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The conversion of racemic terminal epoxides into either (+)- or (−)-diol γ- and δ-lactones

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The conversion of racemic terminal epoxides into either (+)- or (−)-diol γ- and δ-lactones is described with hydrolytic kinetic resolution (HKR) as the key step.

Hydrolytic kinetic resolution (HKR) as developed by Jacobsen's group[1] provided practical access to both terminal epoxides and 1,2-diols in excellent ee using (*R*,*R*)-(salen)-Co(OAc) complex **A** as the catalyst and water as the only reagent. However, HKR afforded two kinds of compounds, epoxides and diols, with the opposite configuration and the two products have to be separated for further use in most cases.[2–5] Considering the advantages of configuration inversion of terminal epoxides in the reaction of intramolecular ring opening of the epoxide, we are interested in designing a proper procedure to convert the two products of HKR into the same diol γ- or δ-lactones (Scheme 1) in the theoretical maximum yield of 100% from racemic terminal epoxides.

Optically active diol γ- and δ-lactones are important intermediates in the synthesis of natural products and biologically active compounds.[6–11] Until now, (*R*)-(−)-diol γ-lactone could be obtained starting from its (*S*)-(+)-enantiomer,[12] which was prepared from (*S*)-(+)-glutamic acid.[13] (*S*)-(+)-δ-Lactone could be obtained starting from the expensive commercially available tri-*O*-acetyl-D-glucal[10] or from D-mannitol[14] by a relative long route. In the present work, either (+)- or (−)-diol γ- and δ-lactones were prepared from racemic terminal epoxides in high yields and excellent ee with HKR as the key step.

Results and discussion

At first, the HKR of racemic terminal epoxides gave optically active epoxides and diols, which were separated from the reaction mixture and converted into the corresponding lactones.

The epoxidation of **1a** with MCPBA gave **2a** (Scheme 2), which was proposed to undergo HKR by the general procedure to afford epoxide **3a** and diol **4a**. In fact, the lactone **5a** in 50% yield and 94% ee, not the diol **4a**, was separated from the mixture of products as well as the epoxide **3a** in 45% yield. Evidently, the lactonization of diol **4a** occurred spontaneously. Subsequent treatment[12] of **3a** with TFA gave the same lactone **5a** in 87% yield and 96% ee.

Terminal epoxide **2b** was prepared by the epoxidation of **1b** with MCPBA. Similarly, treatment of **2b** under the general procedure of HKR afforded epoxide **3b** in 46% yield and diol **4b** in 49% yield. Unfortunately, the conversion of **3b** to **5b** with TFA using the same procedure as for **5a** gave an unsatisfactory yield. The successful lactonization of **3b** by a two-step procedure (Scheme 3), hydrolysis with LiOH and lactonization with CSA gave lactone **5b** in 86% overall yield and 98% ee. The same lactone was obtained by lactonization of diol **4b** in the presence of H^+-exchange resin in 89% yield and 95% ee.

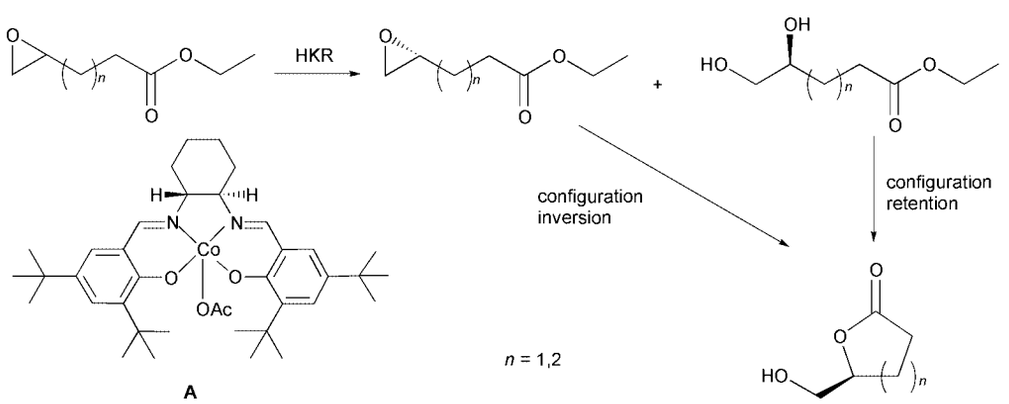
It is more convenient that **5a** and **5b** could also be obtained directly by a one-pot procedure from the mixture of the products of HKR reaction. Treatment of the mixture of **3a** and **4a** with TFA gave **5a** in 88% yield and 95% ee. Hydrolysis of the mixture of **3b** and **4b** gave a mixture of crude products, subsequent treatment of which with CAS gave **5b** in 83% yield and 96% ee. The enantiomers of **4a** and **4b** were obtained when the (*S*,*S*)-(salen)Co(OAc) complex was used for HKR.

