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Lipase-catalyzed Asymmetric Synthesis of 6-(3-Chloro-2-hydroxypropyl)-1,3-dioxin-4-ones and Their Conversion to Chiral 5,6-Epoxyhexanoates[1]

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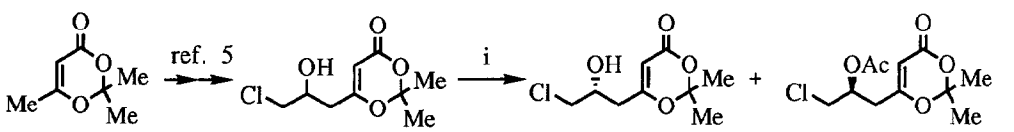
Abstract: Highly enantioselective syntheses of (*R*)- and (*S*)-6-(3-chloro-2-hydroxypropyl)-1,3-dioxin-4-ones by means of lipase-catalyzed kinetic resolutions are described. Chiral dioxinones thus obtained have been converted to optically active 5,6-epoxyhexanoates, which are important precursors for a series of biologically active compounds.

During recent years enzyme-catalyzed asymmetric synthesis has been well recognized as one of the most effective methods for the synthesis of chiral building blocks.[2] Previously, we reported that prochiral methyl ketones having 4-oxo-1,3-dioxin-6-yl group as the terminal unit were enantioselectively reduced by baker's yeast.[3] The same reduction if applied to the higher methylene homologs (RCO: R≠Me), however, gave poor chemical and optical yields. For the purpose of creating more versatile chiral synthons, we have been interested in the lipase-catalyzed asymmetric synthesis of (*R*)- and/or (*S*)-6-(3-chloro-2-hydroxypropyl)-1,3-dioxin-4-ones (***R*-3**, ***S*-3**). Since the dioxinones are known as the manipulatable synthons in a variety of ways under mild conditions,[4] chiral ones if obtained as EPC can be converted to optically active 5,6-epoxyhexanoates: the precursors either of chiral 6-substituted δ-lactones or of 4-hydroxy δ-lactones.

According to the two-step procedure elaborated recently by us,[5] racemic chloroalcohol (**2**) was prepared from 2,2,6-trimethyldioxinone (**1**). After some preliminary screening to find the suitable enzyme for asymmetric transesterification of **2** in vinyl acetate, Amano PS (*Pseudomonas sp.*) was found to be the best choice.[6]



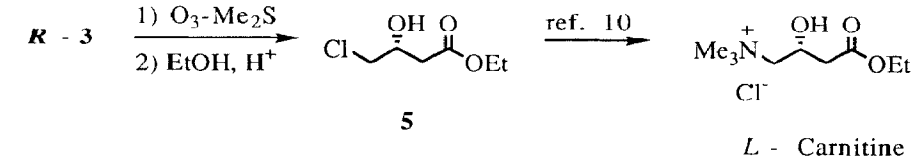
1 **2** ***R* - 3** ***S* - 4**

Conditions: i) Amano PS, vinyl acetate, 28 °C, 7 d.

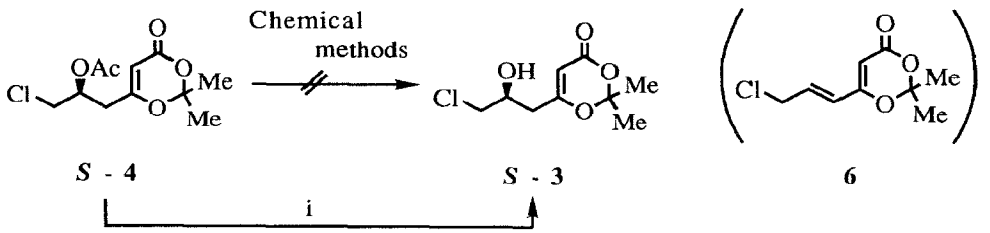
Scheme 1

Both isomers (***R*-3**, ***S*-4**)[7] were obtained in quantitative chemical yields with high enantiomeric excesses (≥98% e.e.).[8]

