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MULTIGRAM LIPASE-CATALYZED ENANTIOSELECTIVE ACYLATION IN THE SYNTHESIS OF THE FOUR STEREOISOMERS OF A NEW BIOLOGICALLY ACTIVE α-ARYL-4-PIPERIDINEMETHANOL DERIVATIVE

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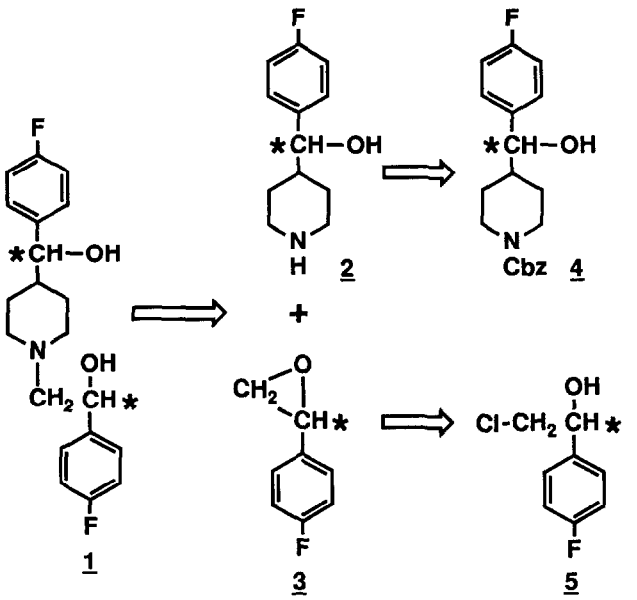
Abstract: The four stereoisomers of the novel non-narcotic analgesic 1-[2-(4-fluorophenyl)-2-hydroxyethyl]-4-[(4-fluorophenyl)hydroxymethyl]-piperidine 1 were synthesized in a convergent manner from chiral precursors 2 and 3. Optical resolution via enantioselective acylation in organic media, catalyzed by a lipase from Pseudomonas sp., was utilized in the preparation of 2 and 3 on a multigram scale with high enantiomeric purity (≥97% ee).

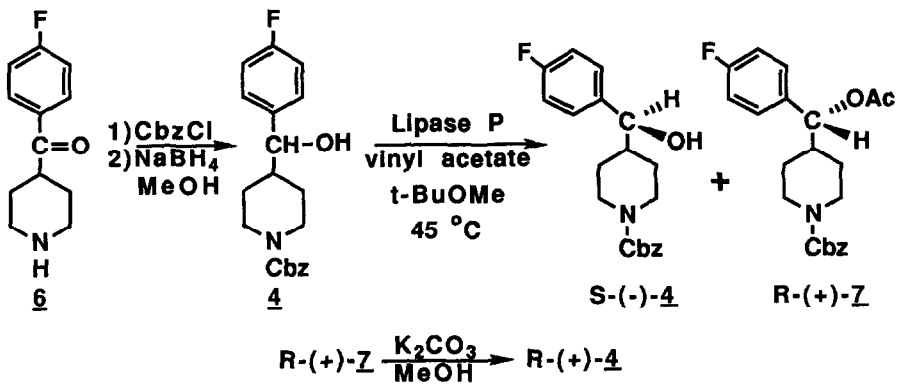
The recent trend toward the synthesis and development of single stereoisomers of chiral drugs relates to the effect that stereochemistry may have on a drug's biological activity, toxicity, metabolism and disposition.[1,2] Biocatalytic methods[3] figure prominently among the modern techniques used for the asymmetric synthesis and kinetic resolution of compounds.[4] We have recently disclosed the use of lipase-catalyzed resolution for the preparation of a new unlabeled and ^{14}C-labeled serotonin uptake inhibitor,[5] selective adenosine receptor antagonists,[6] and a new antiarrhythmic agent.[7] These compounds contained a single asymmetric center and thus were resolved into their enantiomeric pairs. Here we report the stereoselective synthesis of a new α-aryl-4-piperidinemethanol derivative 1 which has two asymmetric centers. Diol 1, which exists as a mixture of four stereoisomers, was identified as a non-narcotic analgesic and muscle relaxant.[8]

A general synthetic approach to these isomers calls for the coupling of chiral precursors 2 and 3, prepared from piperidine and halohydrin derivatives 4 and 5, respectively (Scheme I). Straightforward stereoselective synthesis of all four stereoisomers of 1 would then rely on the resolution of alcohols 4 and 5.