Thus, we have developed a practical and efficient method to convert racemic terminal epoxides into either (+)- or (−)-diol γ- and δ-lactones in high chemical yield and excellent ee *via* HKR and simple transformations.

Experimental

General details

IR spectra were recorded as neat films on a Bio-Rad FTS-185



Scheme 1

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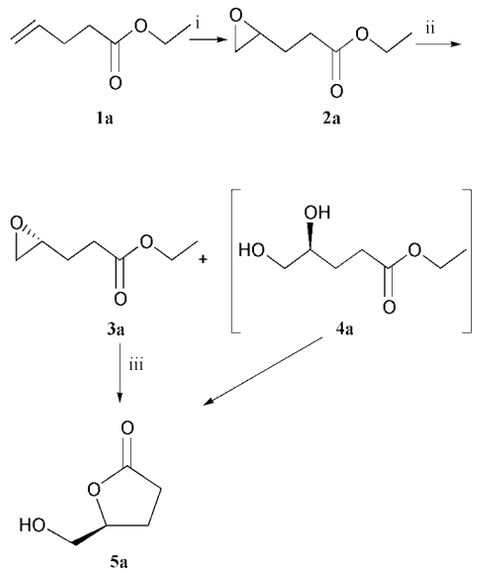
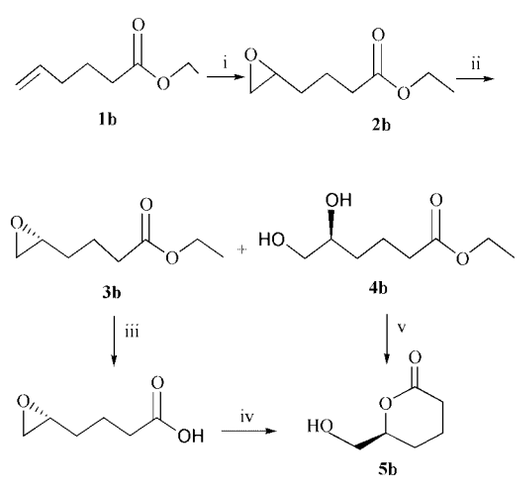


Scheme 2 *Reagents and conditions*: i, MCPBA, 6 h, 91%; ii, 1% mol (*R*,*R*)-(salen)Co(OAc), 0.55 equiv. H_2O, rt, 30 h, 45% of **3a**, 50% of **5a**; iii, TFA, −10 °C, 15 min, 87%.



Scheme 3 *Reagents and conditions*: i, MCPBA, 6 h, 93%; ii, 1% mol (*R*,*R*)-(salen)Co(OAc), 0.55 equiv. H_2O, rt, 30 h, 46% of **3b**, 49% of **4b**; iii, LiOH, H_2O, THF; iv, CSA, CH_2Cl_2, 0 °C, 15 min, 86%; v, Amberlyst-15, a few 4 Å molecular sieves, CH_3CN, 30 °C, 3 h, 89%.

spectrometer. ^{1}H NMR spectra were determined with TMS as an internal standard in $CDCl_3$ at 300 MHz on a Bruker AM-300 spectrometer; *J* values are given in Hz. Mass spectra were obtained on a HP-5989A spectrometer using the electron impact technique. Microanalysis was performed using an Elementar Vario EL. Optical rotations were measured on a Perkin-Elmer 341 polarimeter. Enantiomeric excesses were determined by HPLC analysis with an Chiralpak AS column. Solvents were dried and distilled prior to use. Flash column chromatography was conducted silica gel H (100–400 mesh) from Qingdao Haiyang Chemical Works.

Compounds **1a**[15] and **1b**[16] were prepared by literature methods.

