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Journal of Molecular Catalysis B: Enzymatic 4 (1998) 237–252

JOURNAL OF MOLECULAR CATALYSIS B: ENZYMATIC

Review

Chiral C3 epoxides and halohydrins: Their preparation and synthetic application

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Received 4 December 1996; accepted 17 October 1997

Abstract

Epichlorohydrin, 3-chloro-1,2-propanediol and glycidol are versatile chiral C3 syntons in organic synthesis. For the production of these, more efficient and more practical methods are required and many studies have been reported. In this review, biological and synthetic preparations of their synthons and microbial dehalogenation of halohydrins connected with the biological methods are described. Several of their synthetic applications are also introduced. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Chiral; Resolution; Optically active; Epichlorohydrin; 2,3-Dichloro-1-propanol; 3-Chloro-1,2-propanediol; Glycidol; Dehalogenation

1. Introduction

Recently, the importance of optically active compounds has been increasingly recognized in the fields of pharmaceuticals, agrochemicals, perfumery and liquid crystals, and versatile chiral synthons are desired [1]. Optically active epoxides and halohydrins which are precursors of the epoxides are important compounds in organic synthesis, because the epoxy ring is very reactive with nucleophiles and easily yields asymmetric alcohols. Particularly, optically active epichlorohydrin (EP*), glycidol (GLD*), 2,3-dichloro-1-propanol (DCP*) and 3-chloro-1,2-propanediol (CPD*) or their derivatives have a compact skeleton of glycerol and have broad potentials for synthesis; they are considered to be versatile chiral synthetic units (Fig. 1). Therefore, their practical preparation have been desired and various kinds of chemical and biological methods have been investigated for production. Some reviews such as those on chiral epoxidation by chemical methods or formation of optically active epoxides by bio methods were already described [2–4], so that we will not discuss epoxidation here. In this review, we would like to introduce specifying C3 chiral building blocks such as EP*, GLD*, DCP* and CPD*.

In viewing reported preparations for EP*, GLD*, DCP* and CPD*, each strategy includes interesting and unique contents and some

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1381-1177/98/$19.00
PII S1381-1177(97)00034-9

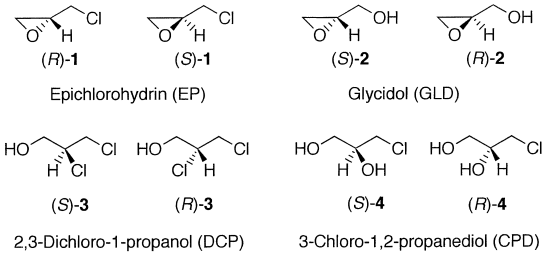


Fig. 1. Structures of EP*, GLD*, DCP* and CPD*.

methods are practical and functioning in production on an industrial scale. However, the best method could not be simply determined, because each method has both advantages and disadvantages from the background of production. Further investigation and improvement for the methodology yield make a new or more practical method.

On the other hand, large amounts of racemic EP and the relative halohydrins have been produced and used on an industrial scale [5]; their microbial degradation and metabolites have been studied [6,7]. In these reports, there are non-stereoselective dehalogenation for complete degradation and stereoselective dehalogenations for preparation of chiral halohydrins. The characteristics of the microorganisms and the enzymes are also shown in this paper because this information is essential and useful for new types of biological or chiral catalysis.

This review focuses on the preparation of EP*, GLD*, DCP* and CPD*, and the microbial degradation of C3 halohydrins. In addition, introducing synthetic applications of EP* and GLD* for important chiral pharmaceuticals, natural compounds, liquid crystals and the potentials for synthesis will be discussed.

2. Preparation of EP* and DCP*

Racemic EP is made from 2,3-dichloro-1-propanol (DCP) and 1,3-dichloro-2-propanol, which are provided from propylene in large quantities by the petrochemical industry. The total world production amounted to $>743{,}000$ ton in 1995. It is primarily used in the production of epoxy resins, epoxy rubbers, adhesives, paints and also used as an intermediate in the synthesis of medicines and agrochemicals [5].

For preparation of EP*, the first reliable synthesis from D-mannitol was reported by Baldwin et al. in 1978 [8]. Afterwards, several preparations have been investigated, but EP* was not produced even as a reagent for laboratory use until our microbial resolution was operated on the industrial scale. This EP* is a simple molecule, but the preparation is difficult.

Table 1 shows several typical preparation methods for EP* and the methodology is classified as follows.

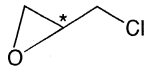
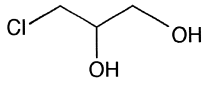
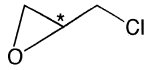
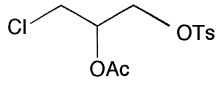
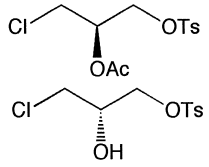
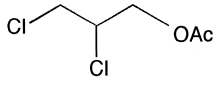
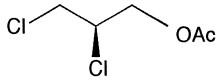
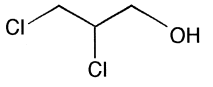
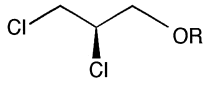
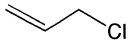
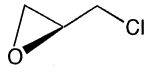
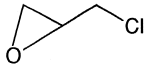
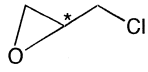
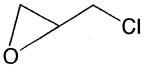
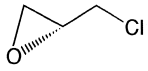
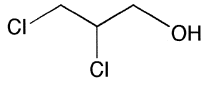
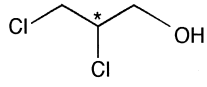
2.1. Synthetic preparation (entries 1 and 2)

Natural products, especially D-mannitol, had been used as a chiral pool for chiral C3 compounds. The method of Baldwin et al. also used D-mannitol. Their report described the first reliable preparation of pure EP* (entry 1) [8]. Ellis et al. reported the separation using diastereomers of camphorquinone derivatives with CPD (entry 2) [9]. These preparations are reliable but require skill and are not practical on a large production scale [10].