Initial attempts of the enzyme-catalyzed resolution of piperidine derivative 2, protected as its acetamide or t-butyl carbamate, proceeded slowly and with poor stereoselectivity.[9] On the other hand, use of benzyl carbamate (Cbz) protection resulted in a high degree of enantioselectivity. Thus, reaction of 4-(4-fluorobenzoyl)-piperidine 6[10] with benzyl chloroformate (CbzCl) followed by reduction using sodium borohydride gave racemic 4 (Scheme II). This N-protected amino alcohol was subjected to the action of a lipase from Pseudomonas sp (Amano Lipase P)[11] in a mixture of vinyl acetate and t-butyl methyl ether at 45°C.[12] The lipase preferentially acetylated the (+)-enantiomer of alcohol 4. Silica gel chromatography of the easily separable mixture provided alcohol (-)-4 and acetate (+)-7 which upon saponification yielded (+)-4. The high enantiomeric purity (≥97% ee) for each enantiomer was determined by HPLC[13] as well as ^{19}F NMR analysis of their respective α-methoxy-α-trifluoromethylphenyl acetate (MTPA) esters.[14] From ^{1}H NMR analysis of their O-methylmandelate esters,[15] (-)-4 was assigned the S-configuration and (+)-4 the



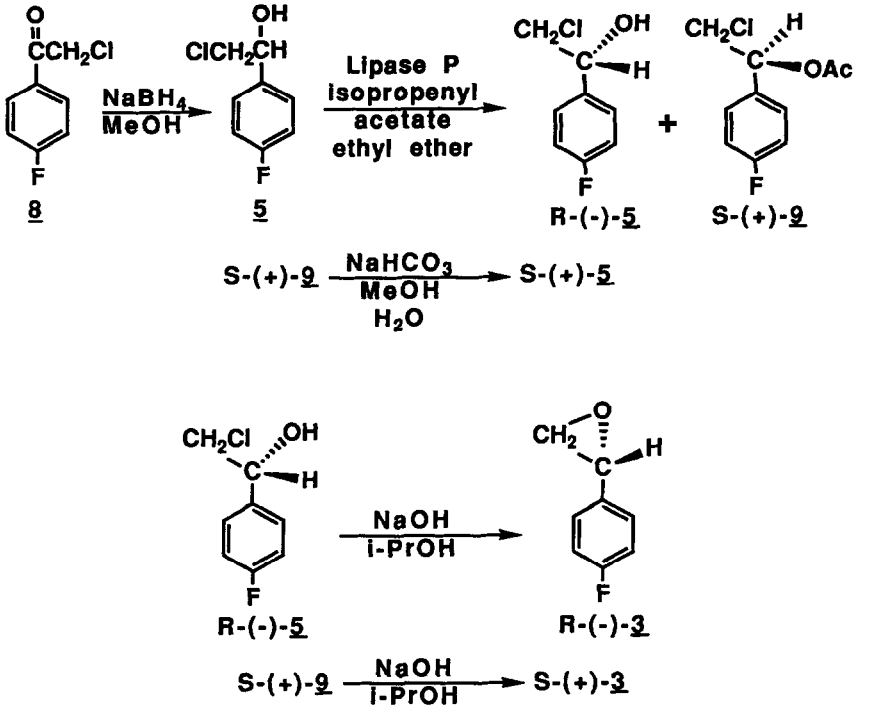
Scheme I



Scheme II

R-configuration. Eight to ten grams of (-)-4 and (+)-4 were readily obtained utilizing this methodology.

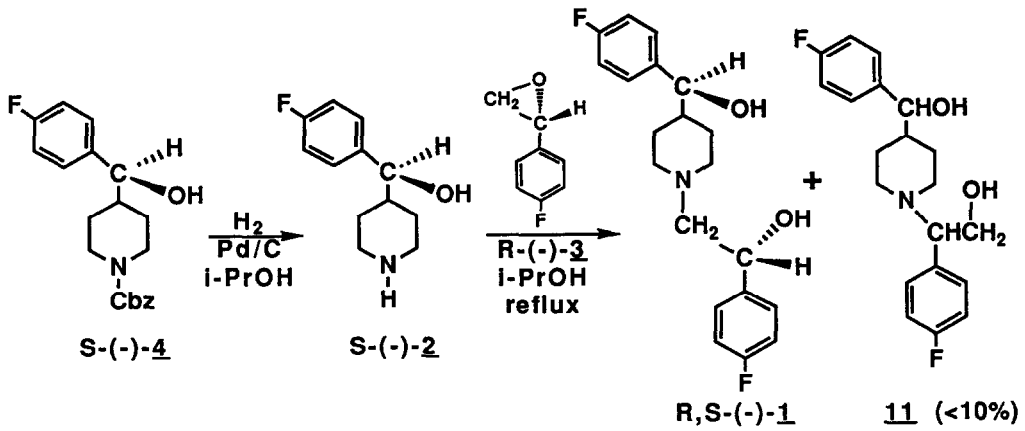
An analogous approach was used for the resolution of halohydrin derivative 5.[16] 2-Chloro-4'-fluoroacetophenone 8[17] was reduced to alcohol 5 and subjected to lipase catalyzed resolution using lipase P in a mixture of isopropenyl acetate and ethyl ether


