ASYMMETRIC SYNTHESIS OF THE ENANTIOMERS OF 2-AMINOMETHYL-4-(4-FLUOROBENZYL)MORPHOLINE, AN INTERMEDIATE OF MOSAPRIDE, A GASTROPROKINETIC AGENT

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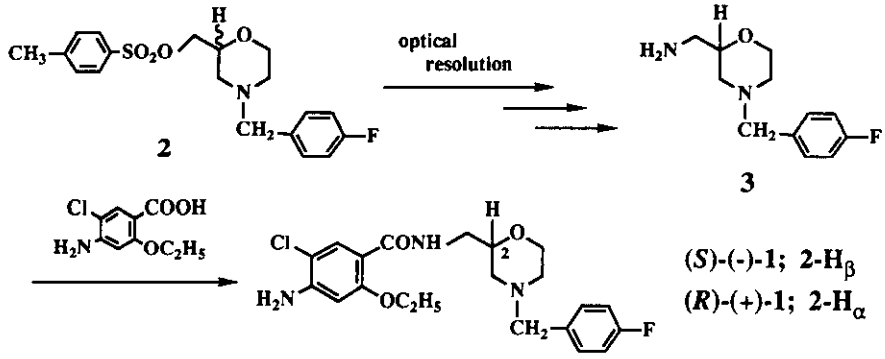
Abstract- An efficient asymmetric synthesis of the enantiomers of 2-aminomethyl-4-(4-fluorobenzyl)morpholine (**3**) which has served as an intermediate of mosapride (**1**), a potential gastroprokinetic agent, was achieved by the conversion of enantiomeric 3-chloro-1-(4-fluorobenzylamino)-2-propanol (**8**) to the oxomorpholine (**10**) followed by reduction and amination, in approximately 35% overall yield with >98% ee. This synthetic route comprises the regioselective opening of homochiral epichlorohydrin (**4**) with 4-fluorobenzylamine, with retention of the configuration.

Mosapride [(±)-4-amino-5-chloro-2-ethoxy-*N*-{[4-(4-fluorobenzyl)-2-morpholinyl]methyl}benzamide, **1**][1] is a potential gastroprokinetic agent without the dopamine D_2 receptor antagonistic activity and presently under clinical studies. In order to gain an insight into the pharmacological properties of mosapride (**1**), the synthesis of its enantiomers [(*S*)-(-)-**1** and (*R*)-(+)-**1**] and their biological evaluation appeared essential. We previously reported the synthesis of (*R*)-(+)-**1** and (*S*)-(-)-**1**, involving the resolution of the salt of (±)-4-(4-fluorobenzyl)-2-(*p*-toluenesulfonyloxymethyl)morpholine (**2**) with (+)- or (-)-*N*-(*p*-toluenesulfonyl)glutamic acid, followed by the amination of the optically active morpholine (**2**) and the subsequent condensation of the resultant 2-aminomethyl-4-(4-fluorobenzyl)morpholine (**3**)

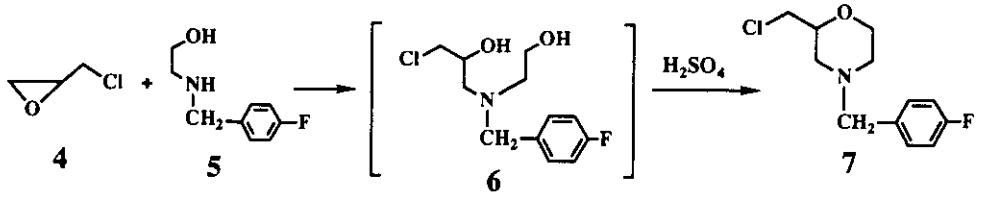
with 4-amino-5-chloro-2-ethoxybenzoic acid (Scheme 1).[2] The resolution of **2**, however, requires a considerable quantity of the resolving agent, and the procedure for the resolution is tedious. Development of a more efficient method for the asymmetric synthesis of chiral amines (*S*)-(-)-**3** and (*R*)-(+)-**3** hence became practically important. In this paper, we wish to describe a more practical asymmetric synthesis of (*S*)-(-)-**3** and (*R*)-(+)-**3**, synthesis which involves the key reaction of the commercially available (*R*)- and (*S*)-epichlorohydrins [(*R*)-(-)-**4** and (*S*)-(+)-**4**] with 4-fluorobenzylamine.