2.2. Stereoselective hydrolysis using lipases (entries 3–5)

Lipases are often used to generate chiral alcohols, e.g. by stereoselective hydrolysis or esterification for chiral alcohols [11]. Stereoselective lipase-hydrolysis is effective for resolving compounds of alcohol on asymmetric carbon such as 3-chloro-1-tosyloxy-2-propanol (entry 3) [12]. This chiral derivative of propanol was a important precursor of EP* in Baldwin's synthesis (described in Section 2.1) and the racemate is easily made from EP and *p*-toluenesulfonic acid; the methodology was excellent. On the other hand, Iriuchijima et al. reported the

Table 1
Preparation of EP * and DCP *

Entry	Starting compounds	Obtained products	Methods and the references	optical purity (% ee)	yield (%)
1	D-Mannitol		Organic synthesis [8]	R; >99 S; >99	27
2			Resolution via diastereomer with D-camphor quinone [9]	R; >99 S; >99	26
3			Hydrolysis with lipases [12]	R; >99 S; >99	72
4			Hydrolysis with lipases [13]	S; 90	20
5			Esterification with lipases [14]	R; 67	10.5
6			Microbial oxidation [16]	S; >98 R; 20	
7			Ring opening reaction [18]	R; >98 S; >98	18
8			Stereoselective degradation [19]	R; >98	19
9			Bacterial assimilation [20-22]	R; 100 S; 100	38

asymmetric hydrolysis of 1-acetoxy-DCP (entry 4) [13]. Cambou et al. also tried to prepare optically active DCP esters using stereoselective esterification by lipases (entry 5) [14]. DCP and 1,3-dichloro-2-propanol are mass-produced in the production of industrial racemic EP [5]. DCP is an economical material and the strategies in both reports are interesting, but their yield and optically purity were low. In the case of DCP, the OH group is apart from an asymmetric carbon, thus, the enantioselective hydrolysis was difficult.

2.3. Asymmetric epoxidation (entry 6)

The stereoselective epoxidation of alkenes utilizing microorganisms is well-known [15]; de Bont et al. reported the production of highly pure EP* from allyl chloride using several unique alkene-utilizing bacteria (entry 6) [16]. The ee value of the formed EP* was excellent, however, problems in practical production are that the allylchloride concentration was low and its boiling point was lower than that of water. On the other hand, in the synthetic method, asymmetric epoxidation of olefins by Sharpless oxidation is effective for allyl alcohols to prepare GLD* [17]; however, there are no reports on effective asymmetric epoxidation of allyl chloride.

2.4. Stereoselective ring opening reaction and degradation (entries 7 and 8)

Synthetic and bio-methods were reported, these methods gave a maximum yield of 50%. Jacobsen et al. reported enantioselective epoxy ring opening using a chiral catalyst, (salen)Cr(III) complexes (entry 7) [18]. (*R*)-EP was preferentially opened, but (*S*)-EP was not converted. The ee value was high and various epoxides were applicable. In the bio-method, de Bont et al. reported an enantioselective ring opening reaction using bacteria (entry 8). A high ee value of EP was achieved, but the yield was only 19% [19]. The problem in biological methods seemed that EP has biological toxicity and violent reactivity. For example, a high concentration of EP will cause to aggregation and death of cells.

2.5. Stereoselective degradation of halohydrins (entry 9)

We tried the microbial resolution of DCP using stereoselective assimilation and developed the preparation of EP* (entry 9) [20–22]. As a result, we isolated an (*R*)-DCP-assimilating bacterium, *Pseudomonas* sp. OS-K-29 and a (*S*)-DCP assimilating bacterium, *Alcaligenes* sp. DS-K-S38. These stereoselective DCP-assimilating bacteria are novel and this was the first report of the isolation of optically pure (*R*)- and (*S*)-DCP. The yield was a maximum of 50%; one enantiomer was lost. However, DCP is not expensive, so that this method would be considered simple and practical. We showed that the reactor for the immobilized cells was stable [21] and had attempted to establish industrial scale production. The industrial production by fermentation was established in 1994 in Japan. A more economical production of a higher DCP concentration and with higher degradation activity in the fermentation is important.

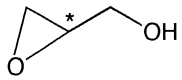
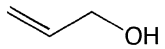
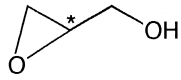
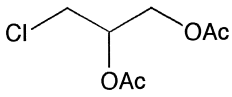
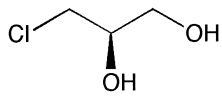
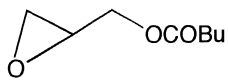
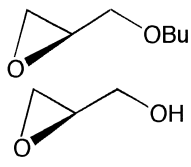
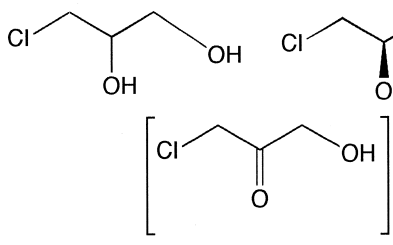
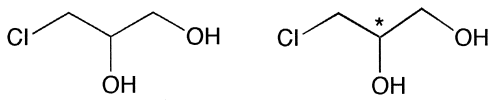
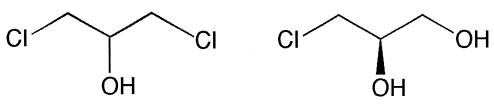
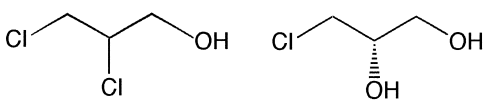
3. Preparation of GLD* and CPD*

GLD (2,3-epoxy-1-propanol) is also an important intermediate as is EP. In practical use, protected or activated GLD derivatives such as glycidyl butyrate and glycidyl tosylate or equivalent precursor such as CPD* are often used, because GLD itself has both an electrophilic epoxy ring and a nucleophilic hydroxy group and is very labile. Therefore, typical methods including these GLD* derivatives and CPD* are shown in Table 2.

