# Stereoselective Synthesis of (*R*)-glycidyl Butyrate from Racemic Glycidyl Butyrate or Epichlorohydrin *Via* Hydrolytic Kinetic Resolution

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**Abstract:** The differences of (*R*)-glycidyl butyrate synthesis *via* hydrolytic kinetic resolution of glycidyl butyrate directly or regioselective opening epichlorohydrin as key steps by using Jacobsen's hydrotic kinetic resolution are compared. In the view of separation problem, it is hard to get the pure (*R*)-glycidyl butyrate by kinetic resolution of glycidyl butyrate directly. *Via* kinetic resolution of epichlorohydrin, treatment with butyric acid in the presence of $CrCl_3$ and then epoxidation with NaOH, the total yield of 38.5% and optical purity of 99% are obtained.

**Keywords:** (*R*)-glycidyl butyrate, hydrolytic kinetic resolution, epichlorohydrin.

Optically pure glycidyl butyrate has been widely used as starting materials for the synthesis of many interesting compounds, such as β-blocker drugs, anticancer drugs, protein synthesis inhibitors, as well as 2-oxazolidinone derivatives used against depression [1]. The demand for these valuable intermediates is expected to increase in the near future. Particularly, (*R*)-glycidyl butyrate has been used to introduce a stereoisomeric center in the synthesis of Linezolid which is currently marketed for the treatment of multidrug resistant Gram-positive infections such as nosocomial community acquired pheumonia, and skin infections [2, 3].

Due to the interest of the product with high enantiomeric purity, several alternative biocatalytic processes have been developed recently [4, 5]. In most cases, the commercial lipase prepared from porcine pancreas has been used in resolution of (±)glycidyl esters. However, these lipases show low enantioselectivity against these compounds, probably due to the small size of the substrate, which reduces the yield of the enantiomerically pure product. The chemical synthesis of chiral glycidol is performed by the Sharpless epoxidation [6]. The allylic alcohol is epoxidized with the yield more than 90% by using [$Ti(O\text{-}iPr)_4$, TBHP] and titanium diisopropyl tartrate (DIPT) as oxygen donor, These reactions are of good atom economy, but they use very expensive chemical reagents.

There are many references about the hydrolytic kinetic resolution in fine chemicals [7-10]. Our research program aimed at developing enantioselective synthesis of (*R*)-glycidyl butyrate.

We have two choices, one is kinetic resolution of glycidyl butyrate directly (Scheme **1**), and the other is kinetic resolution of epichlorohydrin first (Scheme **2**).

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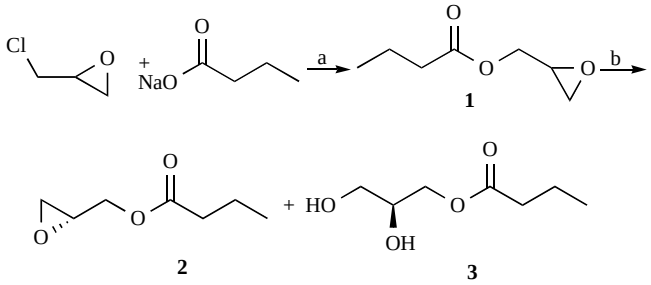


**Scheme 1.** Reagents and conditions: (a) 60 °C, 8 h, 95%; (b) (*S*,*S*)-salen-Co-(OAc) (0.5 mol%), dist. $H_2O$ (0.55 equiv), 0 °C, 12 h.

Scheme **1** shows our general synthetic strategy to construct (*R*)-glycidyl butyrate which is based on two-step reactions sequence employing displacement reaction and hydrolytic kinetic resolution reaction. In this experiment, epichlorohydrin is relatively easy to react with sodium butyrate, and racemic glycidylbutyrate is treated with (*S*,*S*)-salen-Co-OAc complex (0.5 mol%) and water (0.55 equiv in THF) to afford (*R*)-glycidyl butyrate as a single enantiomer. Control reactions illustrate that the (salen)Co(III) complex is also active in the racemization/decomposition reactions involving (*R*)-glycidyl butyrate and (*S*)-2,3-dihydroxypropyl butyrate separation. With this result in hand, convenient chemical reductants are screened for the ability to reduce all Co(III) species after the hydrolytic kinetic resolution to form the inactive Co(II) complex. L-ascorbic acid (vitamin C) is the best at stabilizing the reaction mixture and preventing thermal degradation. The use of two equivalents of L-ascorbic acid relative to Co(III) species results in the quantitative reduction of Co(III) species to the Co(II) species, and allows for the isolation of the resolved (*R*)-glycidyl butyrate by simple vacuum distillation. As we known, the boiling point of (*R*)-glycidyl butyrate is 192.6 ºC, so it is hard to get the pure (R)-glycidyl butyrate and (*S*)-2,3-dihydroxypropyl butyrate (153 °C / 7 mmHg) with high