Scheme 1



In the previous paper[2] we reported that the reaction of epichlorohydrin (**4**) with 2-(4-fluorobenzylamino)ethanol (**5**), followed by cyclization of the intermediate diol (**6**) with concd H_2SO_4, gave (±)-2-chloromethyl-4-(4-fluorobenzyl)morpholine (**7**) as a precursor of **3** (Scheme 2). This route however is unsuitable for the stereospecific synthesis of the enantiomers of **7** owing to racemization during the ring closure of the diol (**6**). To overcome this problem, we intended to develop an alternative synthesis of the morpholine (**7**) or its equivalent without affecting the asymmetric center of **4**.

Scheme 2

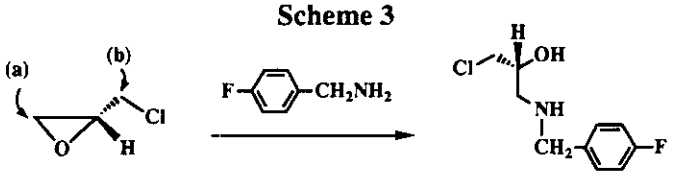


In the reaction of **4** with sterically non-hindered primary amines such as benzylamine, attack of amines on the terminal epoxide carbon gives 2-aminoethanol derivatives.[3] Morpholine rings from such 2-aminoethanols are prepared by treatment with halogenoacetyl halide in the presence of an appropriate

base, followed by cyclization of the resultant *N*-halogenoacetylaminoethanols and the subsequent reduction of the corresponding oxomorpholines.[4]

In the light of these reported facts, it was expected that the reaction of the enantiomer of **4** with 4-fluorobenzylamine as a non-hindered primary amine should give, *via* path a, optically active 3-chloro-(4-fluorobenzylamino)-2-propanol (**8**) with the same configuration of the starting enantiomer of **4** (Scheme 3). In fact, the treatment of (***R***)-(-)-**4** with 4-fluorobenzylamine in hydrocarbon such as *n*-hexane, cyclohexane, ligroin, and petroleum ether at room temperature furnished the expected (***R***)-(+)-**8** in good

