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Exploration of chiral induction on epoxides in lipase-catalyzed epoxidation of alkenes using (2*R*,3*S*,4*R*,5*S*)-(–)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate

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ABSTRACT

Epoxidation of alkenes by peracid, generated in situ from (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate [(−)-DIKGA] and hydrogen peroxide by lipase catalysis induces chirality on the product epoxides with moderate to good enantioselectivity (35–71%). Alkoxy/aralkyloxy styrenes however did not undergo any epoxidation. (*R*)-(+)-4-Hydroxy styrene-7,8-oxide was formed and isolated with moderate enantiomeric excess (57%) but was found to have poor stability.

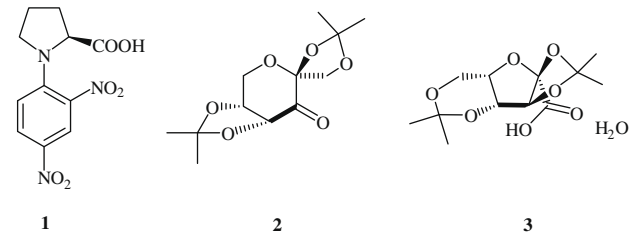
1. Introduction

Epoxides are very important synthetic intermediates for a variety of biologically active and synthetic molecules such as β-amino alcohols[1] used as β-blockers, antibiotics,[2] neuroprotective agents,[3] antidepressents,[4] as well as other natural and clinical products. Chiral epoxides whether produced from alkenes or other sources have the same advantages as electrophilic intermediates for stereochemical synthesis involving reactions with nucleophiles.

With regard to the stereoselectivity, although the problem has been solved by the formation of enantiomerically pure epoxides from achiral alkenes using various metal catalyst,[5] the more environmentally desirable organic molecule that catalyzed the formation of epoxides is not as abundant.[6] Following the pioneering work of Bjorkling et al.,[7] the use of a lipase in epoxidation reactions of alkenes by peracid generating in situ from a suitable acid and a peroxide, has become a valuable addition to the synthetic repertoire. Also this method is one of the chalked out area for further exploration in the Round table of the ACS and several leading global pharmaceutical industries meet held during 2005.[8]

In our original protocol,[9] the use of a chirality inducer *N*-2,4-dinitrophenyl-L-proline **1** (Fig. 1) to prepare chiral epoxides with 70–81% enantiomeric excess through lipase-catalyzed formation was reported. The approach can be used in the efficient synthesis of members of a large family of chiral intermediates without the need to design custom chiral synthesis for each new compound. However, the highly associative nature of this intensely yellow coloured chiral acid with the products detracted our interest to look for an alternative in order to prepare a few chirally pure epoxide intermediates of pharmaceutical value.

Chiral ketones, in particular the carbocyclic analogues of fructose[10] **2** (Fig. 1) have been reported to be effective organocatalysts for the asymmetric epoxidation of *cis*- and *trans*-alkenes through formation peroxo ketone **4** with oxone (Scheme 1).



1 2 3

Figure 1. *N*-2,4-Dinitrophenyl-L-proline **1**, 1,2:4,5-di-*O*-isopropylidene-β-D-erythro-2,3-hexodiulo-2,6-pyranose **2** and (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate [(−)-DIKGA] **3**.

A major disadvantage of this expensive organocatalyst is its simultaneous decomposition through the Baeyer–Villiger oxidation in the reaction with oxone. A similar molecule in the natural chiral pool is the carbohydrate (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate [(−)-DIKGA)] **3** and has been reported[11] for use in the resolution of various important racemic amines. The molecule is less expensive than **2** and until now, the catalytic activity of it as an oxygen carrier from different oxygen sources via peracid formation to alkenes in the epoxidation reactions and its ability for chiral induction in products have not yet been explored.