Ethyl 4,5-epoxypentanoate (2a)

To a solution of **1a** (2.56 g, 20 mmol) in CH_2Cl_2 (100 mL) was added MCPBA (5.05 g, 22 mmol). After stirring for 6 h, the reaction mixture was diluted with ether, washed with sat. $Na_2S_2O_3$ (20 mL), sat. Na_2CO_3 (20 mL), brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was subjected to distillation to afford **2a** (2.6 g, 93% yield). Bp 76 °C/5 Torr (Found: C, 58.11; H, 8.41. $C_7H_{12}O_3$ requires: C, 58.32; H, 8.39%); ν_{max}/cm^{-1} 1182, 1736; δ_H 4.10 (q, *J* = 7.6, 2H), 2.95 (m, 1H), 2.72 (m, 1H), 2.45 (m,1H), 2.44–2.38 (t, *J* = 7.4, 2H), 2.0–1.85 (m, 1H), 1.80–1.65 (m, 1H), 1.25 (t, *J* = 7.2, 3H); *m*/*z* 145 (M^+ + 1, 2%), 115 (14), 99 (56), 85 (57), 71 (99), 55 (100).

General procedure of HKR

To a mixture of terminal epoxide (10 mmol) and (*R*,*R*) or (*S*,*S*)-(salen)Co(OAc) complex (34 mg, 0.05 mmol), water (100 mg, 0.55 mmol) was slowly added and the reaction mixture was stirred at rt for 30 h after the addition. The optically active epoxide and diol were isolated together from the reaction mixture by bulb-to-bulb distillation and subsequent flash chromatography of the distillate gave epoxide (hexane–EtOAc, 9 : 1) and diol (hexane–EtOAc, 2 : 8).

Ethyl (*R*)-(+)-4,5-epoxypentanoate (3a)

Treatment of **2a** (1.44 g, 10 mmol) under the general procedure of HKR using (*R*,*R*)-(salen)Co(OAc) complex as the catalyst gave **3a** (0.65 g, 45% yield). $[\alpha]_D^{20}$ = +16.9 (*c* 0.9, $CHCl_3$). The other spectra data were identical in all respects to those of **2a**.

Method A for (*S*)-(+)-γ-hydroxymethyl-γ-butyrolactone (5a)

Treatment of **2a** (2.56 g, 20 mmol) under the general procedure of HKR using (*R*,*R*)-(salen)Co(OAc) complex as the catalyst gave **5a** (580 mg, 50% yield, 94% ee). The ee value of **5a** was determined by chiral HPLC using a Chiralpak AS column with UV detection (201 nm) and an eluant of propan-2-ol–heptane (4 : 6). Peaks were observed at 10.81 and 12.41 min. $[\alpha]_D^{20}$ = +50.7 (*c* 1.2, $CHCl_3$) [lit.[12] $[\alpha]_D$ = +53.5 (*c* 5.7, $CHCl_3$)]; ν_{max}/cm^{-1} 1192, 1767, 3400; δ_H 4.63 (m, 1H), 3.95–3.82 (dd, J_1 = 12.5, J_2 = 2.7, 1H), 3.70–3.60 (dd, J_1 = 12.5, J_2 = 4.6, 1H), 2.70–2.35 (m, 1H), 2.34–2.10 (m, 1H); *m*/*z* 117 (M^+ + 1, 1%), 85 (100), 57 (17), 42 (11).

Method B for 5a

A mixture of **3a** (287 mg, 2 mmol) and TFA (1 mL) was stirred at −10 °C for 15 min. Then benzene (10 mL) was added and most of the solvent was removed under vacuum. Purification of the residue by flash chromatography (EtOAC) gave **5a** (202 mg, 87% yield, 96% ee). $[\alpha]_D^{20}$ = +51.5 (*c* 0.6, $CHCl_3$).

One-pot procedure for 5a

HKR of **2a** (721 mg, 5 mmol) under the general procedure using (*R*,*R*)-(salen)Co(OAc) complex as the catalyst gave a mixture of epoxide and diol by bulb-to-bulb distillation. To the mixture was added TFA (2 mL) at −15 °C. After the solution was stirred at −10 °C for 15 min, benzene (25 mL) was added. Most of the solvent was removed *in vacuo* and purification of the residue by flash chromatography (hexane–EtOAc, 2 : 8) gave **5a** (510 mg, 88% yield, 95% ee). $[\alpha]_D^{20}$ = +51.1 (*c* 0.9, $CHCl_3$).

Ethyl 5,6-epoxyhexanoate (2b)

The same procedure as described for the preparation of **2a** was used. The epoxidation of **1b** (2.84 g, 20 mmol) with MCPBA (5.10 g, 22 mmol) gave **2b** (2.94 g, 93% yield). Bp 93 °C/5 Torr (Found: C, 60.49; H, 9.00. $C_8H_{14}O_3$ requires C, 60.74; H, 8.92%); ν_{max}/cm^{-1} 1176, 1735; δ_H 4.16–4.08 (q, *J* = 7.1, 2H), 2.90 (m, 1H), 2.72 (m, 1H), 2.43 (m, 1H), 2.35 (t, *J* = 7.0, 2H), 1.87–1.70 (m, 2H), 1.68–1.40 (m, 2H), 1.23 (t, *J* = 7.5, 3H); *m*/*z* 159 (M^+ + 1, 1%), 113 (28), 84 (52), 71 (64), 55 (100).