O
CCH2Cl
F
8
NaBH4
MeOH
OH
ClCH2CH
F
5
Lipase P
isopropenyl
acetate
ethyl ether
CH2Cl
OH
H
F
R-(-)-5
+
CH2Cl
H
OAc
F
S-(+)-9
S-(+)-9 NaHCO3 MeOH H2O S-(+)-5
CH2Cl
OH
H
F
R-(-)-5
NaOH
i-PrOH
O
CH2
H
F
R-(-)-3
S-(+)-9 NaOH i-PrOH S-(+)-3
O
CH2
H
F
S-(+)-3
or
CH2Cl
H
OH
F
S-(+)-5
or
CH2Cl
H
OAc
F
S-(+)-9
LiAlH4
THF
CH3
H
OH
F
R-(+)-10
R-(-)-3 or R-(-)-5 LiAlH4 THF S-(-)-10

Scheme III

(Scheme III). As with piperidine derivative 4 the lipase preferentially acetylated the (+)-enantiomer of 5. In this way, 3.7 g of (-)-5 and 3.5 g of (+)-5 (from acetate (+)-9 through the action of sodium bicarbonate in aqueous methanol) were prepared from 8.0 g of (±)-5. Treatment with a stronger base yielded epoxide (-)-3 from (-)-5 and epoxide (+)-3 directly from acetate (+)-9. Reaction of (+)-3, (+)-5 or (+)-9 with lithium aluminum hydride gave alcohol (+)-10. Similarly, reduction of (-)-3 or (-)-5 gave (-)-10. The optical purity (≥97% ee) as well as absolute configuration of these compounds were assessed by NMR analysis of the MTPA[14] and O-methylmandelate[15] esters of p-fluorophenethyl alcohol 10. Halohydrins (-)-5 and (+)-5 were also derivatized as their MTPA esters for enantiomeric purity measurement.[14] Absolute stereochemistry was assigned as: S-(+)-3, R-(-)-3, R-(-)-5, S-(+)-5, S-(+)-9, R-(+)-10, and S-(-)-10.

With the resolution now complete, all four stereoisomers of 1 were generated from the optically pure epoxides S-(+)-3, R-(-)-3 and piperidine derivatives R-(+)-4, S-(-)-4. The preparation of 1-[(R)-2-(4-fluorophenyl)-2-hydroxyethyl]-4-[(S)-(4-fluorophenyl)hydroxymethyl]-piperidine (denoted as R,S-(-)-1 in Scheme IV) from its complementary precursors is illustrative of the method used for the remaining three isomers. Hydrogenolysis of carbamate S-(-)-4 followed by treatment of the resulting piperidine S-(-)-2 with epoxide



R-(+)-2 + S-(+)-3 ⟶ S,R-(+)-1 + 11

R-(+)-2 + R-(-)-3 ⟶ R,R-(-)-1 + 11

S-(-)-2 + S-(+)-3 ⟶ S,S-(+)-1 + 11

Scheme IV

R-(-)-3 gave the desired diol and a small amount (<10%) of side product 11. Stereoisomers S,R-(+)-1, R,R-(-)-1 and S,S-(+)-1 were likewise prepared

In conclusion, enantiomeric resolution through the use of enzymes in organic media allowed for the straightforward synthesis of all four stereoisomers of 1. Furthermore, the

versatility of the described synthetic approach enables one to incorporate any or all of the asymmetry present in 1 into future targets. Since preliminary studies show that the biological effects of 1 are directly linked to the stereochemistry of one or both chiral centers, the illustrated method offers the opportunity for the rational synthesis of pharmaceuticals with specific biological activities. The biological data on the stereoisomers of 1 will be published elsewhere.

EXPERIMENTAL

1-Benzyloxycarbonyl-4-(4-fluorobenzoyl)-piperidine. To a mixture of 17.0 g (82.2 mmol) of 4-(4-fluorobenzoyl)-piperidine and 11.3 g (82.2 mmol) of potassium carbonate in 500 mL of water was added 16.8 g (98.8 mmol) of benzyl chloroformate. The reaction was stirred for 3 h at room temperature and extracted with ether. The organic layer was dried with magnesium sulfate, filtered and concentrated. Chromatography on silica gel (15% ethyl acetate/hexane), followed by recrystallization from cyclohexane, gave 28.0 g (82.2 mmol) of a white solid: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.80 (m, 4H), 3.00 (m, 2H), 3.40 (m, 1H), 4.25 (m, 2H), 5.15 (s, 2H), 7.15 (m, 2H), 7.38 (m, 5H), 7.99 (m, 2H). IR (KBr) cm^{-1} 3440, 2954, 1694, 1678, 1598, 1444, 1204. MS (CI/CH_4) m/e 342 (M^++1), 298, 250, 234, 206, 91. Anal Calcd: C, 70.37; H, 5.90; N, 4.10; Found: C, 70.51; H, 5.94; N, 4.08 mp = 66-69°C