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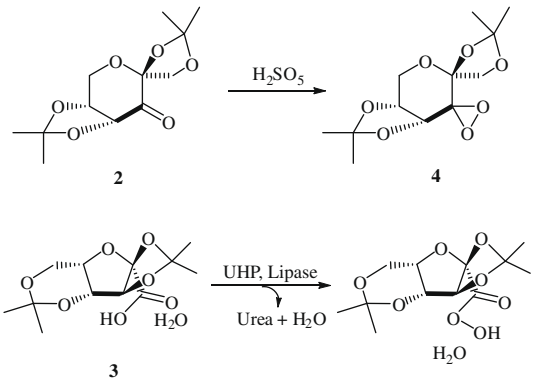
2. Results and discussion

This molecule was chosen[11] as a chiral oxygen transferring agent to alkenes through lipase-based peracid formation using *Candida antarctica B* in its immobilized form (*Novozyme* [*435*]) in order to prepare three industrially very important intermediates, (*R*)-4-alkoxystyrene-7,8-oxide **5** for (*R*)-(−)-denopamine- a selective β*1*-adrenoreceptor agonist, effective against refractory vasospastic angina pectoris, (2*R*,3*R*)-epoxybut-1-ol **6b**, an intermediate for a macrolide antibiotic erythromycin, 2*S*,3*S*-epoxy-2-methylpentan-1-ol **8**, another intermediate for a macrolide antibiotic methymycin (Fig. 2).

The main reason for the synthetic importance of epoxide intermediates for these drugs is the economic and environmental requirement of reducing the number of steps during synthesis.

The necessity of the gradual addition of aqueous hydrogen peroxide to the reaction mixture over several hours in the original protocol, in order to avoid enzyme deactivation, has been overcome by using the adduct of urea and hydrogen peroxide (UHP) that has the potential to release the oxidant in a controlled manner.[12]



Scheme 1.

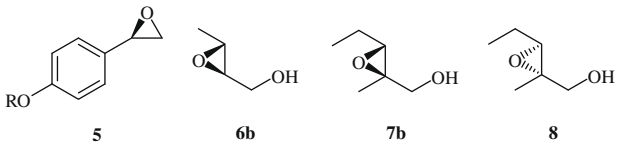


Figure 2.

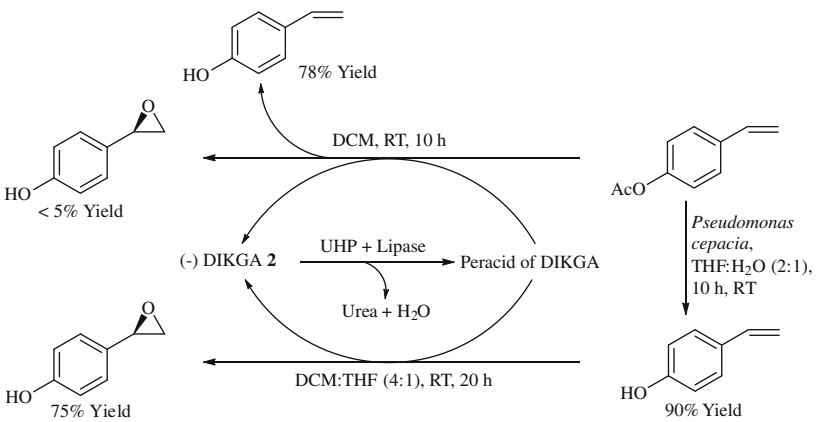
As proposed, three alternative styrene derivatives, 4-acetoxy styrene, 4-benzyloxy styrene and 4-methoxy styrene, were taken as substrates initially to synthesize the configurationally desired styrene oxide for (*R*)-(−)-denopamine. The peracid of (−)-DIKGA was generated in situ by treatment with UHP in the presence of lipase at 0–5 °C in a dichloromethane and tetrahydrofuran mixture in a 4:1 ratio and then after about 1 h, 4-acetoxy styrene was added. A problem was however encountered with the substrate due to parallel lipase-catalyzed hydrolysis of it to 4-hydroxy styrene **2a**. 4-Methoxy styrene and 4-benzyloxy styrene did not turn up to give any product under the reaction conditions.

Taking the 4-hydroxy styrene obtained by the lipase hydrolysis (using *Pseudomonas cepacia* for better yield) of 4-acetoxy styrene, the reaction was carried out for about 20 h, whereby (*R*)-(−)-4-hydroxystyrene-7,8-oxide **2b** was furnished in good yield (Scheme 2). It could also be isolated immediately by filtration under cold condition and thus characterized after purification from its NMR (^{1}H and ^{13}C), IR and mass spectroscopic data. The product isolated was found to undergo rapid decomposition at room temperature. From the specific rotation data and HPLC analysis of 4-hydroxy styrene-7,8-oxide on a chiral column, the configuration has been found to be (*R*) with an enantiomeric excess of 57% (Table 1).