Ethyl (*R*)-(+)-5,6-epoxyhexanoate (3b)

Treatment of **2b** (1.58 g, 10 mmol) under the general procedure of HKR using (*R*,*R*)-(salen)Co(OAc) complex as the catalyst gave **3b** (727 mg, 46% yield). $[\alpha]_D^{20}$ = +14.9 (*c* 0.2, $CHCl_3$). The other spectra data were identical in all respects to those of **2b**.

Ethyl (*S*)-(−)-5,6-dihydroxyhexanoate (4b)

Treatment of **2b** (1.58 g, 10 mmol) under the general procedure of HKR using (*R*,*R*)-(salen)Co(OAc) complex as the catalyst gave **4b** (862 mg, 49% yield). $[\alpha]_D^{20} = -14.1$ (*c* 2.0, EtOH) (Found: C, 54.47; H, 9.17. $C_8H_{16}O_4$ requires: C, 54.53; H, 9.15%); ν_{max}/cm^{-1} 1035, 1193, 1734, 3399; δ_H 4.12 (q, *J* = 7.1, 2H), 3.70–3.56 (m, 2H), 3.46–3.30 (m, 2H), 3.28–3.15 (m, 1H), 2.22 (t, *J* = 7.3, 2H), 1.48–1.38 (m, 2H), 1.25 (t, *J* = 6.4, 3H); *m*/*z* 177 ($M^+ + 1$, 6%), 113 (98), 99 (91), 71 (100), 55 (79).

Method A for (*S*)-(+)-δ-hydroxymethyl-δ-valerolactone (5b)

A solution of **3b** (316 mg, 2 mmol) and LiOH (120 mg, 3 mmol) in THF–H_2O (1:1, 10 mL) was stirred at rt for 1.5 h, acidified to a pH 4 and extracted with EtOAc. The combined extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. To the resulting crude product in dry CH_2Cl_2 (10 mL) was added CSA (46 mg, 0.2 mmol). After stirring at −5 °C for 20 min, the reaction was quenched with Et_3N and the solvent was evaporated. Purification of the residue by flash chromatography (hexane–EtOAc, 2:8) gave **5b** (224 mg, 86% overall yield from **4b**, 98% ee). The ee value of **5b** was determined by chiral HPLC using a Chiralpak AS column with UV (201 nm) and an eluant of propan-2-ol–heptane (2:8). Peaks were observed at 11.57 and 12.30. $[\alpha]_D^{20} = +34.5$ (*c* 0.6, $CHCl_3$) [lit.[10] $[\alpha]_D^{20} = +34.68$ (*c* 1.3, $CHCl_3$)]; ν_{max}/cm^{-1} 1055, 1248, 1725, 3403; δ_H 4.46–4.36 (m, 1H), 3.86–3.72 (m, 1H), 3.70–3.60 (m, 1H), 2.75 (m, 1H), 2.65–2.55 (m, 1H), 2.50–2.40 (m, 1H), 2.0–1.80 (m, 3H), 1.78–1.60 (m, 1H); *m*/*z* 131 ($M^+ + 1$, 8%), 113 (15), 99 (100), 71 (75), 55 (45), 43(47).

Method B for 5b

To a solution of **4b** (352 mg, 2 mmol) in CH_3CN (10 mL) was added a catalytic amount of H^+-ion-exchange resin (Amberlyst-15) and a few 4 Å molecular sieves. The reaction mixture was stirred at rt for 3.5 h, and then filtered. The solvent was removed *in vacuo*. Purification of the residue by flash chromatography (hexane–EtOAc, 2:8) gave **5b** (231 mg, 89% yield, 95% ee). $[\alpha]_D^{20} = +33.2$ (*c* 2.1, $CHCl_3$).