The absolute configuration of chiral chloroalcohol [***R*-3**: $[\alpha]_D^{20}$ +19.3 (*c* 1.67, $CHCl_3$)] thus obtained was determined by conversion to ethyl (*R*)-4-chloro-3-hydroxybutanoate (**5**)[9] (degradation of a dioxinone ring by ozonolysis followed by acid mediated esterification), which was synthesized previously by Sih *et al.* as the key intermediate of *L*-carnitine (Scheme 2).[10] Attempted hydrolysis of the acetylated product [***S*-4**: $[\alpha]_D^{20}$ +0.12 (*c* 1.20, $CHCl_3$)] in basic medium failed to give the desired alcohol and the deacetylated product (**6**) was obtained as the major product, irrespective of the reaction conditions (*e.g.* K_2CO_3/MeOH, 2*N* NaOH/ether, etc.). It has been found, however, that enzyme-mediated hydrolysis of ***S*-4** by lipase MY (Meito, *Candida Cylindracea nov. sp.*) preceeded smoothly to give the antipode (***S*-3**) in 83% chemical yield with ≥98% e.e.



Scheme 2

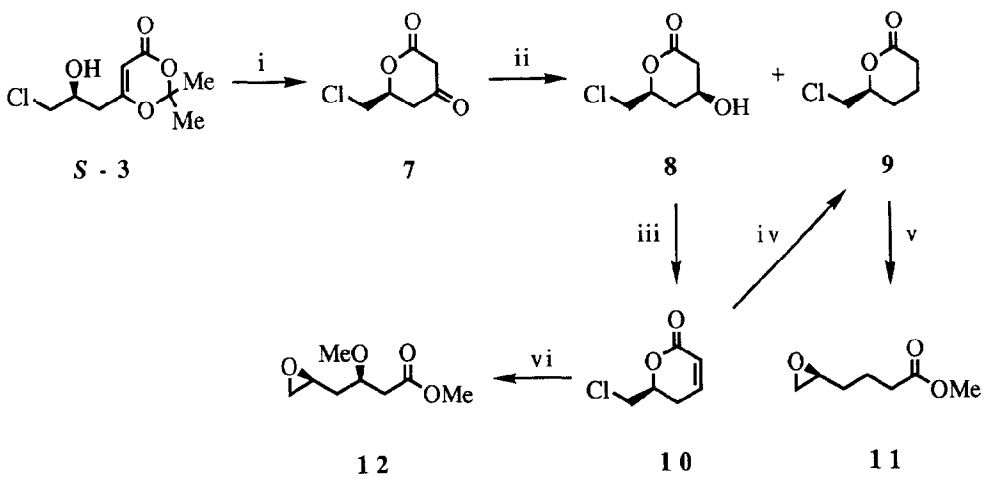


Conditions: i) Lipase MY, 0.1*M* pH 7.2 phosphate buffer, 28 °C, 4 d

Scheme 3

5,6-Epoxyhexanoates are known as efficient precursors for 6-substituted δ-lactone derivatives which are fairly common units among natural products and in a variety of biologically active molecules.[11] Thus 5,6-epoxyhexanoate derivatives (**11**, **12**) were prepared from the corresponding chiral chloroalcohol (***S*-3**). Following one-