3.1. Synthetic preparation (entries 1 and 2)

GLD* was synthesized by Fischer et al. from D-mannitol in 1942 [23] (entry 1). Chemical syntheses of CPD* from methyl 6-chloro-6-deoxy-α-D-glucopyranoside [24] and methyl 5-chloro-5-deoxy-α-L-arabinofuranoside [25] were reported. These reports were important as authentic preparations of GLD* and CPD* but were not practical.

Table 2
Preparation of CPD* and GLD*

Entry	Starting compounds	Obtained products	Methods and the references	Optical purity (%ee)	yield (%)
1	D-Mannitol or Sugar		Organic synthesis [23-25]	R; >82 S; >87	94 52
2			Sharpless Oxidation [17, 26]	R; 91 S; 91	65
3			Hydrolysis with lipase [27]	R; 90	20
4			Hydrolysis with lipase [28]	R; 96-98	90
5			Bacterial reduction [29]	R; >99	40
6			Microbial resolution [30-32]	R; >99 S; >99	40-45
7			Microbial conversion with halohydrin-hydrogen-halide-lyase [33,34]	R; 83.8	97.3
8			Bacterial degradation [20]	S; 90	-

Sharpless asymmetric oxidation is a famous process and is applicable for the manufacture of GLD* (entry 2) [17]; the commercial production was first established by Arco Chemicals. The (*R*)- and (*S*)-GLD* are prepared using Ti complex catalysts with D- or L-diisopropyl tar-

trate and cumene hydroperoxide. However, the optical purity is low (91% ee) [26] and GLD* itself is labile, so that GLD* tosylate would generally be used (97% ee).

3.2. Stereoselective hydrolysis using lipases (entries 3 and 4)

Iriuchijima et al. also reported asymmetric kinetic resolution of 1,2-diacetoxy-3-chloropropane using lipases [27]. The strategy was the same as in the case of DCP*; both the optical purity and the yield were low (entry 3).

Optically active (*R*)-glycidyl butyrate was resolved using porcine pancreatic lipase. The original method was reported by Whiteside et al. (entry 4). Andeno-DSM established the commercial production of (*R*)-glycidyl butyrate. The optical purity and the yield were also comparatively good; however, the only product was the (*R*)-form [28]. The by-product of the optical purity of (*R*)-GLD was low, it was not useful.

3.3. Stereoselective degradation of halohydrins (entries 5–8)

Stereoselective metabolites or degradation by microorganisms has been used to resolve CPD. Hasegawa et al. (entry 5) [29] reported bacterial stereoselective conversion of CPD using the resting cells; (*S*)-CPD was converted to (*S*)-mercapto-1,2-propanediol and the residual (*R*)-CPD was obtained. We found stereoselective degradators of CPD by screening with (*R*)- and (*S*)-CPD from (*R*)- and (*S*)-EP and several desired (*R*)- and (*S*)-CPD-assimilating bacteria were isolated; highly pure (*R*)- and (*S*)-CPD were obtained and (*R*)- and (*S*)-GLD were easily prepared [30–32]. The principal fermentative conditions are the same as that for stereoselective DCP-assimilating bacteria. The industrial production is currently in operation in our plant (entry 6). The method of microbial stereoselective epoxidation and epoxy ring opening was reported by Nakamura et al. (entry 7). The enzyme in this method was novel; they designated it halohydrin–halide-lyase. The starting material was easy to obtain and the yield was comparatively good. However, the optical purity was low and the only enantiomer obtained was the (*R*)-form [33,34]. Our stereoslective DCP-assimilating bacteria also gave (*S*)-CPD from DCP (entry 8) [20]. CPD has higher solubility and lower biological toxicity than DCP. These characteristics of CPD make it easy to use in biological methods.

3.4. Resolution using GC

Physiochemical resolution with GC or HPLC is difficult for practical preparation of optically active EP* and GLD*, but it is effectively used in analysis. Several reports showed that gas chromatography using a capillary column coated with an chiral metal complex or a chemically-modified cyclodextrin is very effective in the analysis of EP* [35] and GLD* [36], respectively. Reliable analysis of highly pure EP* or GLD* is supported by these GC methods; these analyses are essential for aiding the studies of production. The analysis of NMR with shift reagents is difficult to estimate exactly.

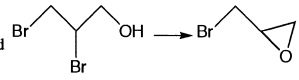
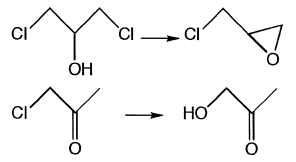
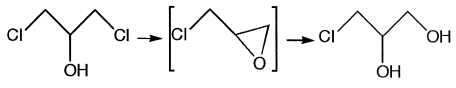
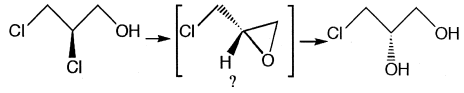
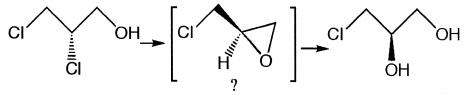
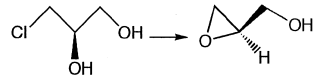
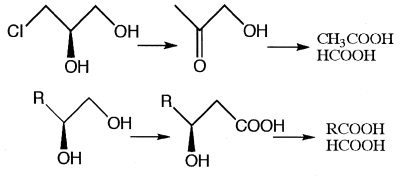
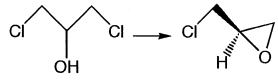
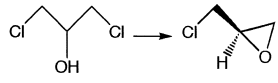
4. Microbial dehalogenation of C3 halohydrins

In this session, we would like to introduce microbial dehalogenating enzymes acting on C3 halohydrins which are practical precursors of EP and GLD. The production amounts of propylene, which is a worldwide fundamental C3 compound, was estimated to be 11,560 thousands tons in 1995 [37]. It is noteworthy that C3 non-halogenated and halogenated compounds, e.g. propylene oxide and EP, respectively, have been mass-produced from propylene on an industrial scale. Interestingly, synthetic glycerol is

made from EP via CPD with hydration, and propylene glycol, which is known as a food additive, is made from propylene oxide. These compounds are very important not only as petroleum chemicals in chemical industries but also are familiar ones for daily life. On the other hand, from this background, a large number of studies on biological degradation of chemical compounds have been done. In particular, the microbial degradation of halogenated compounds has been extensively investigated. Recently, there have been many reports concerning the microbial degradation of low molecular weight halogenated aliphatics and dehalogenating enzymes [7]. The enzymatic dehalogenation of haloacids [38–41], halo alkanes [42–46] and dichloromethane [47,48] is well-known. Most of all, halo acid dehalogenases have been examined in detail for many years. For example, the 2-halo acid dehalogenases are found to be classified into four groups based on their substrate specificities and reactions [49–52]. With respect to the enzymes dehalogenating halogenated alcohols, some have been reported [7].

