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A facile and convenient chemoenzymatic synthesis of optically active *O*-(4-methoxyphenyl)-glycidol and 1,2-diacyl-*sn*-glycerol

Ahmed Kamal,* Mahendra Sandbhor, Ahmad Ali Shaik and M. Shaheer Malik

Biotransformations Laboratory, Division of Organic Chemistry, Indian Institute of Chemical Technology, Hyderabad 500 007, India

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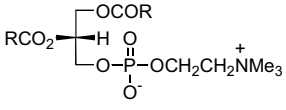
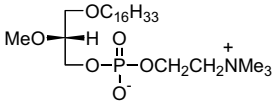
Abstract—A convenient preparation of the (*R*)- and (*S*)-enantiomers of *O*-(4-methoxyphenyl)-glycidol by a one-pot reduction of ketone **3** and in situ lipase mediated resolution is described. Activated moist aluminium oxide in the presence of *Pseudomonas cepacia* lipase immobilized on ceramic particles (PS-C) has been found effective for the transesterification leading to a high degree of enantioselectivity. These chiral glycidols were further used as a chiral precursor for the synthesis of biologically important 1,2-*O*-diacyl-*sn*-glycerol under mild reaction conditions. The present method is facile for the synthesis of chiral glycidols in high enantioselectivity when compared to the previously reported methods.

1. Introduction

Syntheses of optically active glycerolipids have attracted a great deal of attention, mainly because of their structural features and importance in the biological membrane. Many analogues of 1,2-diacyl-*sn*-glycerol have been synthesized because the diacylglycerol requiring enzymes play a key role in phospholipid metabolism.[1] Diacylphosophatidylcholine **1** constitutes the major structural component of the cell membranes and has been widely used to study the drug delivery in liposomes.[2]



Diacylphosphatidylcholine **1**



Glycerophosphocholine **2**

Unnatural phospholipids containing a 16- or 18-carbon aliphatic chain at the *sn*-1 position and an *O*-methyl group at the *sn*-2 position of glycerophosphocholine, **2** have potent cytotoxic activity towards various tumour cells.[3] The classical route from D-mannitol to diacylglycerol is lengthy and involves the possible racemization of the intermediates on storage.[4] Other synthetic approaches have used chiral precursors such as L-serine, L-arabinose, L-ascorbic acid, L-tartaric acid, (*S*)-maleic acid, L-glyceric acid and glycidols.[4c] Very recently, enantiomerically pure diacylglycerols have also been synthesized by lipase mediated sequential transesterification of the racemic *O*-alkyl glycerols with various lipases.[5a,b] However, the enantiopurity of the resolved products was lower in one of the enantiomers. Therefore, the double kinetic resolution method was employed in order to increase the enantiopurity.[5b] Such double kinetic resolution strategies have also been employed earlier for the enhancement of enantiomeric purity.[5c] Nevertheless, this method enhances the enantiopurity but requires longer reaction times for this resolution process. 1,2-*O*-Diacyl-*sn*-glycerol phospolipid **9** is an important intermediate and has been used for the synthesis of mixed diacylglycerol. A direct approach to mixed 1,2-*O*-diacyl-*sn*-glycerols has been investigated by sequential acetylation of protected chiral 1,2-diol.[5c] Bittman et al. have synthesized 1-*O*-benzyl-*sn*-glycerol and 3-*O*-(4′-methoxyphenyl)-*sn*-glycerol **7** via the asymmetric dihydroxylation of allyl 4-methoxyphenyl ether using an AD-mix.[6]

Homochiral glycidol, *O*-benzyl glycidol and related C_3 synthons have found widespread application as chiral building blocks for asymmetric syntheses.[7–9] Removal of the benzyl group from *O*-benzyl glycidol caused some difficulties, therefore the synthesis of its equivalent

* Corresponding author. Tel.: +91 40 27193157; fax: +91 40 27193189; e-mail: ahmedkamal@iict.res.in