1-Benzyloxycarbonyl-4-(4-fluorophenyl)hydroxymethyl-piperidine [(±)-4). To a 0°C solution of 28 0 g (82.2 mmol) of 1-benzyloxycarbonyl-4-(4-fluorobenzoyl)-piperidine in 500 mL of methanol was added 9.4 g (250 mmol) of sodium borohydride. The cooling bath was removed and the reaction stirred for 6 h after which it was concentrated to 150 mL. The mixture was diluted with 400 mL of 1 N sodium hydroxide and extracted with ether. The organic layer was dried with magnesium sulfate, filtered, concentrated and chromatographed (30% ethyl acetate/ hexane) to yield 28.1 g (82 2 mmol) of a clear colorless thick oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1 20 (m, 3H), 1.70 (m, 1H), 1.97 (m, 1H), 2.03 (s, 1H), 2.69 (m, 2H), 4.20 (m, 2H), 4.37 (d, 1H, J=7.8 Hz), 5 11 (s, 2H), 7.05 (m, 2H), 7.34 (m, 7H). ^{19}F NMR CF_3 resonance of MTPA ester ($CDCl_3$) δ -113 63, -113.25. IR (KBr) cm^{-1} 3472, 2956, 2916, 2872, 1670, 1510, 1222. MS (70 eV) m/e 343 (M^+), 252, 208, 91. Anal Calcd: C, 69.95; H, 6.46; N, 4.08. Found: C, 69 73; H, 6.59; N, 3.99.

S-(-)-1-Benzyloxycarbonyl-4-(4-fluorophenyl)hydroxymethyl-piperidine [S-(-)-4] and R-(+)-1-Benzyloxycarbonyl-4-(4-fluorophenyl)acetoxymethyl-piperidine [R-(+)-7]. To a solution of 20.0 g (58.2 mmol) of alcohol (±)-4 in 300 mL of t-butyl methyl ether was added 10 g (116.1 mmol) of vinyl acetate followed by 30 g of crude lipase P. After stirring for 5 days at 45°C the suspension was filtered and concentrated. Silica gel chromatography (15% ethyl acetate/hexane) provided 9.7 g (28.2 mmol) of (-)-4 and 9.4 g (24.4 mmol) of (+)-7 as clear colorless oils: (-)-4 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.2 (m, 3H), 1.70 (m, 1H), 1.97 (m, 1H), 2.20 (s, 1H), 2.69 (m, 2H), 4.20 (m, 2H), 4.37 (d, 1H, J=7.8 Hz), 5.11 (s, 2H), 7.05 (m, 2H), 7.34 (m, 7H). ^{19}F NMR CF_3 resonance of MTPA ester ($CDCl_3$) δ -113.63. IR (KBr) cm^{-1} 3472, 2956, 2916, 2872, 1670, 1510, 1222. MS (70 eV) m/e 343 (M^+), 252, 208, 91. Anal Calcd· C, 69 95; H, 6.46; N, 4.08. Found: C, 69.73; H, 6.68; N, 3.98. $[\alpha]_D^{20}$ = -1.0,

c=1.10 $CHCl_3$. (+)-7 300 MHz H NMR ($CDCl_3$) δ 1.3 (m, 3H), 1.85 (m, 2H), 2.07 (s, 3H), 2.71 (m, 2H), 4.22 (m, 2H), 5.11 (s, 2H), 5.48 (d, 1H, J=10.4 Hz), 7.03 (m, 2H), 7.25 (m, 2H), 7.35 (m, 5H). IR (KBr) cm^{-1} 2946, 2860, 1744, 1700, 1606, 1512, 1432, 1224 MS (CI/CH_4) 386 (M^++1), 326, 282, 236, 192, 91. Anal Calcd: C, 68.55; H, 6.28; N, 3.63. Found: C, 68.37, H, 6.54; N, 3.48 $[\alpha]_D^{20}$ = +13.7, c=1.15 $CHCl_3$.