The properties, the substrate specificities and the action modes of C3 halohydrin dehalogenating enzymes are summarized in Table 3. There are nine entries of dehalogenation; non stereoselective ones are shown in entries 1–3 and stereoselectives in entries 4–9, especially, in entries 4–7 our studies are described. Formerly, Castro and Bartnicki reported the bacterial degradation of 2,3-dibromo-1-propanol (DBP) by *Flavobacterium* sp. [53]. This enzyme, halohydrin epoxidase, exhibited dehalogenating action for halohydrins having a vicinal halide atom and a hydroxyl function and gave the corresponding epoxide (entry 1). In the bioprocess for production of propylene oxide, this epoxidase and chloroperoxidase from *Caldariomyces fumago* were well-known as key enzymes [54,55]. They were very remarkable in the Cetus project, in which production of propylene oxide from propylene via halohydrin using these enzymes was planned and studied [56]. In general, the lack of stereoselectivity of epoxidase [53] and haloperoxidases such as chloroperoxidase and bromoperoxidase [57–59] has been widely reported. Recently, the group of Janssen et al. isolated three bacteria capable of growing on 1,3-dichloro-2-propanol, EP and CPD, and purified the haloalcohol dehalogenase from the strain, *Arthrobacter* sp. AD2 [6,60]. This enzyme catalyzed the conversion of halogenated alcohols such as 1,3-dichloro-2-propanol, 1,3-dibromo-2-propanol, CPD, 1-chloro-2-propanol and 1-bromo-2-propanol to the corresponding epoxides. In addition, chloroacetone and 1,3-dichloroacetone were also dehalogenated (entries 2,3). Moreover, Janssen et al. reported the primary structure and reaction mechanism of epoxide hydrolase from *Pseudomonas* sp. AD1 [61,62]. Studies on microbial dehalogenation by Castro et al. and Janssen et al. have started from the standpoint of environmental pollution [63]. For an application in this field, Bull and Hardman developed a bioprocessing system removing DCP and CPD from cationic polymer in a paper manufacturing process [7,64]. Thus, it did not matter that whether or not the dehalogenation proceeded with stereoselectivity. In contrast, we have been seeking microorganisms stereoselectively dehalogenating halohydrin for the biotransformation of halogenated compounds to optically active ones. We selected DCP and CPD as target halohydrins because they were practical and economical precursors of EP and GLD, respectively, and then succeeded in the isolation of some bacteria stereoselectively assimilating DCP and CPD [20–22,30–32]. Microbial dehalogenases with stereoselectivity for D- and L-2-halo acids already have been studied; their dehalogenating mechanisms and genes have been investigated in detail [65–68]. However, there have been no reports on stereoselective dehalogenation and assimilation of halohydrins by microorganisms. So far, the preparation of (*R*)- and (*S*)-DCP (100% ee) using bacterial resolution followed by the conversion of optically active EP ($>$ 99% ee) by alkaline treatment of aqueous NaOH was the first report [20–22]. Based on detailed enzy-

Table 3
Profiles of C3 halohydrins dehalogenating enzymes

Entry	Origine	Characterization of dehalogenation [Reference]	Molecular mass	Typical reaction mode for dehalogenation	Characterization of substrate specificity [1)]
1	*Flavobacterium* sp.	Halohydrin epoxidase: [53]	Not shown; partially purified		DHP : + DH2P : + HPD : + H2P : + H3P : – DCA : – CA : – AD : –
2	*Arthrobacter* sp.	Haloalcohol dehalogenase: [6, 60]	65-69kDa; dimer, 29kDa		DHP : – DH2P : + HPD : + H2P : + H3P : – DCA : + CA : + AD : –
3	*Pseudomonas* sp.	Haloalcohol dehalogenase: [6]	Not shown; partially purified		DHP : – DH2P : + HPD : + H2P : + H3P : – DCA : + CA : + AD : –
4	*Pseudomonas* sp.	Halohydrin dehalogenase: [20]	Not shown; partially purified		DHP : + DH2P : + HPD : + H2P : – H3P : – DCA : – CA : – AD : –
5	*Alcaligenes* sp.	Halohydrin dehalogenase: [22]	Not shown; partially purified		DHP : + DH2P : + HPD : + H2P : + H3P : – DCA : – CA : – AD : –
6	*Pseudomonas* sp.	Halohydrin dehalogenase: [30, 31]	Not shown; partially purified		DHP : + DH2P : + HPD : + H2P : + H3P : – DCA : – CA : – AD : –
7	*Alcaligenes* sp.	Halohydrin dehydro-dehalogenase: [30, 32, 71, 72]	70kDa; dimer, 14kDa and 58kDa		DHP : + DH2P : + HPD : + H2P : + H3P : – DCA : – CA : – AD : +
8	*Corynebacterium* sp.	Halohydrin hydrogen-halide lyase: [33, 75]	a.108kDa; tetramer, 28kDa b. 115kDa; tetramer, 35kDa and 32kDa		a b DHP : – : + DH2P : + : + HPD : + : – H2P : – : – H3P : – : – DCA : – : – CA : – : – AD : – : –
9	*Escherichia coli* containing the gene from *Corynebacterium* sp.	Halohydrin hydrogen-halide lyase: [33, 34]	105kDa; tetramer, 28kDa		DHP : – DH2P : + HPD : + H2P : + H3P : – DCA : – CA : – AD : –

1) DHP, 2,3-Dihalogeno-1-propanol; DH2P, 1,3-Dihalogeno-2-propanol; HPD, 3-Halogeno-1,2-propanediol; H2P, 1-Halogeno-2-propanol; H3P, 1-Halogeno-3-propanol; DCA, 1,3-Dichloroacetone; CA, Chloroacetone; AD, Alkane-1,2-diol.
Symbols show degrading activity for various substrates; +, degradable; –, non-degradable.

matic studies, we proposed the possible assimilation routes in which DCP and CPD were degraded into glycerol through the corresponding epoxides [20,22,30–32]. Furthermore, we reported the effective preparation of chiral C4 halohydrins such as optically active 4-chloro-3-hydroxybutyronitrile and 4-chloro-3-hydroxybutyrate with resting cells of these (*R*)- and (*S*)-DCP-assimilating bacteria [69,70].