Under identical reaction condition, the reaction of 2-methylpent-2-en-1-ol, however, gave (2*R*,3*R*)-epoxy-2-methylpent-1-ol **7b** instead of (2*S*,3*S*)-epoxy-2-methylpent-1-ol **8** with 71% ee. On the other hand, but-2-en-1-ol obtained by the reduction of but-2-en-diethylacetal by a novel bimetal redox system[13] under lipase-catalyzed epoxidation with UHP and (−)-DIKGA yielded (2*R*,3*R*)-epoxy but-1-ol in 35% enantiomeric excess as determined from its specific rotation data and HPLC chiral column analysis. The other epoxides from the corresponding styrene derivatives were prepared in an analogous manner.

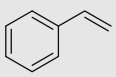
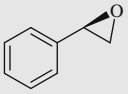
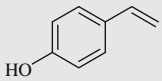
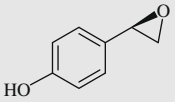
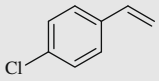
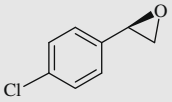
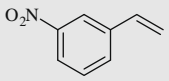
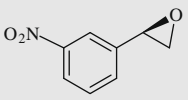
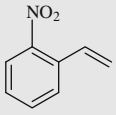
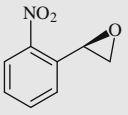
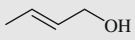
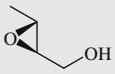
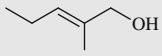
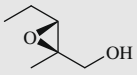
2.1. Solvent effect

The catalytic epoxidation of the styrene derivative was also studied in various solvents for better yield and selectivity (Table 2); dichloromethane (DCM), dry tetrahydrofuran (THF), a mixture of dry dichloromethane and tetrahydrofuran in a 4:1 ratio, ionic liquid 1-butyl-3-methyl imidazolium bromide ([bmim]Br) and fluorous solvent 1,1,1,3,3,3-hexafluoropropan-2-ol. Among all these solvents used, the solvent system consisting of dry DCM and THF in 4:1 proved to be the best system in the epoxidation of all of the alkenes in terms of both yield and enantiomeric excess. This indicates that although lipases perform well in ionic liquids in



Scheme 2.

Table 1
Epoxidation of the styrene derivatives using UHP in the presence of chiral acid (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate **3** and *Novozyme* [*435*] in dry dichloromethane solvent unless otherwise stated

Entry	Substrates **1a–7a**	Products[a] **1b–7b**	Time (h)	Yield[b] (%)	ee[c] (%)
1			20	70	46
2[d]			20	75	57
3			48	20	46
4			20	78	63
5			20	74	68
6			20	65	35
7			20	70	71

[a] The products were characterized from their respective IR, NMR and mass spectroscopic data and by comparison with the literature data.
[b] Isolated yields of products.
[c] Determined from specific rotation data, HPLC and GC analysis.
[d] The reaction was carried out in the solvent system DCM/THF, 4:1.

Table 2
Effect of solvents in the epoxidation of 4-hydroxy styrene **2a** using UHP in presence of (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate and *Novozyme* [*435*][a]

Entry	Solvent	Time (h)	Conversion[b] (%)	ee[c] (%)
1	Dry dichloromethane (DCM)	30	65	55
2	Dry tetrahydrofuran (THF)	30	48	53
3	Dry DCM/dry THF = 4:1	20	75	57
4	1-Butyl-3-methylimidazolium bromide ([bmim]Br)	30	45	50
5	1,1,1,3,3,3-Hexafluoropropan-2-ol	30	40	51

[a] Reaction conditions: 4-Hydroxystyrene: 1 g (8.3 mmol), urea hydrogen peroxide: 3 g (32 mmol), immobilized lipase: 100 mg, 2*R*,3*S*,4*R*,5*S*-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate **3**: 0.3 g (1.03 mmol), solvent (total): 15 mL.
[b] Conversions were determined by GC analysis as well as from crude NMR spectra.
[c] Determined from specific rotation data, HPLC and GC analysis.

