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CONFIGURATIONAL STUDIES ON 2-[α-(2-ETHOXYPHENOXY)BENZYL]MORPHOLINE FCE 20124

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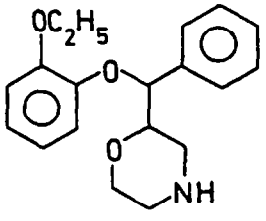
Abstract - The relative configuration of the two diastereoisomers of (±)2-[α-(2-ethoxyphenoxy)benzyl]morpholine is determined by a synthesis involving regio and stereo specific reactions. (RS,RS) diastereoisomer FCE 20124 was separated into its (+) and (-) enantiomers both by crystallization of the optically active mandelate salt and by a multi-step synthesis from (+)-(2S,3R)-3-phenylglycidic acid.

A recent paper[1] reported the activities in vivo of many 2-(α-aryloxybenzyl)morpholine derivatives as antagonists of reserpine-induced blepharospasm and reserpine and clonidine-induced hypothermia. One of these compounds, FCE 20124, showed pharmacological activity, indicative of possible therapeutic use as a potent antidepressant agent with rapid onset of action and few side-effects. Compound FCE 20124 is one of the two possible diastereoisomers for 2-[α-(2-ethoxyphenoxy)benzyl] morpholine (formula I, fig. 1).

This paper describes a new regio and stereo-specific synthesis of FCE 20124 and the determination of the relative configuration of its chiral carbon atoms : the absolute configurations of its (+) and (-) enantiomers is also established.

Fig. 1

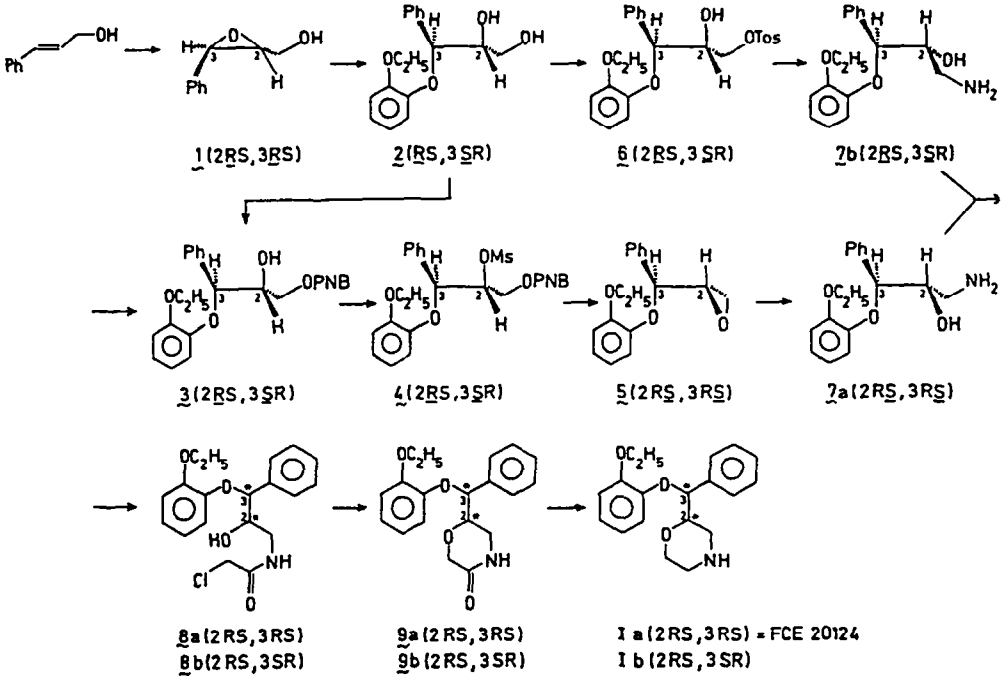


I

The goal was to synthesize and assign the right configuration to intermediate amino-alcohols 7 (see Scheme 1); the morpholino derivatives I had the same stereochemistry as the corresponding amino-alcohols since the chiral centres were not involved in the reactions from 7 to I. We were particularly interested in the relative configuration of the amino-alcohol with m.p. 105-107°C which we already knew as the key intermediate for FCE 20124[1].

The synthesis of this diastereoisomer started from the readily available trans cinnamyl alcohol as shown in Scheme 1 (compounds 1-7 are racemic mixtures, but for the sake of clarity only one enantiomer is reported in the scheme and is underlined in the subscript).