More detailed studies on the stereoselectively dehalogenating enzymes for DCP and CPD are in progress (entries 4–6). The structures of (*R*)- and (*S*)-DCP are substantially similar to those of D- and L-2-chloropropionic acid, because they are C3 compounds having a chlorinated chiral center in the C2 position. A different point is that DCP has a hydroxy group instead of a carboxylic one in the C1 position. Thus, comparative studies on their dehalogenating mechanisms or genes encoding each dehalogenase would be quite interesting. More recently, we succeeded in purification of a novel type of dehalogenating enzyme designated as halohydrin dehydro-dehalogenase (HDDase) (entry 7) from *Alcaligenes* sp., one of the (*R*)-CPD assimilating bacteria. HDDase was involved in oxidative dehalogenation in the presence of electron acceptors such as NAD^+, phenazine methosulfate (PMS) and 2,6-dichloroindophenol (DCIP) [71,72]. Interestingly, this dehalogenating enzyme exhibited stereoselectively dehydrogenating activity for alkane-1,2-diols as well as for halohydrins (entry 7) [72]. Therefore, we could apply this catalyzing action to obtain (*R*)-alkane-1,2-diols (Table 4). In the case of using resting cells, the activity was considerably stable so that repeated resolution reaction was carried out 8 times within 200 h [73].

Also, Nakamura et al. isolated the bacterium, *Corynebacterium* sp. N-1074, which had the activity to convert 1,3-dichloro-2-propanol into (*R*)-CPD via EP [33]. This dehalogenation exhibited stereospecificity so that preparation of (*R*)-CPD showed an optical purity of 83.8% ee in a high yield of 97.3% [74]. In this dehalogenation, four kinds of enzymes were purified from this strain and found to be involved in the above reaction [75], that is, two kinds each of the dehalogenating enzymes and epoxy opening enzymes. One of the dehalogenating enzymes is designated as halohydrin–halide-lyase, which converted 1,3-dichloro-2-propanol to (*R*)-EP, and the gene encoding this halohydrin–halide-lyase was found to be expressed in *Escherichia coli* (entries 8, 9) [34].

As shown above, we reviewed the microbial dehalogenation of C3 halogenated compounds. At first, microbial dehalogenation was considered only as a technology for removing environmental pollution, and a number of research stud-

Table 4
Preparation of optically active halohydrins and 1,2-diols by enzymatic resolution

Substrate[a]	Optical purity (% ee, configuration)	Residual substrate (%)[b]
1,2 Propanediol	60.0 (*R*)	42.3
1,2-Butanediol	97.5 (*R*)	48.2
1,2-Pentanediol	98.2 (*R*)	50.2
1,2-Hexanediol	98.2 (*R*)	50.0
1,2-Dihydroxy-3-butene	98.0 (*R*)	49 1
1,2-Dihydroxy-5-hexene	98.3 (*R*)	40 1
1-Phenyl-1,2-ethanediol	95.1 (*R*)	39.5
CPD	98.5 (*S*)	50.2
3-Bromo-1,2-propanediol	98.5 (*S*)	49.3
DCP	99.0 (*R*)	46.2
DBP	99.0 (*R*)	48.1

[a] Racemic forms were used as a substrates.
[b] At initial time, each reaction solution contained 0.2% (v/v) of substrate.

Notes to Table 3:
[a] DHP, 2,3-dihalogeno-1-propanol; DH2P, 1,3-dihalogeno-2-propanol; HPD, 3-halogeno-1,2-propanediol; H2P, 1-halogeno-2-propanol; H3P, 1-halogeno-3-propanol; DCA, 1,3-dichloroacetone; CA, chloroacetone; AD, alkane-1,2-diol.
Symbols show degrading activity for various substrates; +, degradable; −, non-degradable.

ies have been done based on the concept of environmental cleaning. Today, as more studies on regio- and stereo-selective dehalogenation and halogenation by microorganisms and enzymes are progressing, the application fields are becoming larger. Actually, the chiral C3 units we developed are effective during syntheses of some kinds of chiral pharmaceuticals and new materials; microbial resolution of C3 halohydrins based on stereoselective dehalogenation is considered to be a practical technology for the production of EP*, CPD* and GLD*.

5. Synthetic applications

Chiral C3 units shown in Fig. 1, that are EP* (1), GLD* (2), DCP* (3) and CPD* (4), have simple structures and the various transformations are possible. Here, we would like to introduce our synthetic applications mainly employing EP*. EP* has a reactive epoxy ring and a chlorine atom in the molecule and it works as an electrophilic reagent with a good regioselectivity. The nucleophile attacks first the C3 carbon atom of the epoxy ring and then the another neucleophile attacks the C1 carbon atom. Therefore, two kinds of nucleophile can be introduced regioselectively, stepwise to afford optically active secondary alcohol (Fig. 2). We introduce the reactions of EP* with some nucleophiles and their applications. Firstly, the typical applications of oxygen, and sulfur nucleophilic reactions; alcohols, phenols and thiols regioselective reaction with EP* are described.

5.1. Optically active O-benzyl glycidyl ether

Optically active *O*-benzyl glycidyl ether (6) is a useful synthon in organic synthesis due to

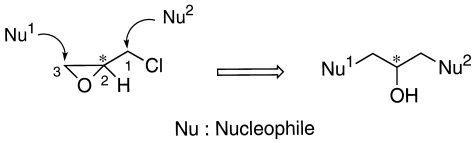


Fig. 2. Reactivity of epichlorohydrin.