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synthon *O*-(4-methoxyphenyl)-glycidol, which can be easily deprotected to glycidol was employed.[10a] Schneider et al. and Takano et al. have previously resolved the racemic chlorohydrin **4** and *O*-(4-methoxyphenyl)-glycidol **6**, respectively, by employing both enzymatic hydrolysis and acyl transfer reactions catalyzed by lipase from *pseudomonas* species.[10b,c] It can be seen that in the case of the resolution process developed by Takano, one of the enantiomers is usually obtained in much lower enantiopurity over longer reaction times. Herein, we report the synthesis of enantiopure (*S*)- and (*R*)-*O*-(4-methoxyphenyl)-glycidol by a one-pot reduction of ketone **3** and in situ lipase mediated resolution, which has been further utilized as a chiral precursor for the synthesis of both the enantiomers of 1,2-*O*-diacyl-*sn*-glycerol in high enantiopurity.

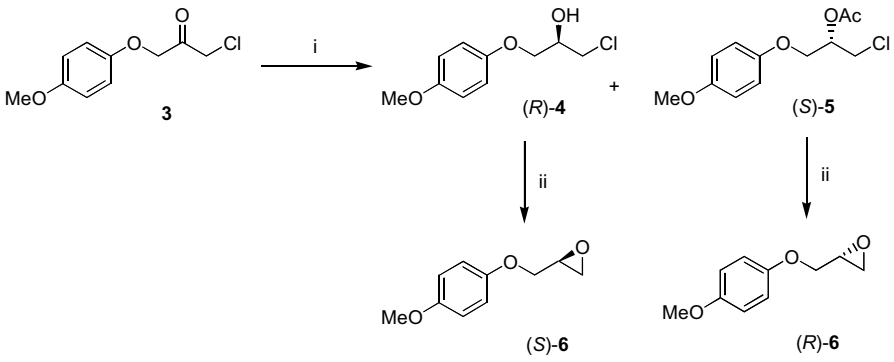
2. Result and discussion

In continuation of our previous studies for the one-pot reduction of a ketone and in situ lipase-mediated resolution of secondary alcohols, allylic alcohols, azidoalcohols and 1,2-diols,[11] we investigated a new one-pot protocol for the synthesis of enantiomerically pure chlorohydrins by a lipase-mediated resolution, which leads to the synthesis of chiral 1,2-diols and PMP protected glycidol. A one-pot reduction of ketone **3**[10d] with sodium borohydride in the presence of moist alumina followed by in situ lipase mediated resolution employing *Pseudomonas cepacia* lipase immobilized on ceramic particles (PS-C) and isopropenyl acetate in diisopropyl ether afforded the corresponding chiral alcohol (*R*)-**4** and acetate (*S*)-**5** with >99% and 92% ee, respectively (Scheme 1). The reaction progress was monitored on chiral HPLC[12] and stopped upon reaching about 50% conversion (2 h at 40 °C). In our previous studies, we have observed that activated moist alumina plays a vital role in the lipase mediated transesterification of secondary alcohols.[11a] The effect of alumina was studied by carrying out the transesterification of racemic chlorohydrin **4** in the presence of alumina and without alumina. It was observed that in the absence of alumina, the reaction goes beyond 50% conversion in a rapid manner and is difficult to control, leading to a decrease in the enantioselectivity of the acetate (*S*)-**5**. Hydrolysis of acetate (*S*)-**5** and in situ epoxide ring formation of chlorohydrin **4** was carried out with 10% aqueous NaOH under controlled conditions (Scheme 1).