pot lactonization reaction developed in our laboratory,[12] 6-chloromethyl-β-keto-δ-lactone [**7**: mp 98-99 °C, $[\alpha]_D^{25}$ -83.4 (*c* 1.07, MeOH)] was prepared from ***S*-3** in 84% yield. Catalytic hydrogenation of keto lactone (**7**) over PtO_2 gave *cis*-4-hydroxy lactone [**8**: $[\alpha]_D^{20}$ +13.3 (*c* 1.25, $CHCl_3$)] and its deoxy derivative [**9**: $[\alpha]_D^{30}$ -0.77 (*c* 1.03, $CHCl_3$)] in 73% and 20% yields, respectively. The latter lactone (**9**) was also prepared by two-step procedure[13] (acid-catalyzed dehydration followed by catalytic hydrogenation over 10% Pd-C) from **8** *via* unsaturated lactone [**10**: $[\alpha]_D^{23}$ -144.8 (*c* 3.09, $CHCl_3$)] in satisfactory overall yield. When saturated lactone (**9**) was treated with K_2CO_3 in MeOH at room temperature, epoxyester [**11**: $[\alpha]_D^{24}$ -15.7 (*c* 1.94, $CHCl_3$): lit.[11] $[\alpha]_D^{23}$ -16.2 (*c* 0.58, $CHCl_3$)] was obtained directly in 79% yield. The reaction proceeded obviously by methoxide mediated lactone ring opening followed by formation of epoxide ring. Nishida *et al.* has demonstrated that this epoxide (**11**) can be used as the common precursor for a variety of optically active 6-substituted δ-lactones.[11] Finally, methyl (3*R*, 5*S*)-5,6-epoxy-3-hydroxyhexanoate (**12**),[14] which is the important precursor[15] for compactin or mevinolin (HMG-CoA reductase inhibitor), has been synthesized as a sole product from unsaturated lactone (**10**) by treatment with sodium methoxide in methanol.[16]



***S* - 3** **7** **8** **9**

12 **10** **11**

Conditions: i) K_2CO_3, MeOH, room temp., 84%; ii) H_2, PtO_2, AcOEt, 1 atm, 7 h;
iii) *p*-TsOH, benzene, Δ, 1.5 h, 88%; iv) H_2, Pd-C, MeOH, 30 min, 90%;
v) K_2CO_3, MeOH, room temp., 5 h, 79%; vi) NaOMe, MeOH, -50 °C ~ room temp., 49%

Scheme 4

In summary, successful use of lipase to the readily available chloroalcohol (**2**) provided highly enantioselective route to the versatile synthons [(*R*)- and (*S*)-6-(3-chloro-2-hydroxypropyl)-1,3-dioxin-4-ones] which were efficiently converted to chiral 5,6-epoxyhexanoates.

References and Notes

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6. The reaction was monitored by HPLC analysis. When the integrals due to alcohol (***R*-3**) and acetate (***S*-4**) became almost equal, the raction was terminated.
7. All new compounds exhibited satisfactory spectroscopic (NMR, IR) and combustion or high-resolution mass spectral analytical data.
8. Determined by HPLC analysis using chiral columns [**3**: Chiralcell OD, **4**: Chiralcell OJ (Daicel)].
9. **5**: $[\alpha]_D^{26}$ +21.1° (*c* 3.11, $CHCl_3$). *S*-Isomer (55% e.e.): lit.[10] $[\alpha]_D^{23}$ -11.7° (*c* 5.75, $CHCl_3$).
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13. M. Sato, J. Sakaki, Y. Sugita, T. Nakano, and C. Kaneko, *Tetrahedron Lett.*, **31**, 7463 (1990).
14. **12:** $[\alpha]_D^{24}$ -19.1° (*c* 3.55, $CHCl_3$). IR ($CHCl_3$): 1735 cm^{-1}. 500 MHz-^{1}H-NMR ($CDCl_3$) δ: 1.70-1.77 (1H, m, C_4-H), 1.84-1.91 (1H, m, C_4-H), 2.50 (1H, dd, *J*=3.8, 2.4 Hz, C_2-H), 2.55 (1H, dd, *J*=15.6, 5.8 Hz, C_6-H), 2.68 (1H, dd, *J*=15.6, 7.7 Hz, C_6-H), 2.78 (1H, t, 3.8 Hz, C_2-H), 3.01-3.07 (1H, m, C_5-H), 3.38 (3H, s, CO_2Me), 3.71 (3H, s, OMe), 3.82-3.89 (1H, m, C_3-H).
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16. When this reaction was carried out at higher temperature (-5°~-10 °C), the diastereomeric excess (d.e.) lowered to 33%.