KINETIC RESOLUTION OF ARYL GLYCIDYL ETHERS : A PRACTICAL SYNTHESIS OF OPTICALLY PURE β-BLOCKER - *S*-METOPROLOL

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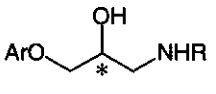
Abstract - Kinetic resolution of (±)-aryl glycidyl ethers using (*R,R*)-salen Co(III)OAc and water provided enantiomerically pure arylglycidyl ether and 1-arylglycerol derivatives with high enantiomeric excess. Application of this approach to (*S*)-metoprolol has been described.

Chirality, in the context of biological activity, is an important phenomenon because great differences in activities are observed for enantiomers of a bioactive substance. For example, (*S*)-isomer of all aryloxy-propanolamine type β-blockers (**1**) is clinically useful, while the corresponding (*R*)-isomer has undesirable properties.[1]

Chiral glycidyl derivatives are perhaps one of the most versatile C_3-chiral synthons with numerous applications for β-blockers, MAO inhibitors, alkyl glycerophospholipids and other pharmaceuticals as well as in organic synthesis.[2] Many protocols have been developed[3] for the synthesis of racemic and nonracemic aryl glycidyl ethers. However, the recently reported technique of hydrolytic kinetic resolution (HKR) of terminal epoxide by Jacobsen *et al.*,[4] has been unexplored. The HKR reaction is highly enantio-selective but most importantly, extremely simple to work with compared to other approaches for chiral glycidyl ethers. This note highlights HKR reaction for obtaining enantiomerically pure aryl glycidyl ether and 1-aryl glycerol derivatives, and its application to the synthesis of (*S*)-metoprolol (**2**).



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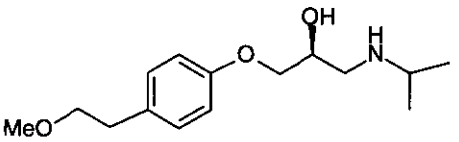
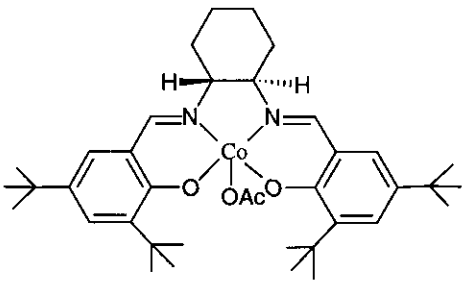


2 (*S*)-metoprolol

In a typical experiment, (±)-phenyl glycidyl ether (**3**), freshly prepared catalyst Salen-Co(III)OAc (**A**) (Figure 1) and water were stirred at room temperature for 5 h and then chromatographed to afford 44% of (*S*)-phenyl glycidyl ether (**4**) (91% ee) {$[\alpha]_D$ +16.0° (c 3.1, MeOH); lit.,[5] $[\alpha]_D$ +14.1° (c 2.36, MeOH)

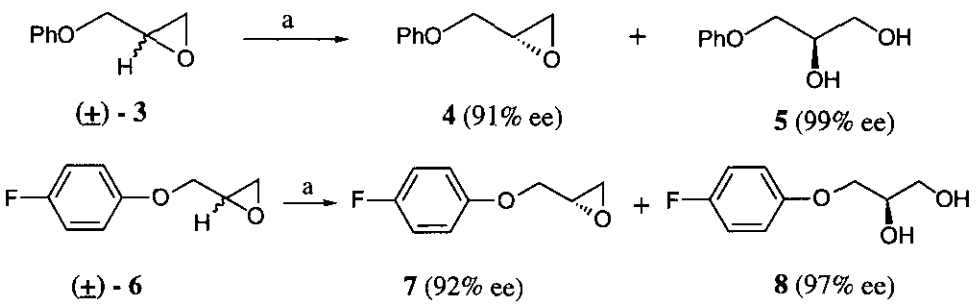
(80% ee)} and 49% of (*R*)-1-phenylglycerol (**5**) (99% ee) {$[\alpha]_D$ -9.6° (c 1.36, EtOH); lit.,[3b] (*S*-isomer with 88% ee) $[\alpha]_D$ +8.6° (c 1.1, EtOH)}.