Scheme 1



Oxidation with MCPBA to the corresponding trans epoxide gave (2RS,3RS) 1[2], which in turn was reacted with sodium 2-ethoxyphenate to give the diol 2 in a regio and stereospecific way[3].

The regiospecificity was confirmed by Mass and NMR spectra and later by comparison with authentic samples of 7a and 7b obtained by a different unambiguous routes[1]. The stereospecificity was proved by the fact that only one diastereoisomer was obtained; as the 2-ethoxyphenate ion was necessary for the reaction, this strongly supports an S_N2 mechanism and makes a syn-addition anchimerically assisted by the phenyl ring extremely improbable[4].

Selective tosylation of 2 gave 6 and reaction of 6 with an aqueous-methanolic solution of ammonia gave the amino-alcohol (2RS,3SR) 7b (m.p. 115-117°C). This compound was not the right intermediate for FCE 20124 (Ia); the right one was then the (2RS,3RS) amino-alcohol 7a.

This was confirmed by the synthesis of 7a starting from compound 2 by a route based on inversion of the configuration of the C-2 carbon atom (Scheme 1). The primary alcoholic group of compound 2 was reacted with p-nitrobenzoyl (PNB) chloride to obtain 3 : this derivative had the advantage of being a solid, and so was easy to purify. Compound 4 was obtained by treatment of compound 3 with methanesulfonylchloride and the epoxide 5 was prepared in high yield by treatment of compound 4 with sodium hydroxide in an aqueous/dioxane solution. This reaction caused inversion of configura-

tion at the chiral C-2 carbon atom through an S_Ni displacement of the mesyloxy group by the alkoxide formed in the basic hydrolysis of the PNB ester.

Finally the reaction of 5 with aqueous-methanolic ammonia gave 7a, m.p. 105–107°, identical (IR, NMR, TLC) to the amino-alcohol previously used to prepare compound FCE 20124[1].

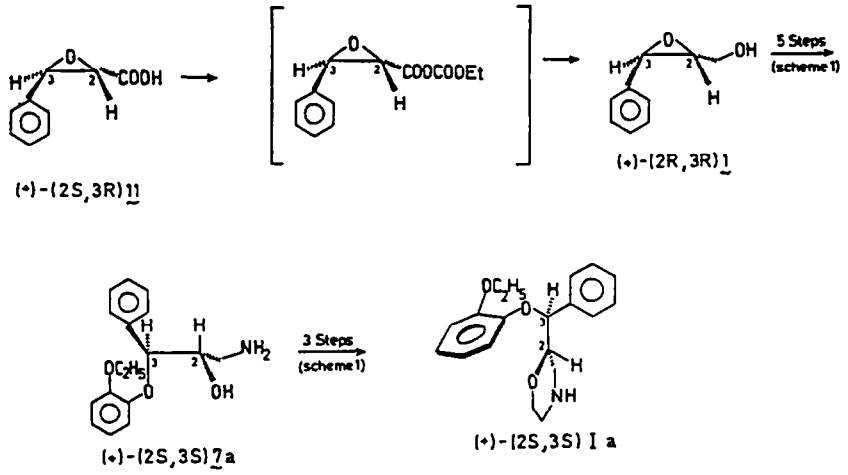
The reactions to tranform amino-alcohols 7a and 7b into the corresponding morpholine derivatives Ia and Ib gave no problems and are described in the Experimental part.

A further step was separation of the enantiomers of FCE 20124 (+)-(2S,3S) Ia and (-)-(2R,3R) Ia. These optically active enantiomers could be obtained crystallizing the L(+) and D(-) mandelic acid salts of FCE 20124 from absolute ethanol. After two crystallizations the melting points and the $[\alpha]_D^{20}$ of the mandelates did not change on further crystallization. It was to be assumed that they were pure diastereoisomers, but this assumption needed to be confirmed.

Since we knew the reactions reported in Scheme 1 were highly specific if we could obtain epoxide 1 of known absolute configuration and in optically pure form as starting material we could both determine the absolute configurations and prove the optical purity of the enantiomers (+) and (-) Ia previously obtained by resolution of racemic (±) Ia provided no racemisation occurred during preparation from 1. In that case the specific rotation of enantiomers obtained by the two different methods should be the same.