ammonolysis, alcoholysis, perhydrolysis, etc. reactions, the peracid formation is poor in such solvents as well as in water miscible organic solvents. This is in agreement with the earlier findings of Bjorkling et al.[7]

2.2. Recycling of chiral acid [(–)-DIKGA] and lipase catalyst

The epoxidation reaction of 4-hydroxy styrene **2a** was repeatedly carried out with the recovered amount of the chiral acid and the enzyme to study their recyclability. It was found that there was no significant loss in the activity of the chiral acid and the enzyme with respect to the isolated yield of the corresponding product (Fig. 3).

3. Conclusion

We have presented a novel chemoenzymatic method for the preparation of enantiomerically pure epoxides via chirality induction from the oxygen carrier chiral acid. The chiral inducing property of the acid (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate [(−)-DIKGA] has been unveiled for the first time and the yields of the resulting epoxides obtained are good; this was achieved by using stoichiometric amounts of UHP and catalytic amount of the chiral acid and lipase enzyme. Although the enantioselectivity of the products is low at this stage, this method has opened up a new route for further improvement.

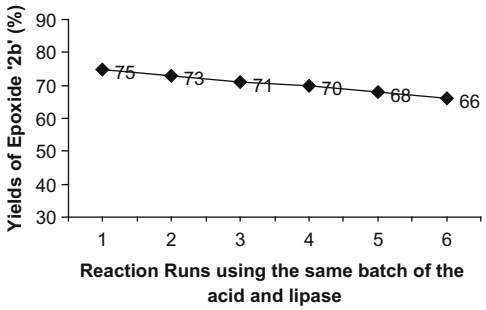


Figure 3. Variation of the yields of the epoxides in six different epoxidation reactions of 4-hydroxy styrene using the same batch of chiral acid (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate **3** and lipase keeping the other reaction condition identical.

4. Experimental

4.1. General methods

All the IR, ^{1}H NMR, ^{13}C NMR and mass spectra were recorded on an FT IR System-2000 PERKIN–ELMER, AVANCE-DPX-300 MHz FT-NMR BRUKER standard and WATERS Micro-mass ZQ 4000 (ESI Probe) spectrometers, respectively. The chemical shifts are reported in ppm relative to $CHCl_3$ ($\delta = 7.26$) for ^{1}H and relative to the central $CDCl_3$ resonance ($\delta = 77.0$) for ^{13}C NMR. GC analyses were carried out using Chemito GC 1000 spectrometers. Optical rotations were measured on a Jasco Digital P-1020 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral HPLC using Chiralcel OD, Chiralcel OJ, Chiralpak AD, Chiralcel OD-R, columns with hexane-2-propanol and methanol–water as eluent.

4.2. Materials

All the starting materials (alkenes), chiral acid (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate [(−)-DIKGA] and UHP were purchased commercially from Aldrich Chemicals. The lipases *Novozyme* [*435*] and *P. cepacia* were purchased from Fluka Chemicals. The dry solvents were purchased from Across Organics. Silica gel G for thin layer chromatography and silica gel 100–200 mesh for column chromatography were purchased from RANKEM, India.

4.3. Preparation of 4-hydroxy styrene 1a from 4-acetoxy styrene

4-Acetoxy styrene (3 g, 18.5 mmol) and *P. cepacia* lipase (30 mg) were taken in a round-bottomed flask in 15 mL THF/H_2O (2:1) and the mixture was stirred for 10 h at room temperature. The crude mixture was then filtered to remove the lipase to reuse it again and the major THF layer was distilled out from the filtrate under reduced pressure. The remaining aqueous layer was then extracted again with ethyl acetate (3 × 15 mL) and then dried over anhydrous Na_2SO_4. After that the organic solvent was distilled out under reduced pressure and the hydrolyzed product was purified with column chromatography to give the pure product 4-hydroxy styrene as a solid (1.99 g, 16.65 mmol, 90% yield), mp 71–72 °C (lit.[14] mp 73 °C). C_8H_8O requires C, 79.97; H, 6.71. Found: C, 79.91; H, 6.77); R_f (in CH_2Cl_2) 0.55. ν_{max} (neat/cm^{-1}) 3405, 2960, 2925, 2855, 1611; δ_H (300 MHz; $CDCl_3$) 4.7 (1H, b, H*H*CCHPh), 4.9 (1H, b, *H*HCCHPh), 5.1 (1H, b, O*H*), 5.6 (1H, b, H_2CCHPh), 6.8–7.3 (4H, m, 4 × C*H*, arom.); δ_C (75 MHz; $CDCl_3$) 110.1 (CH_2CHPh), 136.0 (CH_2*C*HPh), 114.8, 125.5, 127.0, 154.2 (6 × *C*-Ph). MS *m/z*: 120 [M^+].