Scheme 3



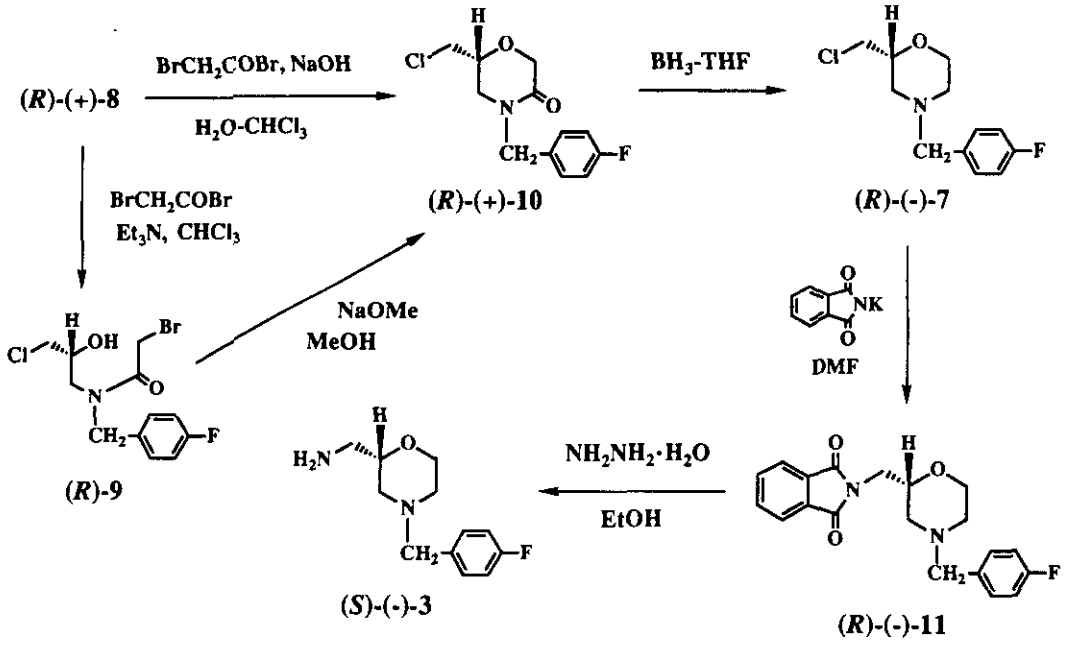
(***R***)-(-)-**4** (***R***)-(+)-**8**

yield. The use of MeOH, $CHCl_3$, and THF as a solvent resulted in unsatisfactory yields (30-40%). The analogous reaction of (***S***)-(+)-**4** with 4-fluorobenzylamine afforded the other enantiomer [(***S***)-(-)-**8**]. The enantiomeric purities of (***R***)-(+)-**8** and (***S***)-(-)-**8** obtained were determined to be more than 98% ee on the basis of hplc with a chiral stationary phase column.

The synthetic route to the optically active amine (**3**) from the homochiral (**8**) is shown in Scheme 4, where the case with the synthesis of the enantiomer (***S***)-(-)-**3** is depicted. The reaction of (***R***)-(+)-**8** with bromoacetyl bromide in the presence of Et_3N in $CHCl_3$ yielded the bromoacetamide [(***R***)-**9**], which was expected to be an intermediate for the morpholine ring closure. The isolated bromoacetamide [(***R***)-**9**], on treatment with sodium methoxide, smoothly cyclized to (*R*)-(+)-2-chloromethyl-4-(4-fluorobenzyl)-5-oxomorpholine [(***R***)-(+)-**10**]. When the reaction of (***R***)-(+)-**8** with bromoacetyl bromide was carried out in a mixture of $CHCl_3$ and *ca.* 30% NaOH solution, the ring closure proceeded directly to give (***R***)-(+)-**10** in 86% yield without isolation of the intermediate [(***R***)-**9**]. The oxomorpholine [(***R***)-(+)-**10**] was treated with BH_3-THF complex to give the morpholine [(***R***)-(-)-**7**] in 75% yield. The displacement reaction of (***R***)-(-)-**7** with potassium phthalimide, followed by treatment of (***R***)-(-)-**11** with hydrazine, gave the (*S*)-(-)-amine [(***S***)-(-)-**3**].

The (*S*)-(-)-**8** was used in the same manner to generate (*R*)-(+)-**3** *via* the corresponding intermediates [(*S*)-(-)-**10**, (*S*)-(+)-**7**, and (*S*)-(+)-**11**]. The enantiomeric purities of (*S*)-(-)-**3** and (*R*)-(+)-**3** thus prepared were determined to be more than 98% ee by chiral hplc.

Scheme 4



In conclusion, an efficient asymmetric synthesis has been developed which provides the enantiomers of amine (**3**) in approximately 35% overall yield with high enantiomeric purity.

EXPERIMENTAL SECTION

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. Ir spectra were recorded on a Hitachi 260-10 spectrometer. Electron ionization (EI) and secondary ion (SI) mass spectra were obtained on a JEOL JMS D-300 spectrometer or a Hitachi M-80B spectrometer. ^{1}H Nmr spectra were taken at 200 MHz with a Varian GEMINI-200 spectrometer. Chemical shifts are expressed as δ (ppm) values with tetramethylsilane as an internal standard, and coupling constants (*J*) are given in Hz. Optical rotations were measured at 589 nm with a Jasco DIP-4 digital polarimeter. Analytical hplc was performed with a Shimadzu LC-6A, SPD-6A instruments. Organic extracts were

dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure. Merck Silica gel 60 (70-230 mesh) was used for column chromatography. The (*R*)-(-)- and (*S*)-(+)-epichlorohydrins [**(*R*)-(-)-4** and **(*S*)-(+)-4**] were purchased from Daiso Co., Ltd. (Japan); enantiomeric excess, >98% ee.