The (+)-(2R,3R)-cinnamylalcohol 2,3-epoxide (+) 1 was synthesized starting from the known trans (+)-(2S,3R)-glycidic acid[5] 11 as shown in Scheme 2.

Scheme 2



Several attempts to reduce the carboxylic group selectively without affecting the epoxide group, for example with BH_3[6], were unsatisfactory. Reduction of the mixed anhydride with sodium borohydride in absolute ethanol gave an acceptable yield of (+) 1 considering recovery of the starting material and of the derived ethyl ester. Solvents other than ethanol, tried in order to avoid the formation of

ethyl ester of 11 as a side product, gave unsatisfactory results. The pathway (and the reaction conditions) to convert (+)-(2S,3R) 1 to (+)-(2S,3S) 7a and then to (+)-(2S,3S) Ia was the same as for racemic compounds shown in Scheme 1 and therefore is not fully reported in Scheme 2.
In the end the $[\alpha]_D^{20}$ of the methanesulfonic acid salt of (+)-(2S,3S) Ia obtained by this method was found to be identical to the (+) enantiomer obtained by resolution of racemic FCE 20124 by the mandelic acid method. This confirmed both that the reactions proceeded without racemisation and the enantiomers obtained from both methods were optically pure isomers.
The melting point of racemic FCE 20124 methanesulfonate (145-146°C) was higher than that of the corresponding enantiomers (100-102°C) which means that FCE 20124 was a racemic compound and not a racemic mixture. This was confirmed by the much greater solubility in organic aprotic solvents (THF, acetone, dioxane) of methanesulfonate of (+)-(2S,3S) Ia compared to methanesulfonate of the racemic FCE 20124.

EXPERIMENTAL

Melting points were taken on a Büchi melting point apparatus and uncorrected; the IR spectra were recorded on a Perkin-Elmer 297 spectrophotometer; NMR spectra were determined on a Brüker-90 MHz spectrometer and are reported in parts per million downfield from internal TMS. Mass spectra were recorded on a CH-7 Varian MAT spectrometer at 70 eV. The rotations $[\alpha]_D^{20}$ (C 1.0, absolute ethanol) of the optically active compounds were measured on a Perkin-Elmer 241 polarimeter. Optically active isomers were obtained in the same reaction conditions as for the corresponding racemic compounds and the yields were analogus. The coincidence of the Rf values in TLC (several eluants) and of NMR spectra of the racemic and of the corresponding optically active compounds was always verified. The enantiomers were more difficult to solidify and almost all of them were oily products. When they were solid, m.p. and IR (KBr) are reported.

(2RS,3RS)-Cinnamyl alcohol-2,3-epoxide 1.
To a solution of 20 g (0.149 mole) of trans-cinnamyl alcohol in 550 ml of CH_2Cl_2 27.6 g (0.160 mole) of MCPBA were added portionwise at 0-5° during 1.5 hr. The temperature was allowed to rise to room temperature and kept for a further 24 hr when the reaction was complete. The reaction mixture was filtered, the organic solvent washed with an aqueous solution of sodium metabisulphite, with a 20% aqueous solution of Na_2CO_3, and then thoroughly with water. Evaporation of the solvent after anhydrification over Na_2SO_4 gave a colorless oil which crystallized on cooling. The yield was 20.7 g (94%). m.p. 20-25° with a gas-chromatographic purity of 90%.
(Found: C, 71.80; H, 6.68. $C_9H_{10}O_2$ requires C, 71.97; H, 6.71%).
^{1}H-NMR ($CDCl_3$) δ 3.24 (1H, ddd, -CH-CH_2OH), 3.76 (1H, dd, CH_AH_B-OH), 3.94 (1H, d, Ph-CH, J = 2.1 Hz), 4.05 (1H, dd, CH_AH_B-OH), 7.35 (5H, s, Ph); IR ($CHCl_3$) cm^{-1} 3590-3450 (OH), 1600, 1490 (arom. C=C), 1220, 1060 (Alk-O-Alk, Alk-OH).