4.4. Preparation of (*R*)-(+)-phenyloxirane 1b

To a mixture of urea hydrogen peroxide (UHP) adduct (3 g, 32 mmol) with (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol) in dry dichloromethane (15 mL) was added, *Novozyme* [*435*] (100 mg) at 0–5 °C and the mixture stirred for about 1 h. Styrene (1 g, 9.6 mmol) was then added dropwise and the reaction continued at room temperature for 20 h. The reaction was monitored by TLC. The mixture was filtered and the residue washed with dichloromethane after which the filtrate was reduced under pressure using a vacuum flash evaporator. The reaction mixture was washed with 10% $NaHCO_3$ solution (2 × 20 mL) to remove any trace amount of the acid present in it. The organic layer was then washed again with fresh water (2 × 10 mL) and dried over anhydrous Na_2SO_4. The product was purified by preparative TLC with 40% CH_2Cl_2/hexane. Yield: 70%; oil (C_8H_8O requires C, 79.97; H, 6.71. Found: C, 79.91; H, 6.65); R_f (40% CH_2Cl_2/hexane) 0.55. The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD column [^{i}PrOH/hexane = 0.2:99.8, flow rate 0.2 $cm^3\ min^{-1}$], $[\alpha]_D^{22} = +21.5$ (*c* 0.8, PhH) 46% ee, (*R*); {lit.,[15] $[\alpha]_D^{22} = +44.5$ (*c* 1.05, PhH) 95% ee (*R*)}. ν_{max} (neat/cm^{-1}) 1496, 1476, 1452, 1390; δ_H (300 MHz; $CDCl_3$) 2.81 (1H, dd, *J* 2.6 and 5.5, HCOC*H*H), 3.15 (1H, dd, *J* 4.1 and 5.5, HCOCH*H*), 3.87 (1H, dd, *J* 2.6 and 4.0, PhC*H*OCH_2), 7.26–7.36 (5H, m, 5 × C*H*, arom.); δ_C (75 MHz; $CDCl_3$) 51.2 (CH_2), 52.4 (CH), 125.5, 128.2, 128.4 and 137.6 (6 × C-Ph). MS *m/z* (rel. intensity %): 122 (M+2, 15), 121 (M+1, 43), 120 (M^+, 20), 105 (100), 91 (68), 77 (88).

4.5. Preparation of (*R*)-(+)-4-hydroxyphenyloxirane 2b

4.5.1. In a DCM/THF system (4:1)

The same procedure was followed as given in Section 4.4. using a 4-hydroxy styrene (1 g, 8.3 mmol), *Novozyme* [*435*] (100 mg), (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol) and UHP (3 g, 32 mmol) in dry dichloromethane/tetrahydrofuran solvent mixture (4:1) (15 mL). The product was purified by preparative TLC in dry DCM/THF in a 4:1 ratio. Yield: 75%; oil ($C_8H_8O_2$ requires C, 70.58; H, 5.88. Found: C, 70.70; H, 5.91); R_f (90% CH_2Cl_2/EtOAc) 0.55. The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD-R column [MeOH, flow rate 0.2 $cm^3\ min^{-1}$], ee 57%, (*R*); $[\alpha]_D^{25} = +4.95$ (*c* 0.8, $CHCl_3$); ν_{max} (neat/cm^{-1}) 3406, 2961, 2924, 2856, 1513, 1457; δ_H (300 MHz; $CDCl_3$) 2.0 (1H, b, HCOCH*H*), 2.2 (1H, br s, HCOC*H*H), 3.4 (1H, br s, C*H*OCH_2), 5.1 (1H, br s, O*H*), 6.7–7.0 (4H, m, 4 × C*H*, arom.); δ_C (300 MHz; $CDCl_3$) 26.4 (CH_2), 48.13 (*C*H), 115.5, 128.2, 137.3, 154.2 (6 × *C*-Ph). MS *m/z*: 136 [M^+].