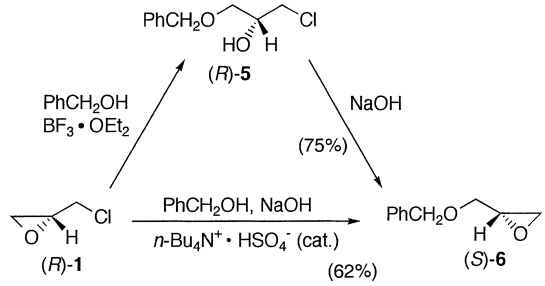


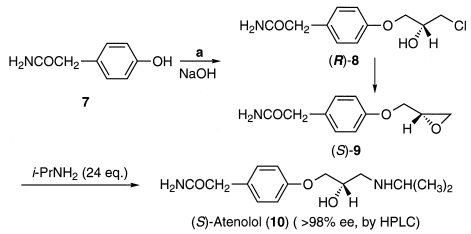
Fig. 3. Synthesis of optical active *O*-benzyl glycidyl ether.

the bulkiness of benzyl group and its easy deprotection [76]. Although the preparation of 6 using D-mannitol as a starting material has been known [77], Takano and Ogasawara have developed a more practical preparation from EP* in a short step [78] (Fig. 3). In the presence of a catalytic amount of BF_3-etherate, treatment of (*R*)-1 with benzyl alcohol affords chlorohydrin (*R*)-5 followed by treatment with sodium hydroxide to give (*S*)-6. With a catalytic amount of *n*-Bu_4NSO_4 and sodium hydroxide as a base, benzyl alcohol reacts with the epoxide group followed by elimination of the chloride ion to give (*S*)-6. The specific rotations of the products obtained were higher than that prepared from D-mannitol; acidic conditions, $[\alpha]_D^{22}$, -1.94 ($c = 5.34$, $CHCl_3$); basic conditions, $[\alpha]_D^{22}$, -2.12 ($c = 4.61$, $CHCl_3$) (lit., $[\alpha]_D^{22}$, -1.79 ($c = 5.02$, $CHCl_3$). These methods were thus shown to be simpler, more practical and more reliable.

The convenient synthesis of platelet-activating factors (PAF) has been reported from EP* and *p*-methoxybenzyl alcohol [79].

5.2. (S)-Atenolol

Racemic atenolol is one of the β-adrenergic blocking agents which are antiarrhythmic and antihypertensive drugs. The (*S*)-isomer has recently attracted much attention in avoiding the occasional side effect of lowered heart rate which is sometimes encountered with the race-



condition a	(S)-9 yield(%)	optical purity(% ee)	(S)-9 yield*(%)	optical purity*(% ee)
(R)-1, 45°C, 5h	80	77	50	80
(R)-1, 17°C, 8h	67	91	59	98
(R)-1, 5°C, 24h	78	96	60	99
(R)-1, BTA, 5°C, 28h	95	97	75	99

BTA = Benzyl trimethyl ammonium chloride
* = isolated yield after recrystallization

Fig. 4. Synthesis of (*S*)-atenolol.

mate [80]. We found that the practical preparations of (*S*)-atenolol (10) from (*R*)-1 [81]. Treatment of *p*-carbamoylmethylphenol 7 with 1.1 eq of (*R*)-1 in the presence of 1.0 eq of sodium hydroxide affords a mixture of (*S*)-1-[*p*-(carbamoylmethyl)phenoxy]-2,3-epoxypropane (9) and (*R*)-1-[*p*-(carbamoylmethyl)phenoxy]-3-chloropropane-2-ol (8) (Fig. 4). The mixture, without separation, was reacted with a further 0.3 eq of sodium hydroxide to give 9 in 67 to 78% conversion. As the reaction proceeds, 9 is precipitated and the precipitated crystals have optical purities of 91 to 96% ee. Enantiomerically pure 9 was obtained by recrystallization from methanol (3 times) to give 98% ee or higher. Moreover, employment of phase-transfer conditions by adding BTA (benzyl trimethylammonium chloride) results in 95% conversion. When the reaction temperature is higher than 5°C, racemization occurs and 9 reacts with the sodium salt of starting 7 to produce side reaction products.

The intermediate glycidyl ether 9 obtained after recrystallization can be easily converted into the desired enantiomerically pure (*S*)-atenolol (10) by reacting with 24 molar eq of isopropylamine in 90% yield and better than 98% ee.

5.3. γ-Lactone for ferroelectric liquid crystal

Ferroelectric liquid crystal (FLC) was discovered in 1975 [82], and it was proposed in 1980 that a display device which has fast switching characteristics of microsecond order and a memory function would be possible with FLC [83]. The FLC must have an asymmetric center in the molecule.

Optically active 2,4-substituted γ-lactone derivatives were found to be useful compounds as the FLC molecules [84,85]. These γ-lactone derivatives were prepared from EP*. EP* was allowed to react with phenol derivative (11) under basic conditions to give optically active epoxide (12) followed by the reaction with malonic ester to form lactone ring [86]. The diastereomers of *cis*-(13) and *trans*-(13) were easily separated with silica gel column chromatography (Fig. 5).

One of the *cis*-lactones thus obtained was found to have the biggest spontaneous polarization in 1992 [87,88]. The spontaneous polarization is a physiological characteristic of the FLC. The bigger the spontaneous polarization is, the faster the switching would possibly be theoretically. In fact, there was a very fast-switching

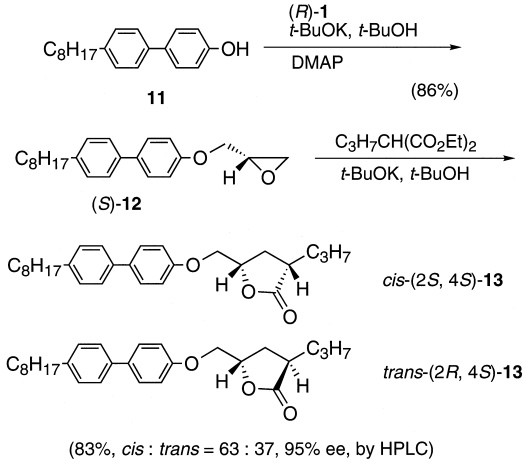


Fig. 5. Synthesis of γ-lactone compounds for FLC.