(+)-(2R,3R)-Cinnamylalcohol 2,3-epoxide 1.
A solution of 3.8 g (13.3 mmole) of (+)-(2S,3R)-phenyl-glycidic acid 11 D(+)-α-methyl-phenethylamine salt[4] was treated with 6.65 ml (13.3 mmole) of 2N HCl. The organic acid was extracted with diethylether and the solvent removed in vacuo after drying over Na_2SO_4. The residue was dissolved in 70 ml of CH_2Cl_2 and 2 ml (14.3 mmole) of triethylamine were added. The solution was cooled to 0°C and 1.36 ml (14.3 mmole) of ethyl-chlorocarbonate were added dropwise under stirring during 1 hr. After 2 hr the solution was slowly added under stirring to a suspension of 2.26 g (59.7 mmole) of sodium borohydride in 17 ml of absolute ethanol, at 0°C. After 0.5 hr the temperature was allowed to rise to room temperature and stirring was continued overnight. The mixture was poured into water and the product extracted with CH_2Cl_2. After separation on a flash chromatography column ($CHCl_3$: CH_3OH 100:2 as eluant) 0.62 g (31%) of (+)-(2R,3R)cinnamyl alcohol-2,3-epoxide 1 were obtained as a colorless oil; $[\alpha]_D^{20}$ = +45.9° (C 1.5, abs. ethanol).
(Found: C, 71.68; H, 6.71. $C_9H_{10}O_2$ requires C, 71.97; H, 6.71%).
^{1}H-NMR and IR were identical to (±) 1; 0.33 g (15.3%) of the starting (+)-(2S,3R) phenyl glycidic acid were recovered together with 0.92 g (36.5%) of its ethyl ester.

(2RS,3SR)-3-(2-Ethoxyphenoxy)-1,2-dihydroxy-3-phenylpropane 2.
To a solution of 2.66 g (66.5 mmole) of NaOH in 100 ml of water, 27.6 g (200 mmole) of 2-ethoxyphenol were added. The mixture was stirred at 70° under nitrogen until the solid completely dissolved, and then 10.0 g (66.5 mmole) of 1 were added in 10 min. The solution was stirred at 70°C for

2.5 hr and then poured into 200 ml of 1N NaOH at 10-15°. After extraction with CH_2Cl_2 the organic solution was washed successively with 1N NaOH and brine. Elimination of the solvent and crystallization from isopropyl ether gave 15.9 g (83%) of a crystalline solid; m.p. 78-79°.
(Found: C, 70.41; H, 6.96. $C_{17}H_{20}O_4$ requires C, 70.81; N, 6.99%).
^{1}H-NMR ($CDCl_3$)δ 1.48 (3H, t, CH_3), 3.28 (2H, brb, 2OH), 3.8-4.0 (3H, m, -CH-CH_2-OH), 4.12 (2H, q, CH_2-CH_3), 5.20 (1H, d, Ph-CH, J = 4.0 Hz), 6.80 (4H, m, Ph-O), 7.35 (5H, s, Ph-C); IR (KBr) cm^{-1} 3430-3370 (OH), 1590, 1490 (arom. C=C), 1240 (Ar-O-Alk).

(+)-(2R,3S)-3-(2-Ethoxyphenoxy)-1,2-dihydro-3-phenylpropane 2.
$[\alpha]_D^{20}$ = +7.8°; m.p. 87-89°; IR (KBr) cm^{-1} 3440-3380 (OH), 1590, 1490 (arom. C=C), 1240 (Ar-O-Alk).

(2RS,3SR)-3-(2-Ethoxyphenoxy)-2-hydroxy-1-(4-nitrobenzoyloxy)-3-phenylpropane 3.
To a solution of 5 g (17.3 mmole) of 2 in 50 ml of pyridine, 3.22 g (17.0 mmole) of 4-nitrobenzoylchloride in 50 ml of pyridine were added at -10° in 1.5 hr. After 0.5 hr the solution was poured into a mixture of 1 l of 2N HCl and 650 g of ice and the oily precipitate was extracted with ethyl acetate. After an usual work-up the product was solidified with an isopropyl ether : ethyl acetate 12:1 mixture. Obtained 4.55 g (61%); m.p. 94-95°.
(Found: C, 65.78; H, 5.28; N, 3.17. $C_{24}H_{23}NO_7$ requires C, 65.89; H, 5.30; N, 3.20%).
^{1}H-NMR ($CDCl_3$)δ 1.50 (3H, t, CH_3), 3.40 (1H, d, OH), 4.18 (2H, q, CH_2CH_3), 4.30 (1H, m, CH-OH), 4.60 (2H, d, CH_2OCO), 5.20 (1H, d, Ph-CH, J = 4.5 Hz), 6.7-7.1 (4H, m, Ph-O), 7.2-7.7 (5H, m, Ph-C), 8.0-8.4 (4H, m, Ph-N); IR (KBr) cm^{-1} 3540 (OH), 1730 (CO), 1590, 1500 (arom. C=C), 1525, 1350 (NO_2).