The residue obtained by filtration of the above reaction mixture in the epoxidation of 4-hydroxystyrene contains *Novozyme* [*435*] and (2*R*, 3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate. The residue was then dried and recycled for the next five successive reactions.

4.5.2. In dry DCM

The same procedure was followed as given in Section 4.4. using 4-hydroxystyrene (1 g, 8.3 mmol), *Novozyme* [*435*] (100 mg), (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and dry dichloromethane (15 mL). Reaction time: 30 h, yield: 60%, $[\alpha]_D^{25} = +4.8$ (*c* 0.9, $CHCl_3$); ee 55%, (*R*).

4.5.3. In dry THF

The same procedure was followed as given in Section 4.4. using 4-hydroxy styrene (1 g, 8.3 mmol), *Novozyme* [*435*] (100 mg), (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and dry tetrahy-

drofuran (15 mL). Reaction time: 30 h, yield: 48%, $[\alpha]_D^{25} = +4.6$ (*c* 0.6, $CHCl_3$); ee 53%, (*R*).

4.5.4. In fluorous solvent 1,1,1,3,3,3-hexafluoropropan-2-ol

The same procedure was followed as given in Section 4.4. using 4-hydroxy styrene (1 g, 8.3 mmol), *Novozyme* [*435*] (100 mg), 2*R*,3*S*,4*R*,5*S*-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and 1,1,1,3,3,3-hexafluoropropan-2-ol (15 mL). Reaction time: 30 h, yield: 45%, $[\alpha]_D^{25} = +4.3$ (*c* 0.6, $CHCl_3$); ee 50%, (*R*).

4.5.5. In ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br)

The same procedure was followed as given in Section 4.4. using 4-hydroxy styrene (1 g, 8.3 mmol), *Novozyme* [*435*] (100 mg), (2*R*, 3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and 1-butyl-3-methylimidazolium bromide ([bmim]Br) (15 mL). Reaction time: 30 h, yield: 40%, $[\alpha]_D^{25} = +4.4$ (*c* 0.6, $CHCl_3$); ee 51%, (*R*).

4.6. Preparation of (*R*)-(−)-(4-chlorophenyl) oxirane 3b

The same procedure was followed as given in Section 4.4. using 4-chlorostyrene (1 g, 6.41 mmol), *Novozyme* [*435*] (100 mg), 2*R*,3*S*,4*R*,5*S*-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and dry dichloromethane (15 mL). Reaction time: 48 h. The product was purified by preparative TLC with 40% CH_2Cl_2/hexane. Yield: 36%; oil (C_8H_7OCl requires C, 62.09; H, 4.53. Found: C, 62.11; H, 4.51); R_f (40% EtOAc/hexane) 0.51; $[\alpha]_D^{22} = -11.5$ (*c* 0.65, $CHCl_3$); {lit.,[16] $[\alpha]_D^{20} = -24.0$ (*c* 1.08, $CHCl_3$), 97% ee, (*R*)}; HPLC analysis using a Chiralcel OJ column showed it to be 46% ee [hexane/2-propanol = 9:1, flow rate 0.8 $cm^3\ min^{-1}$]. ν_{max} (neat/cm^{-1}) 3054, 2992, 2920, 1602, 1496, 1478, 1417, 1381, 1199, 1090, 1015, 987, 879, 831, 769; δ_H (300 MHz; $CDCl_3$) 2.68–2.69 (1H, dd, *J* 2.6 and 5.4, HCOC*H*H), 3.08 (1H, dd, *J* 4.0 and 5.4, HCOCH*H*), 3.77 (1H, dd, *J* 2.6 and 4.0, PhC*H*OCH$_2$), 7.13–7.26 (4H, m, 4 × C*H*, arom.); δ_C (75 MHz; $CDCl_3$) 51.2 (CH_2), 51.8 (CH), 126.7, 126.6, 133.9 and 136.1 (6 × C-Ph). MS *m*/*z* (rel. intensity %): 157, 155, 153 (M^+, 3, 7), 138(3), 125(40), 119(39), 91(29), 89(100), 63(34), 50(17).