R-(+)-1-Benzyloxycarbonyl-4-(4-fluorophenyl)hydroxymethyl-piperidine [R-(+)-4]. To a solution of 9.4 g (24.4 mmol) of acetate (+)-7 in 300 mL of methanol was added 6.7 g (48.8 mmol) of potassium carbonate The reaction mixture was stirred for 3 h at room temperature and concentrated to 100 mL. The resulting paste was diluted with 300 mL of water and extracted with ether. The organic layer was dried with magnesium sulfate filtered, and concentrated to yield 8.4 g (24.5 mmol) of (+)-4 as a clear colorless oil: 300 MHz ^1H NMR ($CDCl_3$) δ 1.2 (m, 3H), 1.70 (m, 1H), 1.97 (m, 1H), 3.00 (s, 1H), 2.69 (m, 2H), 4.20 (m, 2H), 4.37 (d, 1H, J=7.8 Hz), 5.11 (s, 2H), 7.05 (m, 2H), 7.34 (m, 7H). ^{19}F NMR CF_3 resonance of MTPA ester ($CDCl_3$) δ -113.25. IR (KBr) cm^{-1} 3474, 2966, 2956, 2916, 2872, 1670, 1510, 1222. MS ($CI-CH_4$) m/e 344 (M^++1), 326, 300, 282, 236, 91. Anal Calcd: C, 69.95; H, 6.46; N, 4.08. Found: C, 69.72; H, 6.50; N, 4 00. $[\alpha]_D^{20}$ = +1.1, c=0 90 $CHCl_3$.

2-Chloro-1-(4-fluorophenyl)ethanol [(±)-5]. To a 0°C solution of 25.0 g (145.0 mmol) of 2-chloro-4'-fluoroacetophenone in 250 mL of methanol was added 5.5 g (145 mmol) of sodium borohydride. The cooling bath was removed and the reaction stirred for an additional 1.5 h. The mixture was concentrated to 100 mL, diluted with 200 mL of 10% aqueous hydrogen chloride and extracted with dichloromethane. The organic layer was dried with magnesium sulfate, concentrated and distilled to deliver 24.4 g (140 mmol) of a clear colorless liquid: 300 MHz ^1H NMR ($CDCl_3$) δ 3.10 (s, 1H), 3.61 (dd, 1H, J=8.5, 11 2 Hz), 3.70 (dd, 1H, J=3.6, 11 2 Hz), 4.88 (dd, 1H, J=3.6, 8.5 Hz), 7.06 (m, 2H), 7.35 (m, 2H). ^{19}F NMR CF_3 resonance of MTPA ester ($CDCl_3$) δ -112 10, -112.29. IR (neat) cm^{-1} 3400, 1698, 1605, 1511, 1225. MS (70 eV) m/e 174 (M+), 125, 97, 77. Anal Calcd: C, 55.03; H, 4.62. Found: C, 54.84; H, 4 69 bp 105-110°C, 0.8 mm Hg.

R-(-)-2-Chloro-(4-fluorophenyl)ethanol [R-(-)-5] and S-(+)-2-Chloro-(4-fluorophenyl)ethanol acetate [S-(+)-9]. To a solution of 8.0 g (46.0 mmol) of halohydrin (±)-5 in 120 mL of ethyl ether was added 16 g (160 mmol) of isopropenyl acetate followed by 16 g of crude lipase P. After stirring for 2 days at room temperature the suspension was filtered and concentrated. Silica gel chromatography (5% ethyl acetate/hexane) delivered 3.7 g (21.3 mmol) of (-)-5 as a clear colorless oil and 4.3 g (19.8 mmol) of (+)-9 as a white solid: (-)-5 300 MHz ^1H NMR ($CDCl_3$) δ 2.85 (s, 1H); 3.61 (dd, 1H, J=8.5, 11.2 Hz), 3.70 (dd, 1H, J=3.6, 11.2 Hz), 4.88 (dd, 1H, J=3.6, 8.5 Hz), 7.09 (m, 2H), 7.40 (m, 2H). ^{19}F NMR CF_3 resonance of MTPA ester ($CDCl_3$) δ -112.29. IR (neat) cm^{-1} 3404, 1698, 1605, 1512, 1226. MS (70 eV) m/e 174 (M+), 125, 97, 77. Anal Calcd: C, 55.03; H, 4.62. Found: C, 54.80; H, 4.67. $[\alpha]_D^{20}$ = -51.0, c=0.90 $CHCl_3$. (+)-9 300 MHz ^1H NMR ($CDCl_3$) δ 2.14 (s, 3H), 3.70 (dd, 1H, J=4.9, 11.6 Hz), 3.78 (dd, 1H, J=7.7, 11.6 Hz), 5.94 (dd, 1H, J=4.9, 7.7 Hz), 7.07 (m, 2H), 7.36 (m, 2H). IR (KBr) cm^{-1} 3480, 1746, 1512, 1232. MS (70 eV) m/e 216 (M+), 180,

167, 138, 125, 121, 43. Anal Calcd: C, 55.44; H, 4.65. Found: C, 55.17; H, 4.75. $[\alpha]_D^{20}$ = +71.3, c=1.0 $CHCl_3$. mp = 56-59°C.