(+)-(2R,3S)-3-(2-Ethoxyphenoxy)-2-hydroxy-1-(4-nitrobenzoyloxy)-3-phenylpropane 3.
$[\alpha]_D^{20}$ = +11.7°, oil.

(2RS,3SR)-3-(2-Ethoxyphenoxy)-2-mesyloxy-1-(4-nitrobenzoyloxy)-3-phenylpropane 4.
To a solution of 4.0 g (9.1 mmole) of 3 and 1.93 ml (13.7 mmole) of triethylamine in 45 ml of CH_2Cl_2, 0.77 ml (10.0 mmole) of CH_3SO_2Cl were added dropwise at 0-5° and the solution was kept for 0.5 hr at that temperature. After washing with 10% HCl and 5% $NaHCO_3$ solutions and water, the solution was dried over Na_2SO_4 and the solvent evaporated to dryness. The residue was crystallized from isopropyl ether to give 3.95 g (84%) of product, m.p. 89-90°.
(Found: C, 58.11; H, 4.85; N, 2.68; S, 6.19. $C_{25}H_{25}NO_9S$ requires C, 58.24; H, 4.88; N, 2.71; S, 6.22%).
^{1}H-NMR ($CDCl_3$)δ 1.45 (3H, t, CH_2-CH_3), 2.66 (3H, s, CH_3S), 4.05 (2H, q, CH_2-CH_3), 4.56 (1H, dd, CH_AH_B-OCO), 4.99 (1H, dd, CH_AH_B-OCO), 5.30 (1H, d, Ph-CH), 5.43 (1H, ddd, $CHOSO_2$), 6.76 (4H, m, Ph-O) 7.41 (5H, m, Ph-C), 8.20 (4H, br,s, Ph-N); IR (KBr) cm^{-1} 1730 (CO), 1600, 1500 (arom. C=C), 1520 (NO_2), 1350, 1180 (CH_3SO_2), 1250 (Ar-O-Alk).

(+)-(2R,3S)-3-(2-Ethoxyphenoxy)-2-mesyloxy-1-(4-nitrobenzoyloxy)-3-phenylpropane 4.
$[\alpha]_D^{20}$ = +33.6°, oil.

(2RS,3RS)-3-(2-Ethoxyphenoxy)-3-phenylpropene-1,2-epoxide 5.
A solution of 3.95 g (7.7 mmole) of 4 in 40 ml of dioxane and 16 ml of 2N NaOH was stirred for 4 hr at room temperature. After diluting with 200 ml of water the solution was extracted with ethyl acetate and the organic phase washed with a 5% aqueous solution of $NaHCO_3$ then water. After evaporation of the solvent in vacuo the residual oily epoxide weighed g. 2.05 (100%) and was used as such for the preparation of 7a. The purity was 97% by GLC.
(Found:C, 75.45; H, 6.68. $C_{17}H_{18}O_3$ requires C, 75.53; H, 6.71%).
^{1}H-NMR ($CDCl_3$)δ 1.40 (3H, t, CH_3), 2.80 (2H, d, CH_2-CH), 3.35 (1H, m, CH_2-CH), 4.05 (2H, q, CH_2-CH_3), 5.05 (1H, d, Ph-CH), 6.7-7.0 (4H, m, Ar-O), 7.4 (5H, m, Ph-C); IR (film)cm^{-1} 3030 (epoxide), 1600, 1500 (arom C=C), 1250 (Ar-O-Alk).

(-)-(2S,3S)-3-(2-Ethoxyphenoxy)-3-phenylpropene-1,2-epoxide 5.
$[\alpha]_D^{20}$ = -3.1°; oil.