4.7. Preparation of (*R*)-(−)-(3-nitrophenyl) oxirane 4b

The same procedure was followed as given in Section 4.4. using 3-nitrostyrene (1 g, 6.06 mmol), *Novozyme* [*435*] (100 mg), (2*R*, 3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and dry dichloromethane (15 mL). Reaction time: 20 h. The product was purified by preparative TLC with 40% CH_2Cl_2/hexane. Yield: 78%; yellow oil ($C_8H_7NO_3$ requires C, 58.18; H, 4.27; N 8.48. Found: C, 58.22; H, 4.28; N, 8.50); R_f (25% EtOAc/hexane) 0.50; $[\alpha]_D^{20} = -1.6$ (*c* 2.1, $CHCl_3$), (*R*); {lit.,[17] $[\alpha]_D^{18} = +2.5$ (*c* 2.8, $CHCl_3$, (*S*)}; HPLC analysis using a Chiralpak AD column showed it to be 63% ee [hexane/2-propanol = 9:1, flow rate 0.8 $cm^3\ min^{-1}$]. ν_{max} (neat/cm^{-1}) 3113, 2995, 1517, 1343, 1301, 1042, 983, 888, 788, 740; δ_H (300 MHz; $CDCl_3$) 2.80 (1H, dd, *J* 2.5 and 4.8, HCOC*H*H), 3.21 (1H, dd, *J* 3.9 and 4.8, HCOCH*H*), 3.97 (1H, dd, *J* 2.5 and 3.9, PhC*H*OCH$_2$), 7.40–7.75 (2H, m, 2 × C*H*, arom.) and 8.01–8.24 (2H, m, 2 × C*H*, arom.); δ_C (75 MHz; $CDCl_3$) 51.7 (CH_2), 51.9 (CH), 126.0, 126.4, 145.4 and 148.6 (6 × C-Ph); MS *m*/*z* (rel. intensity %): 165(M^+, 18), 150(32), 136(68), 120(25), 105(17), 90(100), 77(22), 74(12), 65(52), 63(59).

4.8. Preparation of (*R*)-(−)-(2-nitrophenyl) oxirane 5b

The same procedure was followed as given in Section 4.4. taking 2-nitrostyrene (1 g, 6.06 mmol), *Novozyme* [*435*] (100 mg), 2*R*,3*S*,4*R*,5*S*-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and dry dichloromethane (15 mL). Reaction time: 20 h. The product was purified by preparative TLC with 40% CH_2Cl_2/hexane. Yield: 74%; light yellow solid; mp 51–52 °C; ($C_8H_7NO_3$ requires C, 58.18; H, 4.27; N, 8.48. Found: C, 58.20; H, 4.28; N, 8.51); R_f (25% EtOAc/hexane) 0.52; $[\alpha]_D^{19.5} = -72.9$ (*c* 1.20, $CHCl_3$), (*R*); {lit.,[17] $[\alpha]_D^{19.5} = -107.2$ (*c* 1.65, $CHCl_3$), (*R*)}; The enantiomeric excess was determined by HPLC analysis using Chiralcel OD column and showed it to be 68% ee (eluent at *V* = 0.8 mL min^{-1}, hexane/2-propanol = 9: 1). ν_{max} (neat/cm^{-1}) 3150, 2997, 1532, 1353, 1254, 899, 859, 809, 737, 684; δ_H (300 MHz; $CDCl_3$) 2.67 (1H, dd, *J* 2.5 and 5.4, HCOC*H*H), 3.30 (1H, dd, *J* 4.2 and 5.4, HCOCH*H*), 4.48 (1H, dd, *J* 2.5 and 4.2, PhC*H*OCH$_2$), 7.41–7.56 (1H, m, 1 × C*H*, arom.), 7.57–7.77 (2H, m, 2 × C*H*, arom.) and 8.14 (1H, dd, *J* 1.21 and 8.13, 1 × C*H*, arom.). δ_C (75 MHz; $CDCl_3$) 50.5 (CH_2), 51.6 (CH), 124.6, 128.5, 128.8, 131.7, 133.5, 149.1 (6 × C-Ph); MS *m*/*z* (rel. intensity %): 165(M^+, 0.3), 149(2), 135(21), 105(10), 104(10), 91(79), 89(21), 79(71), 77(100).