(*R*)-(+)- and (*S*)-(-)-3-Chloro-1-(4-fluorobenzylamino)-2-propanols [(*R*)-(+)-8 and (*S*)-(-)-8]. The method of Higgins *et al.*[3] was applied. A mixture of (*R*)-(-)-epichlorohydrin [**(*R*)-(-)-4**, 20.0 g, 0.22 mol] and 4-fluorobenzylamine (27.0 g, 0.22 mol) in cyclohexane (100 ml) was stirred at room temperature for 16 h. The resulting precipitates were collected and recrystallized from *iso*-PrOH to give 32.6 g (70%) of **(*R*)-(+)-8** as stable colorless fine needles, mp 85-87°C; $[\alpha]_D^{26}$ +10.8° (*c* 1.0, MeOH); *Anal.* Calcd for $C_{10}H_{13}NOClF$: C, 55.18; H, 6.02; N, 6.43; Cl, 16.29; F, 8.73. Found: C, 55.37; H, 6.27; N, 6.36; Cl, 16.45; F, 8.55; ^1H nmr (DMSO-d_6) δ: 2.29 (br s, 1H, OH), 2.43-2.67 (m, 2H), 3.46-3.85 (m, 5H), 5.14 (br s, 1H, NH), 7.05-7.22 (m, 2H), 7.28-7.44 (m, 2H); ir (KBr) ν cm^{-1}, 3280, 1215, 745. In a similar manner, **(*S*)-(-)-8** was prepared from (*S*)-(+)-epichlorohydrin [**(*S*)-(+)-4**] in 68% yield, mp 85-87°C (*iso*-PrOH); $[\alpha]_D^{26}$ -10.8° (*c* 1.0, MeOH); *Anal.* Found: C, 55.37; H, 6.07; N, 6.35; Cl, 16.38; F, 8.55. The enantiomeric excesses (>98% ee) of **(*R*)-(+)-8** and **(*S*)-(-)-8** were analyzed by chiral hplc [column, CHIRALPAK AS (Daicel, Japan); 4.6ø × 250 mm; eluent, *n*-hexane/EtOH = 80/20 + 0.1% Et_2NH; flow rate, 0.8 ml/min; column temperature, 25°C; detection, 254 nm]. *The retention time for* ***(R)-(+)-8*** *and* **(*S*)-(-)-8** was 7.2 min and 11.4 min, respectively.

(*R*)-(+)- and (*S*)-(-)-2-Chloromethyl-4-(4-fluorobenzyl)-5-oxomorpholines [(*R*)-(+)-10 and (*S*)-(-)-10]. (a) To a mixture of **(*R*)-(+)-8** (20.0 g, 92 mmol), NaOH (36.8 g, 0.92 mol), $CHCl_3$ (200 ml), and H_2O (80 ml) was added dropwise a solution of bromoacetyl bromide (50.0 g, 0.25 mol) in $CHCl_3$ (50 ml) over a period of 1 h at 0°C. The mixture was stirred at the same temperature for 1 h and then at room temperature for an additional 18 h. The organic layer was separated and washed successively with water, 1N HCl, and brine. The solvent was evaporated to leave a crude product, which was chromatographed on silica gel with AcOEt-*n*-hexane (1:1) to give 20.3 g (86%) of **(*R*)-(+)-10**, mp 91-92°C ($CHCl_3$-Et_2O); $[\alpha]_D^{26}$ +54.9° (*c* 1.0, MeOH); *Anal.* Calcd for $C_{12}H_{13}NO_2ClF$: C, 55.93; H, 5.09; N, 5.44; Cl, 13.76; F, 7.37. Found: C, 55.90; H, 4.97; N, 5.41; Cl, 13.65; F, 7.28; ^1H nmr ($CDCl_3$) δ: 3.15-3.40 (m, 2H), 3.53 (dd, 1H, J = 11.0, 11.5, $ClC\underline{H}_2$), 3.56 (dd, 1H, J = 11.0, 11.5, $ClC\underline{H}_2$), 4.02 (m, 1H), 4.25 (d, 1H, $J_{6a,\,6e}$ = 16.0, 6-H_a), 4.40 (d, 1H, $J_{6e,\,6a}$ = 16.0, 6-H_e), 4.52 (d, 1H, J = 15.0, $C\underline{H}_2C_6H_4F$), 4.67 (d, 1H, J = 15.0,