(2RS,3SR)-3-(2-Ethoxyphenoxy)-2-hydroxy-3-phenyl-1-tosyloxypropane 6.
To a solution of 5 g (17.3 mmole) of 2 in 50 ml of anhydrous pyridine 3.88 g (20.3 mmole) of tosylchloride in 50 ml of anhydrous pyridine were added in 1.5 hr at -10° under stirring. After 0.5 hr at this temperature and 2 hr at room temperature the solution was poured into 1l of 2N HCl and 650 g of ice. The aqueous solution was extracted with ethyl acetate and the organic layer washed successively with 400 ml of water, 400 ml of 5% sodium bicarbonate solution and 400 ml of brine. The organic solution was dried over Na_2SO_4 and evaporated to dryness in vacuo. The colourless residue was separated by flash column chromatography (toluene:acetone 190:75 as eluant) to give 5.1 g (67%) of an oily product which was used as such for preparation of 7b.
(Found:C, 64.57; H, 6.23; S, 6.80. $C_{24}H_{26}O_6S$ requires C, 65.13; H, 5.92; S, 7.25%).
^{1}H-NMR ($CDCl_3$)δ 1.41 (3H, t, CH_2-CH_3), 2.42 (3H, s, CH_3), 3.13 (1H, br.d, OH), 4.04 (2H, q, CH_2-CH_3), 4.00-4.30 (3H, m, OCH-CH_2O), 5.01 (1H, d, Ph-CH), 6.64-7.00 (4H, m, Ar-O), 7.28 (2H,br.d, H-3 and

H-5 4-$MePhSO_2$), 7.32 (5H, br. s, Ph-C), 7.72 (2H, br. d, H-2 and H-6 4-$MePhSO_2$); IR ($CHCl_3$)cm^{-1} 3600-3300 (OH), 1590, 1490 (arom. C=C), 1355, 1170 (SO_3), 1250 (Ar-O-Alk).

(2RS,3RS)-1-Amino-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropane methanesulphonate 7a.
A solution of 4.6 g (17.0 mmole) of 5 in 80 ml of methanol and 50 ml of 32% NH_4OH was kept standing in a sealed flask for 6 hr. After evaporation of the solvent the residue was dissolved in ethyl acetate, and 1.17 ml (18 mmole) of CH_3SO_3H in 10 ml of ethyl acetate were added to the solution. After 16 hr 4.9 g (75%) of a crystalline product was collected, m.p. 118-120°.
(Found: C, 56.30; H, 6.52; N, 3.60; S, 8.33. $C_{18}H_{25}NO_6S$ requires C, 56.37; H, 6.57; H, 3.65; S, 8.36%).
^{1}H-NMR, free base, ($CDCl_3$)δ 1.49 (3H, t, CH_3), 2.38 (3H, br. b, OH, NH_2), 2.63 (2H, m, CH_2N), 3.93 (1H, m, CH-OH), 4.08 (2H, q, CH_2-CH_3), 4.75 (1H, d, Ph-CH), 6.60-7.0 (4H, m, Ar-O), 7.36 (5H, m, Ph-C); IR (KBr)cm^{-1} 3540 (free OH), 3400 (ass. OH), 3170, ($^+NH_3$), 1595, 1500 (arom. C=C), 1255 (Ar-O-Alk), 1220 (SO_3^-), 750 (disubstit. arom.), 720 (monosubstit. arom.).

(+)-(2S,3S)-1-Amino-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropane 7a.
$[\alpha]_D^{20}$ = +34.4; m.p. 97-99°C.

(2RS,3SR)-1-Amino-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropane 7b.
A solution of 3.3 g (7.5 mmole) of compound 6 in 100 ml of dimethylacetamide and 100 ml 30% NH_4OH was kept overnight in a sealed flask at room temperature. After dilution with 600 ml of a NaCl saturated aqueous solution, the mixture was extracted with ethyl acetate. The organic solution was anhydrified over Na_2SO_4 and evaporated to dryness in vacuo. The residue was taken up with n-hexane and filtered to give 1.77 g (83%) of a colourless solid; m.p. 112-114°.
(Found: C, 70.89; H, 7.40; N, 4.83. $C_{17}H_{21}NO_3$ requires C, 71.05; H, 7.36; N, 4.87%).
^{1}H-NMR, free base, ($CDCl_3$)δ 1.45 (3H, t, CH_3), 2.32 (3H, br. b, OH, NH_2), 2.78 (1H, dd, CH_AH_BN), 3.14 (1H, dd, CH_AH_BN), 3.81 (1H, m, CH-OH), 4.07 (2H, q, CH_2CH_3), 4.09 (1H, d, Ph-CH), 6.68-6.90 (4H, m, Ar-O), 7.30 (5H, m, Ph-C); IR, free base, (KBr) cm^{-1} 3420 (OH), 3350-3310 (NH_2), 1590, 1500 (arom. C=C), 1245 (Ar-O-Alk), 735 (disusbt. arom.), 695 (monosubst. arom.).