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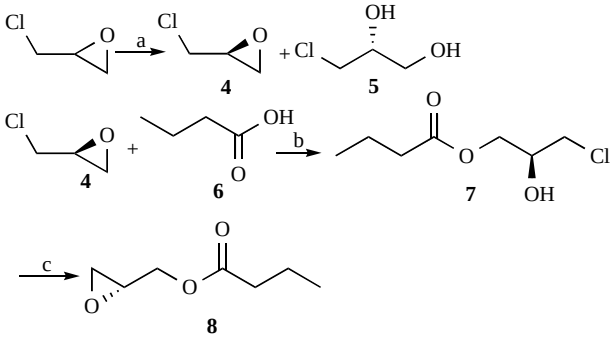
yield. Finally, the ee value of (*R*)-glycidyl butyrate reachs 90%, the yield of 40% is obtained.

In order to achieve the synthesis of target molecule, we can get chiral epichlorohydrin by hydrolytic kinetic resolution epichlorohydrin directly (Scheme **2**).




**Scheme 2.** Reagents and conditions: (a) (*R*,*R*)-salen-Co-(OAc) (0.5 mol%), dist. $H_2O$ (0.55equiv), 0 °C, 1 2h, (45% for **4**, 43% for **5**; (b) $CrCl_3$, 60 °C, 24 h, 95%; (c) NaOH, reflux, 12 h, 90%.

Scheme **2** presents the synthesis of intermediates with hydrolytic kinetic resolution epichlorohydrin first. It is easy to get the corresponding enantiomeric pure (*S*)-epichlorohydrin in 43% yield and 99% optical purity by distillation at reduced pressure, along with the separable diol with the yield of 47% (the boiling point of epichlorohydrin is 115-117 ºC and the boiling point of (*R*)-3-chloropropane-1,2-diol is 213 ºC). The overall yield of the epichlorohydrin is typically 40–45%. Additional 4–5% of epichlorohydrin remains in the pot, which could be recovered by utilizing lower vacuum distillation. The epichlorohydrin shows no loss of enantiomeric excess, and the purity is more than 99% by GC analysis.

With the enatiomerically pure epoxide in hand, our next aim is to react (*S*)-epichlorohydrin with butyric acid, in the presence of Cr(III) as catalyst. Several catalysts are chosen for the reaction, such as $CrCl_3$, $Cr(NO_3)_3$ and $Cr(OH)_3$. It is found that $CrCl_3$ is the best one for this kind reaction with the yield of 95%. Then the compound was subjected to NaOH epoxidation, which provides the target compound (*R*)-glycidyl butyrate in 90% yield, $[\alpha]_D^{25}$ =30º (c=neat). The physical and spectroscopic data of (*S*)-3-chloro-2-hydroxypropyl butyrate (**7**) and (*R*)-glycidyl butyrate (**8**) are determined by $^1$H NMR and $^{13}$C NMR [11].

In conclusion, two efficient strategies amenable to the synthesis of (*R*)-glycidyl butyrate are discussed. The desired stereocenter can simply be achieved by changing the hydrolytic kinetic resolution step. In the view of separation problem, it is a better choice to obtain the product *via* kinetic resolution of epichlorohydrin first. Further application of this methodology to the synthesis of all the similar targets should be taken into account.

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[11] Spectral data of compound **7**. $^1$H NMR (500MHz, $CDCl_3$): δ 4.03-4.03 (m, 2H), 3.92-3.90 (m, 1H), 3.75 (-OH, 1H), 3.47-3.41 (m, 2H), 2.19-2.16 (m, 2H), 1.51-1.46 (m, 2H), 0.80-0.77 (m, 3H); $^{13}$C NMR (500MHz, $CDCl_3$): δ 173.0, 68.9, 68.4, 47.7 , 36.0, 18.5, 13.5. Anal. Calcd for $C_7H_{13}ClO_3$ (180.5): C, 46.55; H, 7.25%. Found: C, 46.55; H,7.25%. Spectral data of compound **8.** $^1$H NMR (500MHz, $CDCl_3$): δ 4.19-4.16 (d, 2H), 3.68-3.64 (m, 1H), 2.60-2.40 (d, 2H), 2.12-2.09 (m, 2H), 1.45-1.41 (m, 2H), 0.74-0.71 (m, 3H); $^{13}$C NMR (500MHz, $CDCl_3$): δ 173.0, 67.0, 49.3, 44.0, 36.1, 18.4, 13.6. Anal. Calcd for $C_{17}H_{12}O_3$ (144): C, 58.32; H, 8.39%. Found: C, 58.31; H, 8.40%.