S-(+)-2-Chloro-(4-fluorophenyl)ethanol [S-(+)-5]. To a solution of 4.3 g (19.8 mmol) of acetate (+)-9 in 80 mL of methanol was added 40 mL of water followed by 4.0 g (47 6 mmol) of sodium bicarbonate. The reaction was stirred for 24 h at room temperature, diluted with 100 mL of water and extracted with ether. The organic layer was dried with magnesium sulfate, filtered and concentrated. Silica gel chromatography (5% ethyl acetate/hexane) yielded 3.4 g (19.5 mmol) of a clear colorless oil: 300 MHz ^1H NMR ($CDCl_3$) δ 3.05 (s, 1H), 3 60 (dd, 1H, J=8.5, 11.2 Hz), 3.69 (dd, 1H, J=3.6, 11.2 Hz), 4.88 (dd, 1H, J=3.6, 8.5 Hz), 7.00 (m, 2H), 7.40 (m, 2H). ^{19}F NMR CF_3 resonance of MTPA ester ($CDCl_3$) δ -112.10. IR (neat) cm^{-1} 3400, 1700, 1510, 1225. MS (70 eV) m/e 174 (M+), 125, 97, 77. Anal Calcd: C, 55 03; H, 4 62. Found: C, 54.88; H, 4.72. $[\alpha]_D^{20}$ = +50.1, c=1.0 $CHCl_3$.

R-(-)-4-Fluorostyreneoxide [R-(-)-3]. To a solution of 8.2 g (47.1 mmol) of halohydrin (-)-5 in 100 mL of methanol and 50 mL of water was added 10 g (72.4 mmol) of potassium carbonate and the reaction mixture stirred for 3 h at room temperature The mixture was concentrated, diluted with 100 mL of water and extracted with ether. The organic layer was dried with magnesium sulfate, filtered and concentrated. Silica gel chromatography (5% ethyl acetate/hexane) yielded 5.7 g (41.3 mmol) of a clear colorless liquid· 300 MHz ^1H NMR ($CDCl_3$) δ 2.77 (dd, 1H, J=3.0, 5.4 Hz), 3.14 (dd, 1H, J=3.0, 5.4 Hz), 3.85 (t, 1H, J=3.0 Hz), 7.04 (m, 2H), 7.25 (m, 2H). IR (neat) cm^{-1} 3054, 2994, 2924, 1608, 1513, 1158. MS (CI/CH_4) m/e 139 (M+), 121, 119, 117, 91. Anal Calcd: C, 69 56; H, 5.11. Found: C, 69.82; H, 5.11. $[\alpha]_D^{20}$ = -17.8, c=1.07 $CHCl_3$.

S-(+)-4-Fluorostyreneoxide [S-(+)-3]. To a solution of 10.0 g (46.3 mmol) of acetate (+)-9 in 300 mL isopropanol was added 4.0 g (100.0 mmol) of sodium hydroxide and the reaction heated to reflux for 0.5 h The mixture was concentrated, diluted with 100 mL water and extracted with ether. The organic layer was dried with magnesium sulfate, filtered and concentrated. Silica gel chromatography (5% ethyl acetate/hexane) yielded 4.9 g (35.5 mmol) of a clear colorless liquid: 300 MHz ^1H NMR ($CDCl_3$) δ 2.77 (dd, 1H, J=3 0, 5.4 Hz), 3.14 (dd, 1H, J=3.0, 5.4 Hz), 3 85 (t, 1H, J=3.0 Hz), 7.04 (m, 2H), 7.25 (m, 2H). IR (neat) cm^{-1} 3054, 2994, 1608, 1514, 1222. MS (CI/CH_4) m/e 139 (M+), 121, 119, 117, 91. Anal Calcd: C, 69 56; H, 5.11. Found· C, 69.88; H, 5.11. $[\alpha]_D^{20}$ = +16.7, c=1.03 $CHCl_3$.

S-(-)-1-(4-Fluorophenyl)ethanol [S-(-)-10]. To a solution of 0.15 g (1.1 mmol) of epoxide (-) 3 in 6 mL of tetrahydrofuran was added 0.12 g (3.3 mmol) of lithium aluminum hydride. After 1 h at room temperature the reaction was quenched with 5 mL of 1 N sodium hydroxide, diluted with 10 mL of water and extracted with ether. The organic layer was dried with magnesium sulfate, filtered and concentrated to deliver 0.12 g (0.86 mmol) of a clear colorless oil: 300 MHz ^1H NMR ($CDCl_3$) δ 1.40 (d, 3H, J=5.7 Hz), 2 94 (s, 1H), 4.78 (q, 1H, J=5 7 Hz), 6.99 (m, 2H), 7.25 (m, 2H). ^{19}F NMR CF_3 resonance of MTPA ester ($CDCl_3$) δ -114.29. $[\alpha]_D^{20}$ = -41.0, c=1.30 $CHCl_3$.

