problems including high cost of reagents for optical resolution and/or, long reaction steps.[1] Recently enzymatic resolution of prochiral substrates is a well established procedure for the preparation of enantiomerically pure products.[3] We report here a more convenient preparation of (+)- and (–)-Corey lactones based on a lipase-catalyzed transesterification of (±)-**1** and enzymatic hydrolysis of (±)-**3** (Chart).[4]

First, we studied the enzymatic transesterification of (±)-Corey lactone diol **1**.[5] After several experiments using lipases in organic solvent, (+)-Corey lactone diol **1** and (–)-Corey lactone acetate **2** were obtained at ≥99% ee[6] in good yield respectively, using lipase AK (Amano, *Pseudomonas sp.*) and vinyl acetate as the acylating reagents.[7]

Next, we tested the enzymatic hydrolysis of (±)-Corey lactone acetate **3**.[8] Treatment of (±)-**3** with lipase PS (Amano, *Pseudomonas sp.*) in 0.1 M phosphate buffer pH 7.6 at 30 °C for 48 h gave (+)-acetate **3** and (–)-alcohol **4** both with ≥99% ee[9] in good yield.[10]

In summary, efficient and expeditious routes for the preparation of both enantiomers of Corey lactone derivatives, (±)-**1**, (±)-**3** under exceptionally mild and easy conditions are reported.[11] The use of these optically pure Corey lactone derivatives in the synthesis of didemnenone C, D and marine prostanoids is currently under investigation.[12]



Chart

ACKNOWLEDGEMENT We thank Amano Pharmaceutical Co. LTD. for supplying us with the lipase AK and PS.

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1) a) A. Mitra, "*The Synthesis of Prostaglandins*", John Wiley & Sons, 1977; b) S. M. Roberts and F. Scheinmann, "*New Synthetic Routes to Prostaglandins and Thromboxanes*," Academic Press, 1982.

2) S. Ikegami and M. Shibasaki, *J. Syn. Org. Chem. Jpn.*, **38**, 1037 (1980); F. Hirata, *ibid.*, **41**, 178 (1983).

3) a) C-S. Chen and C. J. Sih, *Angew. Chem. Int. Ed. Engl.*, **28**, 695 (1989); b) R. Scheffold, "*Modern Synthetic Methods*," Vol. 5, pp 1-114, Springer-Verlag, 1989; c) M. Murata, S. Ikoma and K. Achiwa, *Chem. Pharm. Bull.*, **38**, 2329 (1990); d) Z. -F. Xie, H. Suemune and K. Sakai, *Tetrahedron Asymmetry*, **1**, 395 (1990), and references cited therein.

4) Only one example of the diastereomeric separation of (±)-Corey lactone benzoate by enzymatic resolution is reported; K. Petzoldt, H. Dahl, W. Skuballa and M. Gottwald, *Liebigs Ann. Chem.*, **1990**, 1087.

5) The requisite precursor, (±)-diol **1** was prepared by the methods in the literature: a) P. A. Grieco, *J. Org. Chem.*, **37**, 2362 (1972); b) E. J. Corey and J. Mann, *J. Am. Chem. Soc.*, **95**, 6832 (1973); c) I. Tömösközi, L. Gruber, G. Kovács, I. Székely and V. Simonidesz, *Tetrahedron Lett.*, **1976**, 4639.

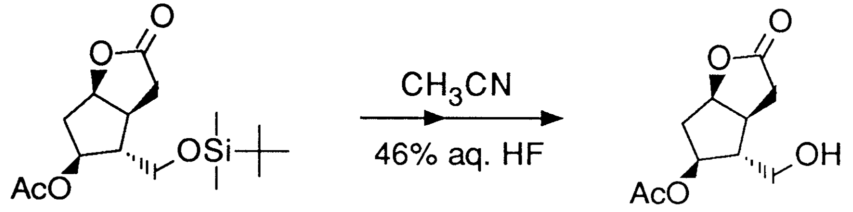
6) The enantio excess of (+)-**1** was determined by the comparison of the NMR spectrum (500 MHz) of the (+)-mono-Mosher ester of its primary alcohol

with the corresponding (+)-mono-Mosher ester of (±)-**1**. And the enantio excess of (−)-**2** was also determined by the comparison of the NMR spectrum (500 MHz) of its (+)-Mosher ester with the (+)-Mosher ester of (±)-**2**, which was prepared from (±)-**1**.

7) 109 mg of (±)-**1**, vinyl acetate (10 eq., 0.59 ml) and 100 mg lipase AK in CH_2Cl_2 were stirred at r.t. for 3 h. After filtration of the enzyme, the products were separated by silica gel column chromatography.

8) (±)-Acetate **3** was prepared by selective silylation of (±)-**1** followed by acetylation.

9) (+)-**3** was converted to (+)-**5** by acid treatment prior to derivatization.



(+)-**3** (+)-**5**

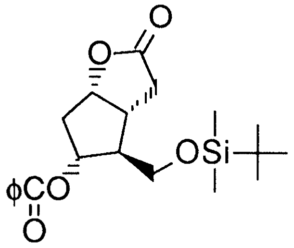
The enantio excess of (+)-**3** and (−)-**4** was determined by the comparison of the NMR spectrum (500 MHz) of their (+)-Mosher esters of (+)-**5** with (−)-**4** and the (+)-Mosher esters of (±)-**5** with (±)-**4**, which were prepared from (±)-**3**.

10) (±)-**3**, 2.3 g, and lipase PS, 1.15 g, were suspended in 230 ml phosphate the buffer and the mixture was stirred at 30 °C for 48 h. After filtration of the enzyme, the products were extracted with AcOEt. (+)-**3** and (−)-**4** were obtained by silica gel column chromatography.

11) All compounds have been fully characterized by ^1H NMR and MS spectrum. Data for optical rotations are as follows: $[\alpha]_D$ +31.6° (*c* 0.688; MeOH) (+)-**1** [lit.,5c) $[\alpha]_D$ −43.4° (*c* 1.46, MeOH) for (−)-**1**] and −16.4° (*c* 1.158, $CHCl_3$) (−)-**2** [lit.,13) $[\alpha]_D$ −17.9° (*c* 0.518, $CHCl_3$)]; $[\alpha]_D$ +48.0° (*c* 1.016, $CHCl_3$) (+)-**3** [lit.,13) $[\alpha]_D$ −47.4° (*c* 1.294, $CHCl_3$) for (−)-**3**] and −14.2° (*c* 1.008, $CHCl_3$) (−)-**4** [lit.,13) $[\alpha]_D$ −15.3° (*c* 1.004, $CHCl_3$)].

12) For earlier application of optically active Corey lactone in natural products synthesis, see; T. Sugahara, T. Ohike, M. Soejima, and S. Takano, *J. Chem. Soc., Perkin Trans. 1*, **1990**, 1824.

13) (−)-**2**, (−)-**3** and (−)-**4** were synthesized respectively from authentic (−)-**6**, which was supplied by NISSAN Chemical Industry Ltd.



(−)-**6**

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