One pot procedure for 5b

HKR of **2b** (791 mg, 5 mmol) under the general procedure using (*R*,*R*)-(salen)Co(OAc) complex as the catalyst gave a mixture of epoxide **3b** and diol **4b** by bulb-to-bulb distillation. The mixture was diluted with THF–H_2O (1:1, 50 mL) and LiOH·H_2O (314 mg, 7.5 mmol) was added. The solution was stirred at rt for 1.5 h, acidified with $KHSO_4$ to pH 4 and extracted with EtOAc (3 × 25 ml). The combined extracts were dried over Na_2SO_4, and the solvent was removed *in vacuo*. To the resulting crude product in CH_2Cl_2 (45 mL), was added CSA (115 mg, 0.5 mmol) at −10 °C. After stirring at −10–+20 °C for 2 h, the reaction was quenched with Et_3N, and the solvent was evaporated. Purification of the residue by flash chromatography (hexane–EtOAc, 2:8) gave **5b** (540 mg, 83% yield, 96% ee). $[\alpha]_D^{20} = +34.0$ (*c* 1.5, $CHCl_3$).

Ethyl (*S*)-(−)-4,5-epoxypentanoate (3a′)

Treatment of **2a** (1.44 g, 10 mmol) under the general procedure of HKR using (*S*,*S*)-(salen)Co(OAc) complex as the catalyst gave **3a′** (620 mg, 43% yield). $[\alpha]_D^{20} = -17.1$ (*c* 0.8, $CHCl_3$). The other spectra data were identical in all respects to those of **2a**.

Method A for (*R*)-(−)-γ-hydroxymethyl-γ-butyrolactone (5a′)

Treatment of **2a** (1.44 g, 10 mmol) under the general procedure of HKR using (*S*,*S*)-(salen)Co(OAc) complex as the catalyst gave **5a′** (580 mg, 50% yield, 95% ee). $[\alpha]_D^{20} = -51.5$ (*c* 1.5, $CHCl_3$) [lit.[13] $[\alpha]_D$ −53.5 (*c* 3.17, $CHCl_3$)]. The other spectra data were identical in all respects to those of **5a**.

Method B for 5a′

Treatment of **3a′** (285 mg, 2 mmol) by method B for **5a** gave **5a′** (207 mg, 89% yield, 96% ee). $[\alpha]_D^{20} = -51.9$ (*c* 2.1, $CHCl_3$).

One-pot procedure for 5a′

Treatment of **2a** (720 mg 5 mmol) under the one-pot procedure as described for the preparation of **5a** except using (*S*,*S*)-(salen)Co(OAc) complex as the catalyst for HKR reaction gave **5a′** (522 mg, 90% yield, 95% ee). $[\alpha]_D^{20} = -51.6$ (c 2.2, $CHCl_3$).

Ethyl (*S*)-(−)-5,6-epoxyhexanoate (3b′)

Treatment of **2b** (1.58 g, 10 mmol) under the general procedure of HKR using (*S*,*S*)-(salen)Co(OAc) complex as the catalyst gave **3b′** (711 mg, 45% yield). $[\alpha]_D^{20} = -15.0$ (*c* 1.1, $CHCl_3$). The other spectra data were identical in all respects to those of **3b**.

Ethyl (*R*)-(+)-5,6-dihydroxyhexanoate (4b′)

Treatment of **2b** (1.58 g, 10 mmol) under the general procedure of HKR using (*S*,*S*)-(salen)Co(OAc) complex as the catalyst gave **4b′** (862 mg, 49% yield). $[\alpha]_D^{20} = -14.2$ (*c* 2.0, EtOH). The other spectra data were identical in all respects to those of **4b**.

Method A for (*R*)-(−)-δ-hydroxymethyl-δ-valerolactone (5b′)

Treatment of **3b′** (318 mg, 2 mmol) by method A for **5b** gave **5b′** (231 mg, 89% yield, 98% ee). $[\alpha]_D^{20} = -34.3$ (*c* 1.3, $CHCl_3$) [lit.[10] $[\alpha]_D^{20} = +34.68$ (*c* 1.3, $CHCl_3$) for its enantiomer]. The other spectra data were identical in all respects to those of **5b**.

Method B for 5b′

Treatment of **4b′** (350 mg, 2 mmol) by method B for **5b** gave **5b′** (234 mg, 90% yield, 96% ee). $[\alpha]_D^{20} = -33.5$ (*c* 1.0, $CHCl_3$).

One-pot procedure for 5b′

Treatment of **2b** (791 mg 5 mmol) under the one-pot procedure as described for the preparation of **5b** except using (*S*,*S*)-(salen)Co(OAc) complex as the catalyst for HKR gave **5b′** (527 mg, 81% yield, 96% ee). $[\alpha]_D^{20} = -33.8$ (*c* 0.8, $CHCl_3$).

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