$C\underline{H}_2C_6H_4F$), 6.96-7.11 (m, 2H), 7.20-7.33 (m, 2H); ir (KBr) ν cm^{-1}, 1625 (NC=O); EIms *m/z*: 257 (M^+). In a similar manner, **(*S*)-(-)-10** was prepared from **(*S*)-(-)-8** in 84% yield, mp 91-92°C ($CHCl_3$-Et_2O); $[\alpha]_D^{26}$ -54.9° (*c* 1.0, MeOH); *Anal.* Found: C, 55.86; H, 4.96; N, 5.42; Cl, 13.78; F, 7.24. (b) To a mixture of **(*R*)-(+)-8** (3.3 g, 15 mmol), Et_3N (3.1 g, 31 mmol), and $CHCl_3$ (100 ml) was added dropwise a solution of bromoacetyl bromide (3.8 g, 19 mmol) in $CHCl_3$ (20 ml) over a period of 10 min at 0°C. The mixture was stirred at room temperature for 1 h and washed successively with 1N HCl, water, and brine. The solvent was evaporated to leave a crude oil, which was chromatographed on silica gel with AcOEt to give 4.4 g (84%) of (*R*)-1-[*N*-bromoacetyl-*N*-(4-fluorobenzyl)amino]-3-chloro-2-propanol [**(*R*)-9**] as a pale yellow oil; ^1H nmr ($CDCl_3$) δ: 1.55 (br s, 1H, OH), 3.35-3.75 (m, 4H), 3.87 (s, 2H, $COCH_2Br$), 4.05 (m, 1H), 4.73 (s, 2H, $C\underline{H}_2C_6H_4F$), 6.59-7.30 (m, 4H); ir (neat) ν cm^{-1}, 1630 (NC=O); SIms *m/z*: 338 (MH^+). A mixture of **(*R*)-9** (4.4 g, 13 mmol), *ca.* 28% MeONa in MeOH (2.8 g, 18 mmol), and MeOH (100 ml) was heated to reflux for 3 h and then cooled to room temperature. The reaction mixture was concentrated to dryness. The residue was taken up in $CHCl_3$ and washed successively with 1N HCl, water, and brine. The solvent was evaporated to give a crude oil, which was crystallized from $CHCl_3$-Et_2O to give 2.0 g (60%) of **(*R*)-(+)-10**. This compound was identified with an authentic sample obtained in the procedure (a), on the basis of mp, tlc, ir, and ^1H nmr comparisons.

(*R*)-(-)- and (*S*)-(+)-2-Chloromethyl-4-(4-fluorobenzyl)morpholines [(*R*)-(-)-7 and (*S*)-(+)-7]. A solution of **(*R*)-(+)-10** (18.0 g, 70 mmol) in anhydrous THF (180 ml) was added to a stirred 1.0M BH_3-THF complex (120 ml) over a period of 0.5 h at -15°C under nitrogen atmosphere. The mixture was stirred at room temperature for 1 h, heated to reflux for 4 h, and then cooled to 0°C. After concd HCl (90 ml) was added to the reaction mixture, THF was evaporated *in vacuo*. The resulting aqueous solution was basified with 10% NaOH and extracted with $CHCl_3$. The extract was washed successively with water and brine, and the $CHCl_3$ was evaporated to leave a crude product, which was chromatographed on silica gel with toluene-AcOEt (1:1) to give 13.8 g (81%) of **(*R*)-(-)-7** as a colorless oil, bp 150-151°C/1 mmHg; $[\alpha]_D^{26}$ -21.3° (*c* 1.0, MeOH); *Anal.* Calcd for $C_{12}H_{15}NOClF$: C, 59.14; H, 6.20; N, 5.75; Cl, 14.55; F, 7.80. Found: C, 59.09; H, 6.22; N, 5.77; Cl, 14.55; F, 7.62; ^1H nmr ($CDCl_3$) δ: 2.02 (dd, 1H, $J_{3a,\,3e}$ = 11.0, $J_{3a,\,2}$ = 11.0, 3-H_a), 2.19 (dt, 1H, $J_{5a,\,5e}$ = 11.0, $J_{5a,\,6a}$ = 11.0, $J_{5a,\,6e}$ = 3.0, 5-H_a), 2.65 (m, 1H), 2.84 (m, 1H), 3.42-3.58 (m, 2H), 3.50 (s, 2H, $C\underline{H}_2C_6H_4F$), 3.62-3.96 (m, 3H), 6.96-7.08 (m, 2H), 7.21-7.35 (m, 2H); ir (neat) ν cm^{-1}, 1495, 1215, 1110; EIms *m/z*: 243 (M^+). In a similar manner, (*S*)-(+)-

7 was prepared from (*S*)-(-)-**10** in 85% yield; bp 150-151°C/1 mmHg; $[\alpha]_D^{26}$ +20.6° (*c* 1.0, MeOH); *Anal.* Found: C, 58.88; H, 6.15; N, 5.80; Cl, 14.62; F, 7.59.