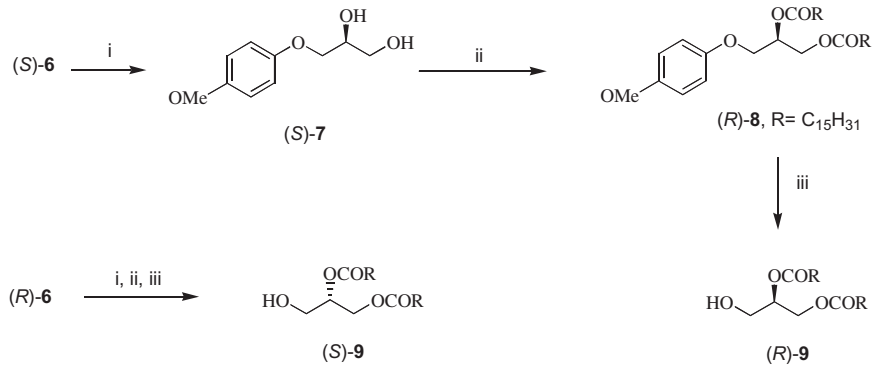
This method describes an efficient synthesis of enantiomerically pure PMP protected glycidol **6** in a shorter synthetic sequence when compared to earlier methods.[10a–c] Glycidol **6** serves as an important chiral building block in organic synthesis and is a source of chirality for the synthesis of optically active diol **7** and diacylglycerols **8** and **9**. Hydrolysis of chiral epoxide **6** by using strong acids such as sulfuric acid and perchloric acid, lead to racemization diol **7** was obtained in low enantioselectivity.[13] However, the chances of the racemization of diol **7** are reduced when the hydrolysis is carried out under mild conditions using HBr, which is in situ generated by catalytic amounts of CBr_4 in water. PMP protected diols (*S*)-**7** and (*R*)-**7** were obtained in 97% and 90% ee respectively (Scheme 2). Condensation of diol **7** with palmitic acid in the presence of DCC and DMAP affords PMP protected dipalmitoyl glycerol **8**. Further, PMP group has been deprotected by the treatment of ceric ammonium nitrate (CAN) to give the corresponding dipalmitoyl glycerols (*R*)-**9** and (*S*)-**9** with 97% and 90% ee respectively, in quantitative yields. Similarly, chiral 1,2-diacylglycerols with various R groups can be synthesized in good to high enantioselectivity by employing the present chemoenzymatic method.

3. Conclusion

Herein, we have reported an efficient short synthetic route for the preparation of both enantiomers of PMP protected glycidol **6**. These are important chiral building blocks for the synthesis of a variety of organic compounds of biological significance. Furthermore, optically active glycerol derivative **7**, which is usually employed as a precursor in many natural products, has been prepared in good enantioselectivity. Moreover, this method is cost-effective and can be extended for the synthesis of other related chiral glycerolipids. This protocol provides high enantiopurity for both the enantiomers with a much more spontaneous reaction process in comparison to conventional resolution processes.



Scheme 1. Reagents and conditions: (i) $NaBH_4$, moist Al_2O_3, diisopropyl ether, 3 h, then lipase PS-C, isopropenyl acetate, 40 °C, 2 h; (ii) 10% aq NaOH, rt, 1 h.



Scheme 2. Reagents and conditions: (i) CBr_4, H_2O, reflux, 4 h; (ii) palmitic acid ($C_{15}H_{31}COOH$), DCC, DMAP, CH_2Cl_2, rt, 60 h; (iii) CAN, CH_3CN, H_2O, rt, 12 h.

4. Experimental

4.1. Material and methods

Enzymatic reactions were carried out on a 'Labline Environ-shaker' at 150 rpm. Infrared spectra of a neat sample are reported in wave numbers (cm^{-1}). ^1H NMR were recorded as solutions in $CDCl_3$ and chemical shifts are reported in parts per million (ppm, δ) on a 200 MHz instrument. Coupling constants are reported in hertz (Hz). LSIMS mass spectra were recorded on an Autospec M with 7 kV acceleration voltage and 25 kV gun voltage. HPLC analyses were performed on 'Shimadzu LC-10AT' system controller, and UV monitor as detector. Specific rotations were recorded on SEPA-300 Horiba high sensitive polarimeter, fixed with sodium lamp of wavelength 589 nm.