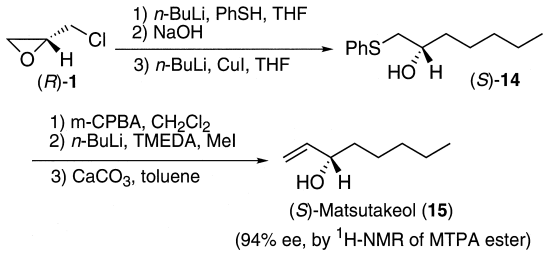


Fig. 6. Synthesis of Matsutakeol.

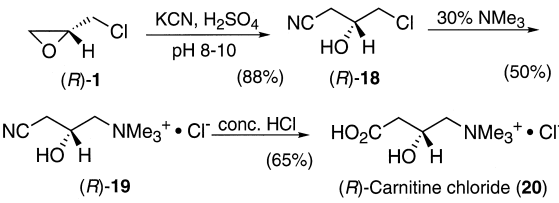


Fig. 8. Synthesis of (*R*)-carnitine from (*R*)-EP.

FLC containing only 2% of one of these *cis*-lactones.

5.4. (S)-Matsutakeol

EP* also reacts regioslectively with sulfur nucleophiles. As one of the examples, the synthesis of (*S*)-matsutakeol has been reported. That is, the reaction of EP* with phenyl sulfide, alkylation, oxidation to the sulfoxide, methylation and basic treatment were subsequently carried out to give (*S*)-matsutakeol (15) (Fig. 6) [89].

6. Carbon nucleophile reactions

Second applications are carbon nucleophile reactions; reactions of EP* with alkali cyanide, alkyl and alkenyl Grignard reagents and aryl metal reagents are shown in this part.

6.1. (R)-Carnitine (β-hydroxyamino acid)

3,4-Epoxybutyronitrile (16), which would be formed in the reaction of EP* with potassium cyanide under basic conditions easily decomposes to allyl alcohol (17) (Fig. 7) [90]. Therefore, in order to avoid this conversion, the reaction was carried out at pH 8 to 10 by controlling by the simultaneous additions of sodium cyanide solution and sulfuric acid. The (*R*)-18 could be converted to (*R*)-carnitine chloride (20) by treatment with trimethylamine and hydrolysis (Fig. 8) [91]. Later, we found a more efficient process in which the nitrile group and amino group were introduced in one pot (Fig. 9) [92]. This reaction was achieved by the additions of trimethylamine and acetone cyanohydrin simultaneously into EP* solution. According to the absolute configuration, the more reactive trimethylamine reacted with the epoxide first. Therefore, the configuration of the starting EP is the reverse of that of the EP used in the previous method.

Aryl lithium also reacts with EP* in the presence of CuCN regioselectively to give 1-chloro-2-hydroxy-3-arylpropane. This reaction was useful for the synthesis of (*R*)-4-amino-3-hydroxybutanoic acid (GABOB) [93].

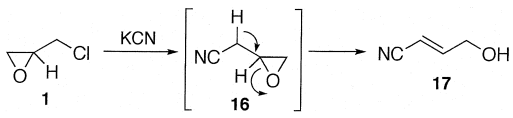


Fig. 7. Decomposition of cyanhydrin.

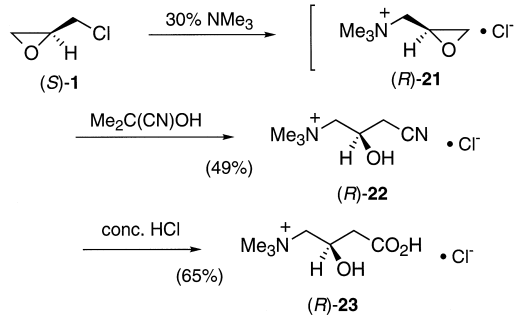


Fig. 9. Synthesis of (*R*)-carnitine from (*S*)-EP.

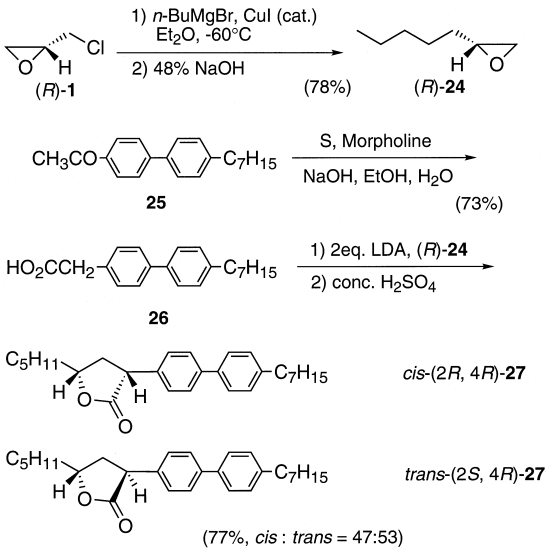


Fig. 10. Synthesis of γ-lactone compounds for FLC using Grignard reagent.

6.2. γ-Lactone for ferroelectric liquid crystal using Grignard reagent

A γ-lactone derivative bearing an aryl group at the C2 position was also synthesized from EP* (Fig. 10) [94]. The reaction of EP* with alkyl Grignard reagent in the presence of a catalytic amount of CuI followed by treatment with a base gave an alkyl epoxide (24). The alkyl epoxide thus obtained was allowed to react with the dianion of phenylacetic acid derivative (26) followed by treatment with conc. H_2SO_4 to afford the desired γ-lactone (27).