R-(+)-1-(4-Fluorophenyl)ethanol [R-(+)-10]. To a solution of 0.30 g (1.40 mmol) of acetate (+)-9 in 15 mL of tetrahydrofuran was added 0.16 g (4.20 mmol) of lithium aluminum hydride. After 1 h at room temperature the reaction was quenched with 5 mL of 1 N sodium hydroxide, diluted with 15 mL of water and extracted with ether. The organic layer was dried with magnesium sulfate, filtered and concentrated to deliver 0.19 g (1.36 mmol) of a clear colorless oil: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.40 (d, 3H, J=5.7 Hz), 2.94 (s, 1H), 4.78 (q, 1H), J=5.7 Hz), 7.00 (m, 2H), 7.28 (m, 2H). ^{19}F NMR CF_3 resonance of MTPA ester ($CDCl_3$) δ -113.99. $[\alpha]_D^{20}$ = +40.2, c=1.20 $CHCl_3$.

S-(-)-4-(4-Fluorophenyl)hydroxymethyl-piperidine [S-(-)-2]. To a solution of 1.5 g (4.37 mmol) of (-)-4 in 50 mL of isopropanol was added a catalytic amount of 10% palladium on carbon. The reaction flask was fitted with a hydrogen balloon and the suspension stirred at room temperature for 1 h The reaction was filtered and concentrated to yield a white solid which was recrystallized from ether/hexane to give 0.86 g (4.11 mmol) of product. 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.10 (m, 2H), 1.24 (m, 2H), 1 78 (m, 1H), 1 96 (m, 1H), 2 11 (s, 2H), 2.51 (m, 2H), 2 98 (m, 1H), 3.09 (m, 1H), 4.33 (d, 1H, J=7 2 Hz), 7.05 (m, 2H), 7 28 (m, 2H). Ir (KBr) cm^{-1} 3270, 3120, 2941, 2860, 1603, 1509, 1223 MS (CI/CH_4) m/e 210 (M^++1), 192,114. Anal Calcd: C, 68.87; H, 7.71; N, 6.69. Found: C, 68 89; H, 7 85; N, 6.59. $[\alpha]_D^{20}$ = -12.0, c=1.0 CH_3OH mp = 141-145°C.

R-(+)-4-(4-Fluorophenyl)hydroxymethyl-piperidine [R-(+)-2]. This compound was prepared as its enantiomer S-(-)-2 above. From 1.5 g (4.37 mmol) of (+)-4 was obtained 0 88 g (4.19 mmol) of (-)-2 300 MHz ^{1}H NMR ($CDCl_3$) δ 1 10 (m, 2H), 1 24 (m, 2H), 1 78 (m, 1H), 1.94 (s, 2H), 1.98 (m, 1H), 2.51 (m, 2H), 2.98 (m, 1H), 3 09 (m, 1H), 4.33 (d, 1H, J=7.2 Hz), 7.07 (m, 2H), 7.29 (m, 2H). IR (KBr) cm^{-1} 3270, 3122, 2941, 2860, 1603, 1509, 1223. MS (CI/CH_4) m/e 210 (M^++1), 192, 114. Anal Calcd. C, 68.87; H, 7.71; N, 6.69. Found. C, 68.82; H, 7 83; N, 6.60. $[\alpha]_D^{20}$ = +11.9, c=1 0 CH_3OH mp = 142-146°C.

(-)-1-[(R)-2-(4-fluorophenyl)-2-hydroxyethyl]-4-[(S)-(4-fluorophenyl)hydroxymethyl-piperidine [R,S-(-)-1]. A solution of 0.72 g (3.5 mmol) of piperidine (-)-2 in 50 mL of isopropanol was treated with 0.60 g (4.35 mmol) of epoxide (-)-3 at reflux for 2 h. Concentration and silica gel chromatography (8% methanol/chloroform) yielded 0.06 g (0.17 mmol) of diol 11 and a white solid which was recrystallized from cyclohexane to give 1.2 g (3.46 mmol) of the desired product: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 2H), 1.38 (m, 1H), 1 61 (m, 1H), 1.87 (s, 2H), 1.98 (m, 1H), 2.03 (m, 1H), 2.20 (m, 1H), 2 39 (m, 1H), 2.45 (m, 1H), 2.74 (m, 1H), 3.21 (m, 1H), 4 40 (d, 1H, J=8.3 Hz), 4 69 (dd, 1H, J=3.7, 11.2 Hz), 7.02 (m, 4H), 7.32 (m, 4H) IR (KBr) cm^{-1} 3472, 2938, 2922, 1604, 1512, 1222. MS (CI/CH_4) m/e 348 (M^++1), 330, 310, 252, 222 Anal Calcd. C, 69 14; H, 6 67; N, 4.03. Found: C, 69.19; H, 6.75; N, 3.92. $[\alpha]_D^{20}$ = -69.7, c=0.80 $CHCl_3$. mp = 135-139°C. 11 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 3H), 1.67 (m, 1H), 1.95 (m, 1H), 1.17 (m, 1H), 2 49 (m, 1H), 2 50 (s, 2H), 2.88 (m, 2H), 3.65 (m, 2H), 3.94 (t, 1H, J=11.4 Hz), 4.35 (d, 1H, J=6.8 Hz), 7.01 (m, 4H), 7.14 (m, 2H), 7.25 (m, 2H).