4.2. Chemicals and enzymes

Neutral alumina, epichlorohydrin, CBr_4, palmitic acid, ceric ammonium nitrate, isopropenyl acetate, DCC, DMAP and solvents were commercial grade and used without purification. Activated moist alumina was prepared by the homogeneous addition of 1.1 mL of water to 10 g of neutral alumina (preheated in oven at 200 °C). Racemic compounds chlorohydrin **4** and acetate **5** were prepared by the usual sodium borohydride reduction in methanol and by acetylation of racemic compound **4** with acetic anhydride and DMAP, respectively. *P. cepacia* lipase immobilized on ceramic particles (PS-C) was purchased from Amano (Nagoya, Japan).

4.3. Typical experimental procedure for the one-pot reduction and in situ lipase-mediated resolution: preparation of optically active (*R*)-4 and (*S*)-5

To a solution of 1-chloro-3-(4-methoxyphenoxy)-2-propanone **3** (1.07 g, 5 mmol) in diisopropyl ether (30 mL) were added activated alumina (3 g) and $NaBH_4$ (0.38 g, 10 mmol). The suspension was shaken at 150 rpm at 40 °C for 3 h and monitored by TLC for the complete reduction. Then lipase PS-C (1.07 g), isopropenyl acetate (4 mL) was added to the reaction mixture and monitored by chiral HPLC[12] analysis until it reached 50% conversion (2 h). The reaction was filtered and washed with water followed by brine. The organic layer was dried over anhydrous sodium sulfate, concentrated under reduced pressure and purified by silica gel column chromatography (EtOAc-hexane, 5:95) to give (*R*)-**4** 0.45 g (42%) and (*S*)-**5** 0.58 g (45%).

(*R*)-**4**:[10c] >99% ee [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46 × 25 cm) column; eluent: hexane/isopropanol = 80/20; flow rate: 0.5 mL/min; detector: 254 nm (t_R = 20.72 min)]; $[\alpha]_D^{25} = -3.3$ (*c* 1, $CHCl_3$); IR (neat): 3443 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 3.6–3.8 (5H, m), 3.9–4.2 (3H, m), 6.8 (4H, s); LSIMS (*m/z*): 216 (M^+); Anal. Calcd for $C_{10}H_{13}ClO_3$: C, 55.44; H, 6.05. Found: C, 55.24; H, 6.02.

(*S*)-**5**:[10c] 92% ee [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46 × 25 cm) column; eluent: hexane/isopropanol = 97.5/2.5; flow rate: 0.4 mL/min; detector: 254 nm (t_R = 27.39 min)]; $[\alpha]_D^{25} = +24.3$ (*c* 1.3, $CHCl_3$); IR (neat): 1744 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.1 (3H, s), 3.7–3.8 (5H, m), 4.1 (2H, d, *J* = 5.12 Hz), 5.3 (1H, quint, *J* = 5.0 Hz), 6.8 (4H, s); LSIMS (*m/z*): 258 (M^+); Anal. Calcd for $C_{12}H_{15}ClO_4$: C, 55.71; H, 5.84. Found: C, 55.25; H, 5.70.

4.4. (*S*)-*O*-(4-Methoxyphenyl)glycidol (*S*)-6[10a]

To a solution of (*R*)-**4** (216 mg, 1 mmol) in isopropyl alcohol (5 mL) was added 10% aqueous NaOH (0.48 mL). The mixture was stirred at room temperature for 1 h. Evaporation of isopropyl alcohol followed by CH_2Cl_2 extraction, water wash, drying and removal of solvent afforded glycidol (*S*)-**6** as a white solid; yield: 135 mg (75%); mp 43 °C; >99% ee [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46 × 25 cm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.7 mL/min; detector: 254 nm (t_R = 17.3 min)]; $[\alpha]_D^{25} = +11.8$ (*c* 0.6, MeOH) {lit.[10a] $[\alpha]_D^{28} = +11.0$ (*c* 1.08, MeOH)}; IR (neat): 3425, 2100 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 2.6–2.7 (1H, m), 2.8–2.9 (1H, m), 3.2–3.3 (1H, m), 3.7 (3H, s), 3.9 (1H, dd, *J* = 10.98, 5.12 Hz), 4.1 (1H, dd, *J* = 10.98, 3.66 Hz), 6.7–6.9 (4H, m); LSIMS (*m/z*): 121 (M^+-59); Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.53; H, 11.59.