4.9. Preparation of (2*R*,3*R*)-epoxybutan-1-ol 6b

The same procedure was followed as given in Section 4.4. using but-2-en-1-ol (1 g, 13.9 mmol), *Novozyme* [*435*] (100 mg), 2*R*,3*S*,4*R*,5*S*-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and dry dichloromethane (15 mL). Reaction time: 20 h. The product was purified by preparative TLC with 70% EtOAc/hexane. Yield: 65%; oil ($C_4H_8O_2$ requires C, 54.5; H, 9.09. Found: C, 54.2; H, 9.2); R_f (70% EtOAc/hexane) 0.45. The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD-R column [MeOH/water (9:1), flow rate 0.5 $cm^3\ min^{-1}$], $[\alpha]_D^{25} = +19.3$ (*c* 0.05, $CHCl_3$) 35% ee; {lit.,[2] $[\alpha]_D^{24} = +55.0$ (*c* 0.36, $CHCl_3$), 95% ee}; ν_{max} (neat/cm^{-1}) 3399, 2957, 2924, 2853, 1464, 1378; δ_H (300 MHz; $CDCl_3$) 1.2 (3H, d, C*H*$_3$CHO), 2.1 (1H, b, CH$_2$O*H*), 2.6 (1H, m, HOCH$_2$C*H*O), 2.7 (1H, m, CH$_3$C*H*O), 3.7 (2H, m, OCHC*H*$_2$OH); δ_C (75 MHz; $CDCl_3$) 16.2 (*C*H$_3$CHO), 46.5 (CH$_3$*C*HO), 62.0 (HOCH$_2$*C*HO), 64.3 (*C*H$_2$OH). MS *m*/*z*: 88 [M^+].

4.10. Preparation of (2*R*,3*R*)-epoxy-2-methylpentan-1-ol 7b

The same procedure was followed as given in Section 4.4. taking 2-methyl-penten-2-ol (1 g, 10 mmol), *Novozyme* [*435*] (100 mg), (2*R*,3*S*,4*R*,5*S*)-(−)-2,3:4,6-di-*O*-isopropylidiene-2-keto-L-gulonic acid monohydrate (0.3 g, 1.03 mmol), UHP (3 g, 32 mmol) and dry dichloromethane (15 mL). Reaction time: 20 h. The product was purified by preparative TLC with 30% EtOAc/hexane. Yield: 70%; oil ($C_6H_{12}O_2$ requires C, 62.07; H, 10.34. Found: C, 62.01; H, 10.65); R_f (30% EtOAc/hexane) 0.65. The enantiomeric excess was determined by HPLC analysis using a Chiralcel OD-R column [MeOH, flow rate 0.5 $cm^3\ min^{-1}$], $[\alpha]_D^{25} = +4.3$ (*c* 0.03, $CHCl_3$) 71% ee; {lit.,[2] $[\alpha]_D^{24} = -5.8$ (*c* 0.36, $CHCl_3$), 95% ee}; ν_{max} (neat/cm^{-1}) 3407, 2963, 2932, 2875, 1457, 1376; δ_H (300 MHz; $CDCl_3$) 0.96 (3H, t, CH$_2$C*H*$_3$), 1.31 (3H, s, OCC*H*$_3$), 1.46 (2H, m, OCHC*H*$_2$CH$_3$), 2.0 (1H, b, O*H*), 2.51 (1H, t, OC*H*CH$_2$), 3.5–3.7 (2H, m, CC*H*$_2$OH); δ_C (300 MHz; $CDCl_3$) 11.0 (*C*H$_3$CH$_2$), 14.5 (*C*H$_3$CO), 21.6 (CH$_2$*C*H$_2$), 61.7 (CH$_2$*C*HO), 62.8 (CH$_3$*C*O), 70.3 (*C*H$_2$OH). MS *m*/*z*: 116 [M^+].

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