A

Figure 1

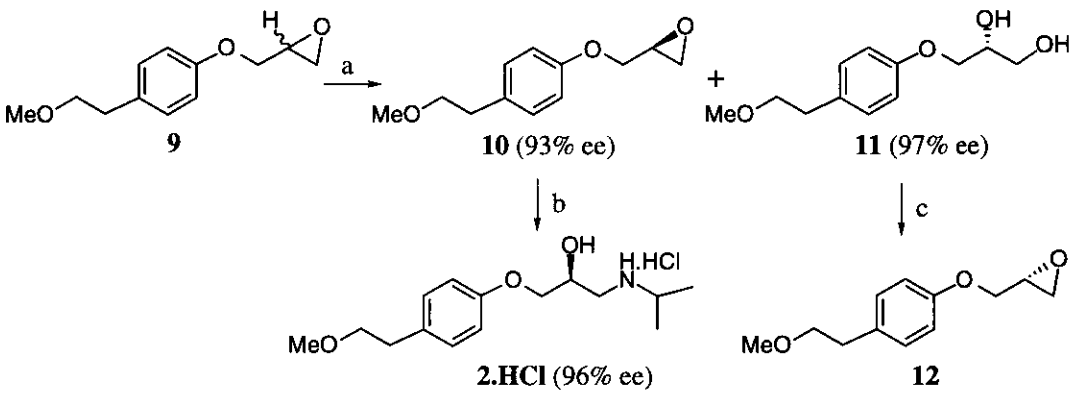
Hydrolytic kinetic resolution of (±)-(4-fluorophenyl) glycidyl ether (**6**) similarly gave (*S*)-4-fluorophenyl glycidyl ether (**7**) (92% ee) {$[\alpha]_D$ +5.0° (c 1.6, $CHCl_3$); lit.,[6] $[\alpha]_D$ +5.4° (c 2.3, $CHCl_3$)} and (*R*)-1-(4-fluorophenyl) glycerol (**8**) (97% ee)[7]{$[\alpha]_D$ -9.6° (c 1.6, EtOH), lit.,[7] $[\alpha]_D$ -9.7° (c 1.0, EtOH)}(Scheme 1).



Scheme 1. a) 0.5 mol% (*R*,*R*)-**A**, H_2O (0.55 eq), rt, 5 h.

The truly fascinating kinetic resolution of (±)-aryl glycidyl ethers (**3** and **6**) prompted us to undertake the synthesis[8] of chiral β-blocker-(*S*)-metoprolol (**2**) starting from (±)-4-(2-methoxyethyl) phenylglycidyl ether[9] (**9**). Compound (**9**), catalytic Salen complex (**A**) and 0.55 eq. of H_2O were stirred for 18 h at room temperature. The reaction mixture was chromatographed on silica gel to give (*R*)-1-[4-(2-methoxyethyl)phenyl]glycerol (**11**) (97% ee) {$[\alpha]_D$ -9.0° (c 2.28, MeOH)}. The ee of 97% was determined by Mosher ester studies. Subsequently compound (**11**) was subjected to Mitsunobu reaction with DEAD and Ph_3P in refluxing benzene to afford the (*R*)-glycidyl ether (**12**) {$[\alpha]_D$ -5.2° (c 1.20, $CHCl_3$)}. The corresponding (*S*)-1-[4-(2-methoxyethyl)phenyl] glycidyl ether (**10**) {$[\alpha]_D$ +4.9° (c 1.27, $CHCl_3$)} was

obtained in 45% yield with 93% ee. Treatment of (*S*)-**10** with isopropylamine and water under reflux for 6 h, followed by treatment with 11N HCl in methanol gave (*S*)-metoprolol hydrochloride (**2.HCl**) {$[\alpha]_D$ -21.0° (c 1.26, MeOH); lit.,[8] $[\alpha]_D$ -21.8° (c 1.0, MeOH)} with 96% ee; mp 92°C, lit.,[8] mp 92-94°C (Scheme 2).



Scheme 2. (a) 0.5 mol% (*R*,*R*)-**A**, (0.55 eq) H_2O, rt, 18 h (b) i. $iPrNH_2$, H_2O, reflux, 3 h ii.HCl, MeOH, 1 h (c) Ph_3P, DEAD, C_6H_6, reflux, 12 h.

In conclusion, it is pertinent to mention that HKR of aryl glycidyl ether has been performed for the first time to afford chiral aryl glycidyl ether and chiral aryl glycerol derivatives with high enantiomeric excess. Both these intermediates have versatile applications and pharmaceutical importance.