4.5. (*R*)-*O*-(4-Methoxyphenyl)-glycidol (*R*)-6[10a]

Prepared from (*S*)-**5** (258 mg, 1 mmol), and 10% NaOH (1 mL) following the same above procedure to get (*R*)-**6** as a white solid; yield: 135 mg (75%); mp 42 °C; 92% ee [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46 × 25 cm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.7 mL/min; detector: 254 nm (t_R = 13.11 min)]; $[\alpha]_D^{25} = -10.8$ (*c* 1.0, MeOH) {lit.[10a] $[\alpha]_D^{26} = -11.7$ (*c* 1.06, MeOH), 100% ee}.

4.6. (*S*)-3-*O*-(4′-Methoxyphenyl)-*sn*-glycerol (*S*)-7

A suspension of ether (*S*)-**6** (160 mg, 0.88 mmol) and CBr_4 (28 mg, 0.086 mmol) in water (5 mL) was refluxed for 5–6 h. After cooling, the reaction mixture was extracted with ethyl acetate. The ethyl acetate layer was washed with water to remove any excess of acid, dried and concentrated to give the crude diol, which after purification by silica gel column chromatography (EtOAc-hexane, 6:4) gave diol (*S*)-**7** as a white crystalline solid; yield: 130 mg (80%); mp 76–78 °C; 97% ee [chiral HPLC analysis; DAICEL CHIRALCEL AD-H (0.46 × 25 cm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.7 mL/min; detector: 254 nm (t_R = 26.26 min)]; $[\alpha]_D^{25} = +7.9$ (*c* 0.5, MeOH) {lit.[10a] $[\alpha]_D^{25} = +7.8$ (*c* 1.03, MeOH), 95% ee}; IR (neat): 3425 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.2 (1H, br s), 2.7 (1H, br s), 3.7 (1H, dd, *J* = 11.33, 5.28 Hz), 3.7 (3H, s), 3.8 (1H, dd, *J* = 11.33, 3.77 Hz) 3.9 (2H, d, *J* = 6.04 Hz), 4.0–4.2 (1H, m), 6.7 (4H, s); LSIMS (*m*/*z*): 198 (M^+), 125 (M^+-73); Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.6; H, 7.12. Found: C, 60.48; H, 7.09.

4.7. (*R*)-3-*O*-(4′-Methoxyphenyl)-*sn*-glycerol (*R*)-7

Prepared from (*R*)-**6** (160 mg, 0.88 mmol) and CBr_4 (0.028 g, 0.086 mmol) following the same above procedure to give (*R*)-**7** as a white crystalline solid; yield: 130 mg (80%); mp 76–77 °C; 90% ee [chiral HPLC analysis; DAICEL CHIRALCEL AD-H (0.46 × 25 cm) column; eluent: hexane/isopropanol = 90/10; flow rate: 0.7 mL/min; detector: 254 nm (t_R = 22.77 min)]; $[\alpha]_D^{25} = -7.4$ (*c* 0.5, MeOH) {lit.[10a] $[\alpha]_D^{25} = -8.25$ (*c* 1.15, MeOH), 100% ee}.

4.8. (*R*)-1,2-Dipalmitoyl-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (*R*)-8