(2RS,3RS)-1-Chloroacetylamino-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropane 8a.
To a solution of 10.63 g (37.0 mmole) of the aminoalcohol 7a and 11.36 ml (81.0 mmole) of triethylamine in 330 ml of CH_2Cl_2 kept at -10° to -5°, 3.20 ml (40.1 mmole) of chloroacetylchloride dissolved in 85 ml of CH_2Cl_2 were added dropwise. After 0.5 hr the solution was washed with water, dried over Na_2SO_4 and evaporated to dryness. The solid residue was ground with n-hexane. Obtained 13.2 g (98%); m.p. 116-119°.
(Found: C, 62.65; H, 6.02; Cl, 9.69; N, 3.85. $C_{19}H_{22}ClNO_4$ requires C, 62.72; H, 6.09; Cl, 9.73; N, 3.87%).
^{1}H-NMR ($CDCl_3$)δ 1.51 (3H, t, CH_3), 3.23 (2H, m, CH_2N), 3.99 (2H, s, CH_2-Cl), 4.10 (2H, q, CH_2-CH_3), 4.15 (1H, m, CH-OH), 4.35 (1H, br. b, OH), 4.60 (1H, d, Ph-CH), 6.50-7.05 (4H, m, ArO), 7.0 (1H, br. b, NH), 7.35 (5H, br. s, Ph-C). IR ($CHCl_3$) cm^{-1} 3500 (OH), 3410 (NH), 1670 (CO), 1600-1500 (arom. C=C), 1250 (Ar-O-Alk).

(+)-(2S,3S)-1-Chloroacetylamino-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropane 8a.
$[\alpha]_D^{20}$ = +18.6°; oil.

(2RS,3SR)-1-Chloroacetylamino-3-(2-ethoxyphenoxy)-2-hydroxy-3-phenylpropane 8b.
This compound was obtained in 79% yield in the same reaction conditions as for 8a.
(Found: C, 62.50; H, 6.00; Cl, 9.85; N, 3.55; $C_{19}H_{22}ClNO_4$ requires C, 62.72; H, 6.09; Cl, 9.73; N, 3.87%).
^{1}H-NMR ($CDCl_3$)δ 1.50 (3H, t, CH_3), 3.31 (1H, ddd, CH_AH_BN), 3.73 (1H, ddd, CH_AH_BN), 3.90 (1H, m, CH-OH), 3.98 (2H, s, CH_2-Cl), 4.13 (2H, q, CH_2CH_3), 5.03 (1H, d, Ph-CH), 6.67-6.98 (4H, m, Ar-O), 7.20 (1H, br b, NH), 7.35 (5H, br s, Ph-C); IR ($CHCl_3$) cm^{-1} 3250-3300 (OH), 3420 (NH), 1660 (CO), 1590-1495 (arom C=C), 1250 (Ar-O-Alk).

(2RS,3RS)-6-[α-(2-Ethoxyphenoxy)benzyl]morpholin-3-one 9a.
To a solution of 8.1 g (72.0 mmole) of potassium t-butoxide in 50 ml of tert-butanol 13.2 g (36.0 mmole) of 8a in 150 ml of tert-butanol were added at room temperature in 2 hr. After a further hour, 8% HCl was added until pH 4-5 was reached and the solution was evaporated to dryness in vacuo. The residue was taken up with water, the solution was neutralized with solid $NaHCO_3$ and extracted with ethyl acetate. The organic phase was thoroughly washed with water, dried over Na_2SO_4 and the solvent distilled in vacuo. The residue was ground with n-hexane and filtered to obtain 10.2 g (86%) of a solid, m.p. 99-102°.
(Found: C, 69.62; H, 6.40; N, 4.23. $C_{19}H_{21}NO_4$ requires C, 69.70; H, 6.46; N, 4.28%).
^{1}H-NMR ($CDCl_3$)δ 1.38 (3H, t, CH_3), 3.00 (1H, ddd, CH_AH_B-N), 3.29 (1H, dd, CH_AH_BN), 4.02 (2H, q, CH_2-CH_3), 4.10 (1H, m, O-CH-CH-Ph), 4.23 (2H, s, CH_2CO), 5.20 (1H, d, Ph-CH), 6.80 (4H, m, Ar-O), 7.32 (5H, br s, Ph-C). IR (KBr) cm^{-1} 3200 (NH, 1685 (CO), 1600, 1505 (arom. C=C), 1260 (Ar-O-Alk), 1220

(Alk-O-Alk), 750 (disubst. atom.), 710 (monosubst. arom.).