(*R*)-(-)- and (*S*)-(+)-*N*-{[4-(4-Fluorobenzyl)-2-morpholinyl]methyl}phthalimides [(*R*)-(-)-11 and (*S*)-(+)-11]. A mixture of (*R*)-(-)-**7** (12.2 g, 50 mmol), potassium phthalimide (10.2 g, 55 mmol), and DMF (90 ml) was heated to reflux for 5 h and then poured into ice-water. The resulting precipitates were collected, washed with water, and recrystallized from *iso*-PrOH to give 13.3 g (75%) of (*R*)-(-)-**11**, mp 91-92°C; $[\alpha]_D^{26}$ -20.9° (*c* 1.0, MeOH); *Anal.* Calcd for $C_{20}H_{19}N_2O_3F$: C, 67.79; H, 5.40; N, 7.91; F, 5.36. Found: C, 67.68; H, 5.34; N, 7.83; F, 5.37; ^{1}H nmr ($CDCl_3$) δ: 1.97-2.28 (m, 2H), 2.50-2.84 (m, 2H), 3.34-3.71 (m, 4H), 3.80-4.00 (m, 3H), 6.92-7.05 (m, 2H), 7.22-7.36 (m, 2H), 7.65-7.90 (m, 4H); ir (KBr) ν cm^{-1}, 1760, 1705 (imide C=O). In a similar manner, (*S*)-(+)-**11** was prepared from (*S*)-(+)-**7** in 78% yield, mp 91-92°C (*iso*-PrOH); $[\alpha]_D^{26}$ +21.0° (*c* 1.0, MeOH); *Anal.* Found: C, 67.63; H, 5.27; N, 7.89; F, 5.30.

(*S*)-(-)- and (*R*)-(+)-2-Aminomethyl-4-(4-fluorobenzyl)morpholines [(*S*)-(-)-3 and (*R*)-(+)-3]. A mixture of (*R*)-(-)-**11** (12.0 g, 34 mmol), 85% hydrazine monohydrate (3.3 g, 56 mmol), and EtOH (40 ml) was heated to reflux for 30 min and then cooled to room temperature. The reaction mixture was diluted with $CHCl_3$ (150 ml). The precipitates were filtered off, and the filtrate was washed successively with a small amount of water and brine and dried. The solvent was evaporated to give quantitatively 8.4 g of (*S*)-(-)-**3** as a pale yellow oil. This compound was confirmed to be identical with the sample[2] obtained from (*R*)-(-)-**2**, on the basis of tlc, ir, hplc, and ^{1}H nmr comparisons. A portion of the oily (*S*)-(-)-**3** was converted to the dimaleate in the usual manner, mp 153-155°C (EtOH); $[\alpha]_D^{26}$ -14.5° (*c* 1.0, MeOH); *Anal.* Calcd for $C_{12}H_{17}N_2OF \cdot 2C_4H_4O_4$: C, 52.63; H, 5.52; N, 6.14; F, 4.16. Found: C, 52.43; H, 5.36; N, 6.12; F, 4.08. In a similar manner, (*R*)-(+)-**3** was prepared from (*S*)-(+)-**11** in almost quantitative yield. (*R*)-(+)-**3** · dimaleate, mp 153-155°C (EtOH); $[\alpha]_D^{26}$ +14.5° (*c* 1.0, MeOH); *Anal.* Found: C, 52.67; H, 5.52; N, 6.06; F, 4.09. The enantiomeric excesses (>98% ee) of (*S*)-(-)-**3** and (*R*)-(+)-**3** were analyzed by chiral hplc [column, CROWNPAK CR (+) (Daicel, Japan); 4.6ø × 150 mm; eluent, $HClO_4$ (pH 1.5)/MeOH = 95/5; flow rate, 0.5 ml/min; column temperature, 10°C; detection, 220 nm]. The retention time for (*S*)-(-)-**3** and (*R*)-(+)-**3** was 23.6 min and 27.0 min, respectively.

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