To a solution of diol (*S*)-**7** (90 mg, 0.45 mmol) in dichloromethane (7 mL) were added DMAP (120 mg, 0.98 mmol), palmitic acid (250 mg, 0.98 mmol) and DCC (400 mg, 1.98 mmol). The reaction mixture was stirred at room temperature for 60 h, filtered and evaporated to give the crude product, which on purification by column chromatography ($CHCl_3$-hexane, 4:6) gave product **8** as a white solid; yield: 260 mg (85%); mp 64–65 °C; 97% ee [chiral HPLC analysis; DAICEL CHIRALCEL AD-H (0.46 × 25 cm) column; eluent: hexane/isopropanol = 97.5/2.5; flow rate: 0.4 mL/min; detector: 254 nm (t_R = 7.65 min)]; $[\alpha]_D^{25} = +11.5$ (*c* 1, $CHCl_3$) {lit.[6b] $[\alpha]_D^{25} = +11.3$ (*c* 6.8, $CHCl_3$), 95% ee}; IR (neat): 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.8–1.0 (6H, m), 1.3 (48H, br s), 1.6 (4H, br s), 2.3–2.4 (4H, m), 3.8 (3H, s), 4.0 (2H, d, *J* = 5.20 Hz), 4.2–4.5 (2H, m), 5.3–5.4 (1H, m), 6.8 (4H, s); LSIMS (*m*/*z*): 577 (M^+-97), 552 (M^+-122); Anal. Calcd for $C_{42}H_{74}O_6$: C, 74.51; H, 11.31. Found: C, 74.29; H, 11.13.

4.9. (*S*)-1,2-Dipalmitoyl-3-*O*-(4′-methoxyphenyl)-*sn*-glycerol (*S*)-8

Prepared from (*R*)-**7** following the same above procedure to give (*S*)-**8** as a white solid; yield: 270 mg (89%); mp 64–65 °C; 90% ee [chiral HPLC analysis; DAICEL CHIRALCEL OD (0.46 × 25 cm) column; eluent: hexane/isopropanol = 97.5/2.5; flow rate: 0.4 mL/min; detector: 254 nm (t_R = 6.87 min)]; $[\alpha]_D^{25} = -10.7$ (*c* 1.1, $CHCl_3$).

4.10. (*S*)-1,2-Dipalmitoyl-*sn*-glycerol (*S*)-9

To a suspension of diester (*S*)-**8** (190 mg, 0.28 mmol) in acetonitrile–water 4:1 (4 mL) was added ceric ammonium nitrate (360 mg, 0.67 mmol) at 0 °C. The mixture was stirred overnight at room temperature. Ethyl acetate (50 mL) and brine (50 mL) were added and the organic layer washed with saturated sodium hydrogen carbonate solution (3 × 50 mL). The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. The crude compound obtained was purified by silica gel column chromatography (EtOAc-hexane, 4:96) to give product (*S*)-**9** as a white solid; yield: 150 mg (94%); mp 66–67 °C [lit.[14] mp 68–69 °C]; 90% ee [determined from HPLC analysis of the precursor (*S*)-**8** (t_R = 6.87 min)]; $[\alpha]_D^{25} = +3.5$ (*c* 1, $CHCl_3$); IR (neat): 3400, 1730 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.9 (6H, m), 1.3 (48H, br s), 1.6 (4H, br s), 2.3–2.4 (4H, m), 3.7 (2H, t, *J* = 5.66 Hz), 4.3 (2H, dd, *J* = 12.08, 4.53 Hz), 4.9–5.1 (1H, m); FABMS (*m*/*z*): 552 (M^+-16); Anal. Calcd for $C_{35}H_{68}O_5$: C, 73.63; H, 12.36. Found: C, 73.29; H, 12.34.

4.11. (*R*)-1,2-Dipalmitoyl-*sn*-glycerol (*R*)-9

Prepared from (*R*)-**8** following the same above procedure to give (*R*)-**9** as a white solid; yield: 150 mg (94%); mp 67 °C; 97% ee [determined from HPLC analysis of the precursor (*R*)-**8** (t_R = 7.65 min)]; $[\alpha]_D^{25} = -2.7$ (*c* 1, $CHCl_3$) {lit.[6b] $[\alpha]_D^{25} = -2.7$ (*c* 3.9, $CHCl_3$), 95% ee}.

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12. Determined by chiral HPLC analysis; DIACEL CHIRALCEL OD (0.46×25 cm) column; eluent: hexane/isopropanol = 80/20; flow rate: 0.5 mL/min; detector: 254 nm.
13. The hydrolysis of chiral epoxide (*S*)-**6** (>99% ee) with H_2SO_4 in THF gave diol (*R*)-**8** with 74% ee while with $HClO_4$, it gave diol (*R*)-**8** with 75% ee.
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