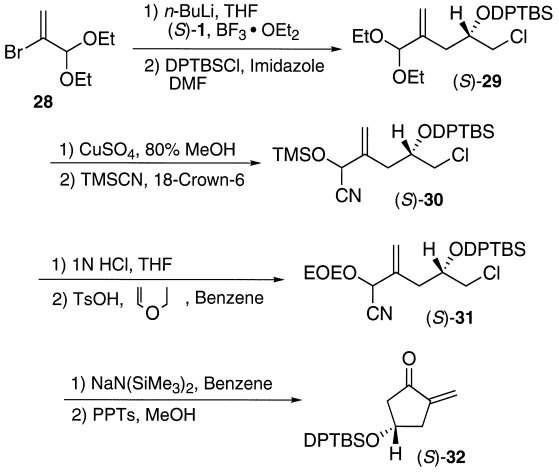


Fig. 11. Synthesis of cyclepentanone derivatives.

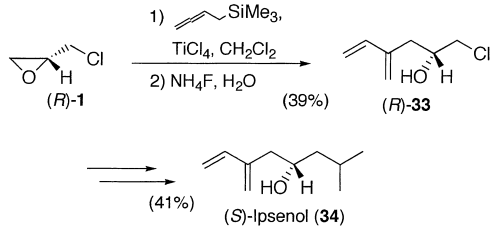


Fig. 12. Synthesis of (S)-ipsenol.

6.3. Cyclopentanone derivatives

Vinyl lithium reagent also reacted regioselectively with EP* in the presence of a Lewis acid. The synthesis of cyclopentanone derivatives (32), an intermediate for prostaglandin syntheses, has been reported (Fig. 11) [95].

6.4. Others

Allyl silane can react regioselectively with EP* in the presence of a Lewis acid. (S)-Ipsenol (34), a beatle pheromone, was synthesized effectively in short steps (Fig. 12) [96].

Usually a nucleophile attacks the C3 carbon of EP and does not attack the C2 carbon. However, if the nucleophile has another nucleophilic center in the molecule, after the first addition to the C3 carbon, the nucleophile can attack the C2 carbon to form ring systems (Fig. 13). An example carried out by Carreira et al. is shown in Fig. 14 [97]. They have accomplished total synthesis of (+)-Trehazolin (38), a potent inhibitor of glycosidases from EP*. First of all,

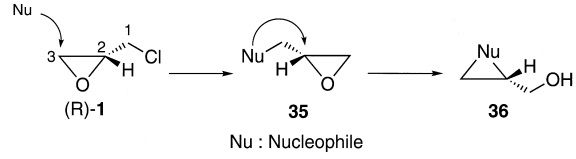


Fig. 13. Synthesis of bicyclic systems.

optically active spirocycloheptadiene (37) was prepared by the treatment of (*R*)-1 with lithium cyclopentadiene. This key precursor was converted to the aminocyclopentiol moiety of Trehazolin.

7. Application of optically active GLD

CPD* (4) is easily convertible to GLD* (2) by treatment with a base without racemization. Therefore, CPD* is a synthetic equivalent of GLD* itself. Since GLD* was prepared by Sharpless asymmetric epoxidation, it has been widely used in organic synthesis [4]. Sharpless asymmetric epoxidation is quite elegant and it is a breakthrough in the industrial production of optically active C3 building blocks. However, the optical purity of GLD* is slightly low, namely, 90% ee. On the other hand, the optical purity of the precursor for GLD*; CPD* which is prepared by our method is more than 98% ee. As a result, the compounds derived from this chloropropanediol have excellent enantiomerically high purities. For example, optically active glycidyl *p*-toluenesulfonate, which is a useful synthetic intermediate is easily obtained from CPD* in more than 98% ee.

The chemistry and various applications of GLD* have already been reported in many publications [98]. Recent application to 4-hydroxymethyl-2-oxazolidinone is shown in Fig. 15. Optically active 4-hydroxymethyl-2-oxazolidinone as an optically active serinol synthon was synthesized from GLD* in a short step. The GLD* was allowed to react with benzyl isocyanate in the presence of triethylamine to give *N*-benzyloxazolidinone (*S*)-39 in one step. The reaction of GLD* with benzoyl isocyanate followed by treatment with potassium carbonate in the presence of a quaternary ammonium salt gave the compound (*R*)-41 in which the benzoyl group was rearranged from the nitrogen of the amide to a hydroxyl group without isomerization of the oxazolidinone ring [99].

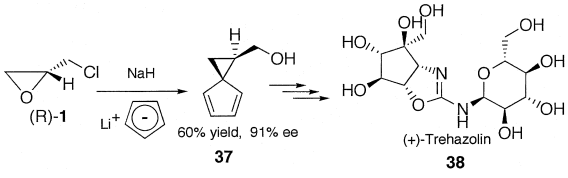


Fig. 14. Synthesis of (+)-trehazolin.

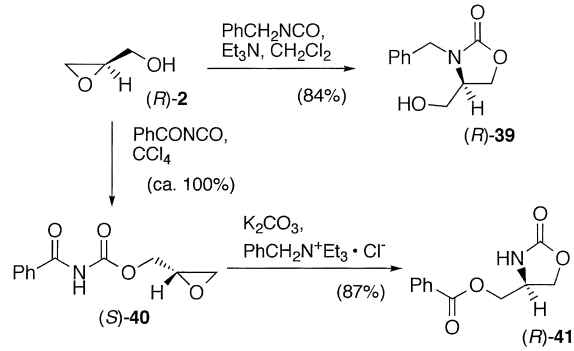


Fig. 15. Synthesis of 4-hydroxymethyl-2-oxazolidinone.

8. Results

In this paper, we reviewed preparations of EP*, GLD* and CPD*, microbial degradation of C3 halogenated compounds and their applications for synthesis. In the past two decades, a number of researches on the preparation and analysis of chiral compounds have been carried out and some practical methods have been tested. On the other hand, halogenation, dehalogenation and epoxidation by microorganisms and their enzymes have been studied in the environmental field and these will be applicable to organic synthesis in the near future. Further studies are being carried out in fields such as pharmacy, agrochemistry, organic chemistry, physiology, electronics and the next new applications are also in progress. Although biological and organic synthetic studies compete in making optically active compounds, they should principally adjoin each other.

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