ACKNOWLEDGEMENTS

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EXPERIMENTAL SECTION

NMR spectra were recorded on Varian Gemini-200 MHz and Varian Unity-400 MHz using TMS as an internal standard in $CDCl_3$. Chemical shifts were expressed in parts per million downfield from TMS. MS spectra were recorded on VG micro Mass 7070H (LRMS) and VG Autospec M (HRMS) spectrometers. Melting point was determined on Buchi 535 apparatus. Optical rotation was measured in JASCO DIP-370 digital polarimeter.

General Procedure for Hydrolytic Kinetic Resolution of Aryl Glycidyl Ethers:

Racemic aryl glycidyl ether (19.23 mmol) and (*R*,*R*)-Salen Co(III)OAc complex (**A**) (64 mg, 0.1 mmol) were vigorously stirred for 15 min and then cooled to 0 °C. Water (0.19 mL, 10.58 mmol) was added over a period of 1 h through syringe pump. The reaction mixture was stirred at rt and monitored by HPLC (ODS

column, UV : 225 nm, 60% MeCN in H_2O). The reaction was diluted with ethyl acetate, dried (Na_2SO_4) and concentrated to afford a residue which was chromatographed on silica gel using ethyl acetate-light petroleum. The first fraction to be eluted with 1:9 ethyl acetate-light petroleum gave the (*S*)-aryl glycidyl ether. Further elution with 1:1 ethyl acetate-light petroleum afforded the (*R*)-1-arylglycerol.

(*S*)-Phenyl glycidyl ether (4)

Colourless liquid; yield 44%; $[\alpha]_D$ +16.0° (c 3.1, MeOH); [lit.,[5] $[\alpha]_D$ +14.1° (c 2.36, MeOH) (80% ee)]; ^1H NMR (200 MHz, $CDCl_3$) δ 2.74 (dd, J = 2.27, 4.5 Hz, 1 H), 2.89 (t, J = 4.5 Hz, 1 H), 3.33 (m, 1 H), 4.00 (dd, J = 4.5, 11.3 Hz, 1 H), 4.17 (dd, J = 4.5, 11.3 Hz, 1 H), 6.90 (m, 3 H), 7.27 (m, 2 H); MS : m/z 150 (M+).

(*R*)-1-Phenyl glycerol (5)

Colourless liquid; yield 49%; $[\alpha]_D$ -9.6° (c 1.36, EtOH); lit.,[3b] (S-isomer with 88% ee) $[\alpha]_D$ +8.6° (c 1.1, EtOH); ^1H NMR (200 MHz, $CDCl_3$) δ 2.05 (br s, 1 H), 2.63 (br s, 1 H), 3.5 -3.89 (m, 3 H), 4.03 (m, 2 H), 6.89 (m, 3 H), 7.25 (m, 2 H); MS : m/z 168 (M+).

(*S*)-4-Fluorophenyl glycidyl ether (7)

Colourless liquid; yield 45%; $[\alpha]_D$ +5.0° (c 1.6, $CHCl_3$); lit.,[6] $[\alpha]_D$ +5.4° (c 2.3, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 2.68 (dd, J = 2.3, 4.5 Hz, 1 H), 2.85 (t, J = 4.5 Hz, 1 H), 3.27 (m, 1 H), 3.89 (dd, J = 6.7, 15.7 Hz, 1 H), 4.11 (dd, J = 6.7, 15.7 Hz, 1 H), 6.74-7.03 (m, 4 H); MS : m/z 168 (M+).

(*R*)-1-(4-Fluoro)phenyl glycerol (8)

Colourless liquid; yield 49%; $[\alpha]_D$ -9.6° (c 1.6, EtOH); lit.,[7] $[\alpha]_D$ -9.7° (c 1.0, EtOH); ^1H NMR (200 MHz, $CDCl_3$) δ 2.22 (br s, 1 H), 2.77 (br s, 1 H), 3.64-3.90 (m, 2 H), 3.93-4.16 (m, 3 H), 6.75-7.03 (m, 4 H); MS : m/z 186 (M+).

(*S*)-1-[4-(2-Methoxyethyl)]phenyl glycidyl ether (10)

Colourless liquid; yield 45%; $[\alpha]_D$ +4.9° (c 1.27, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 2.72-2.88 (m, 4 H), 3.34 (m, 4 H), 3.55 (m, 2 H), 3.98 (dd, J = 5.4, 12.0 Hz, 1 H), 4.18 (dd, J = 4.2, 12.0 Hz, 1 H), 6.82 (d, J = 8.4 Hz, 2 H), 7.10 (d, J = 8.4 Hz, 2 H); HRMS Found m/z 208.1108. Calcd for $C_{12}H_{16}O_3$: M 208.1099.