(+)-1-[(S)-2-(4-Fluorophenyl)-2-hydroxyethyl]-4-[(R)-(4-fluorophenyl)hydroxymethyl]-piperidine[S,R-(+)-1]. This compound was prepared using the same procedure as described for R,S-(-)-1. From 0.90 g (4.37 mmol) of (+)-2 and 0.63 g (4.60 mmol) of epoxide (+)-3 were obtained 0.07 g (0.20 mmol) of 11 and 0.93 g (2.68 mmol) of the desired product: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1 29 (m, 2H), 1.38 (m, 1H), 1.60 (m, 1H), 1.65 (s, 2H), 1.98 (m, 1H), 2.04 (m, 1H), 2.20 (m, 1H), 2.40 (m, 1H), 2.47 (m, 1H), 2.74 (m, 1H), 3.21 (m, 1H), 4 40 (d, 1H, J=8 3 Hz), 4.70 (dd, 1H, J=3 7, 11.2 Hz), 7.03 (m, 4H), 7.30 (m, 4H). IR (KBr) cm^{-1} 3470, 2938, 2922, 1604, 1512, 1222. MS (CI/CH_4) m/e 348 (M^++1), 330, 310, 252, 222. Anal Calcd: C, 69 14; H, 6 67; N, 4 03. Found: C, 69.01; H, 6.71; N, 3.48. $[\alpha]_D^{20}$ = +69.3, c=0.40 $CHCl_3$. mp = 134-136°C

(+)-1-[(S)-2-(4-Fluorophenyl)-2-hydroxyethyl]-4-[(S)-(4-fluorophenyl)hydroxymethyl]-piperidine [S,S-(+)-1]. This compound was prepared using the same procedure as described for R,S-(-)-1 From 1.2 g (5.83 mmol) of (-)-2 and 0.88 g (6.41 mmol) of epoxide (+)-3 were obtained 0.14 g (0.41 mmol) of 11 and 1.2 g (3.56 mmol) of the desired product: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 2H), 1.46 (m, 1H), 1.60 (m, 1H), 1.90 (m, 1H), 1.92 (s, 2H), 1.99 (m, 1H), 2 29 (m, 1H), 2.43 (m, 2H), 2.87 (m, 1H), 3.08 (m, 1H), 4.40 (d, 1H, J=8.6 Hz), 4.66 (dd, 1H, J=5.7, 11.4 Hz), 7.05 (m, 4H), 7 30 (m, 4H). IR (KBr) cm^{-1} 3430, 2946, 2818, 1604, 1510, 1270. MS (CI/CH_4) m/e 348 (M^++1), 330, 310, 252, 222. Anal Calcd: C, 69.14; H, 6.67; N, 4.03; Found: C, 69.16; H, 6.81; N, 3.92. $[\alpha]_D^{20}$ = +20.9, c=0.32 $CHCl_3$. mp = 133-135°C.

(-)-1-[(R)-2-(4-Fluorophenyl)-2-hydroxyethyl]-4-[(R)-(4-fluorophenyl)hydroxymethyl]-piperidine [R,R-(-)-1]. This compound was prepared using the same procedure as described for (R,S)-(-)-1. From 1 1 g (5.25 mmol) of (+)-2 and 0.87 g (6.30 mmol) of epoxide (-)-3 were obtained 0.18 g (0.52 mmol) of 11 and 1.06 g (3.04 mmol) of the desired product: 300 MHz ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 2H), 1.46 (m, 1H), 1.60 (m, 1H), 1.80 (s, 2H), 1.90 (m, 1H), 1.99 (m, 1H), 2 29 (m, 1H), 2.43 (m, 1H), 2.87 (m, 1H), 3.08 (m, 1H), 4 40 (d, 1H, J=8.6 Hz), 4.66 (dd, 1H, J=5.7, 11 4 Hz), 7.03 (m, 4H), 7.29 (m, 4H). IR (KBr) cm^{-1} 3508, 2948, 2770, 1604, 1512, 1220. MS (CI/CH_4) m/e 348 (M^++1), 330, 310, 252, 222. Anal Calcd: C, 69.14; H, 6.67; N, 4.03. Found: C, 69.35; H, 6.78; N, 3.94. $[\alpha]_D^{20}$ = -22.2, c=0.33 $CHCl_3$. mp = 133-136°C.

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