(*R*)-1-[4-(2-Methoxyethyl)]phenyl glycerol (11)

Colourless liquid; yield 49%; $[\alpha]_D$ -9.0° (c 2.28, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (br s, 1 H), 2.60 (br s, 1 H), 2.80 (t, J = 6.9 Hz, 2 H), 3.34 (s, 3 H), 3.55 (t, J = 6.9 Hz, 2 H), 3.67-3.82 (m, 2 H), 4.00-4.14 (m, 3 H), 6.83 (d, J = 8.5 Hz, 2 H), 7.12 (d, J = 8.5 Hz, 2 H); HRMS Found m/z 226.1208. Calcd for $C_{12}H_{18}O_4$: M 226.1205.

(*R*)-1-[4-(2-Methoxyethyl)]phenyl glycidyl ether (12)

A solution of the glycerol derivative (**11**) (2.0 g, 8.85 mmol), Ph_3P (3.5 g, 13.36 mmol) and DEAD (2.1 mL, 13.36 mmol) in benzene (25 mL) was heated under reflux for 20 h. Solvent was removed and the residue was diluted with ether to precipitate Ph_3PO which was filtered. The filtrate was concentrated and the residue was chromatographed on silica gel by using ethyl acetate-light petroleum (1:9) as an eluent to afford **12** as a colourless liquid (1.49 g, 81%); $[\alpha]_D$ -5.2° (c 1.2, $CHCl_3$); the ^{1}H NMR spectrum of **12** was identical with the ^{1}H NMR spectrum of the corresponding (*S*)-isomer (**10**).

(*S*)-Metoprolol hydrochloride (2.HCl)

A mixture of **10** (1.6 g, 7.7 mmol), isopropylamine (6.6 mL, 76.9 mmol) and water (0.15 mL) was heated under reflux for 6 h. The reaction mixture was concentrated to dryness to give crude metoprolol (**2**) as a waxy solid (1.85 g, 90%). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.10 (d, J = 6.4 Hz, 6 H), 2.17 (br s, 1 H), 2.67-2.93 (m, 5 H), 3.38 (s, 3 H), 3.59 (t, J = 7.4 Hz, 2 H), 3.98 (m, 3 H), 6.86 (d, J = 8.5 Hz, 2 H), 7.14 (d, J = 8.5 Hz, 2 H); HRMS Found m/z 252.1602. Calcd for $C_{14}H_{22}NO_3$: M-CH_3 252.1599.
To a solution of **2** (1.85 g, 6.93 mmol) in methanol (15 mL), 11N HCl (2 mL) was added and the mixture was heated under reflux for 1 h. The reaction mixture was concentrated and the residue was recrystallised from ether to afford (*S*)-(**2.HCl**) as a solid (1.9 g, 90%). mp 92°C; lit.,[8] mp 92-94°C; $[\alpha]_D$ -21.0° (c 1.26, MeOH); lit.,[8] $[\alpha]_D$ -21.8° (c 1.0, MeOH).

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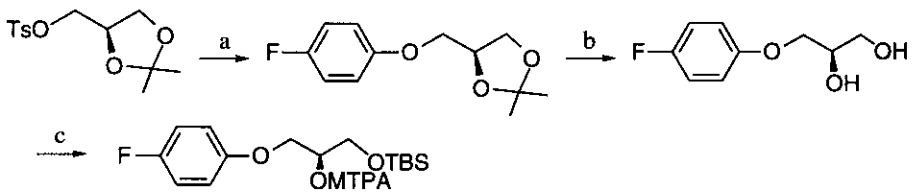
6. Prepared according to the procedure reported in ref. 5.

7. Enantioselective synthesis of compound (**8**) starting from (*R*)-2,3-O-isopropylidine-1-*O*-tosyl glycerol and 4-fluorophenol was performed for comparision. Enantiomeric excess was confirmed by NMR spectral studies of the corresponding MTPA ester.



a) 4-Fluorophenol, NaH, DMF, rt, 3 h (b) HCl, MeOH, rt, 2 h (c) i. TBSCl, Imidazole, CH_2Cl_2, rt, 3 h ii MTPA, DCC, DMAP (cat.), CH_2Cl_2, rt, 12 h.

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