(-)-(2S,3S)-6-[α-(2-Ethoxyphenoxy)benzyl]morpholin-3-one 9a.
$[\alpha]_D^{20}$ = -21.2°; oil.

(2RS,3SR)-6-[α-(2-Ethoxyphenoxy)benzyl]morpholin-3-one 9b.
This compound was obtained in 68% yield in the same reaction conditions as for 9a; m.p. 117-119°. (Found: C, 69.70; H, 6.50; N, 4.32. $C_{19}H_{21}NO_4$ requires C, 69.70; H, 6.46; N, 4.28%). ^{1}H-NMR ($CDCl_3$)δ 1.42 (3H, t, CH_3), 3.65 (2H, m, CH_2N), 4.04 (2H, q, CH_2CH_3), 4.10 (1H, m, O-CH-CH-Ph), 4.14 (2H, q, CH_2CO), 5.11 (1H, d, Ph-CH), 6.60-6.90 (4H, m, Ar-O), 7.07 (1H, br.b, CONH), 7.73 (5H, br.s, Ph-C); IR (KBr)cm^{-1} 3200 (NH), 1680 (CO), 1590, 1500 (arom. C=C), 1250 (Ar-O-Alk), 1225 (Alk-O-Alk); 735 (disubst. arom.), 695 (monosubst. arom.).

(2RS,3RS)-2-[α-(2-Ethoxyphenoxy)benzyl]morpholine methanesulfonate Ia.
To a solution of 5.0 g (15.3 mmole) of 9a in 200 ml of anhydrous toluene, 12.7 ml (45.4 mmole) of 70% toluene solution of RED-AL (Vitride ^{R}), diluted with 40 ml of anhydrous toluene were added at room temperature in 15 min. After 4 hr the excess RED-AL was decomposed with 20 ml of 2N NaOH. The organic phase was separated, washed with water, dried, and evaporated to dryness.The residue was dissolved in ethyl acetate and 1.0 ml (15.4 mmole) of CH_3SO_3H was added to the solution. After standing overnight at room temperature, the solid was collected by filtration; g 4.5 obtained (72%), m.p. 145-146°. (Found: C, 58.59; H, 6.61; N, 3.38; S, 7.79. $C_{20}H_{27}NO_6S$ requires C, 58.65; H, 6.65; N, 3.42; S, 7.83%). ^{1}H-NMR ($CDCl_3$)δ 1.44 (3H, t, CH_2-CH_3), 2.50-3.52 (4H, m, CH_2-N-CH_2), 2.75 (3H, s, CH_3S), 3.80-4.50 (3H, m, CH_2-O-CH), 4.09 (2H, q, CH_2-CH_3), 5.20 (1H, d, Ph-CH), 6.83 (4H, m, Ar-O), 7.38 (5H, m, Ph-C), 9.20 (2H, br.b, $\overset{+}{N}H_2$); IR (KBr)cm^{-1} 3000-2400 ($\overset{+}{N}H_2$), 1590-1500 (arom.C=C), 1250 (Ar-O-Alk), 1210 (Alk-O-Alk), 1190, 1035 (SO_3H).

(+)-(2S,3S)-2-[α-(2-Ethoxyphenoxy)benzyl]morpholine methanesulfonate Ia.
Method a) from racemic I (FCE 20124).
To a solution of 31.3 g (100.0 mmole) of Ia in 100 ml of absolute ethanol 15.2 g (100.0 mmole) of L(+) mandelic acid in 180 ml of absolute ethanol were added. The mixture was allowed to stand overnight and the solid mandelate filtered to obtain 19.0 g of a crystalline solid, m.p. 134-151° $[\alpha]_D^{20}$ = +48.01°. After crystallization from 200 ml of absolute ethanol 17.0 g were collected, m.p. 151-153°, $[\alpha]_D^{20}$ = +49.09° (C, 1.0,80% ethanol). Melting point and the $[\alpha]_D^{20}$ did not improve on further crystallization. The mandelate was partitioned between an aqueous potassium carbonate solution and ethyl acetate, the organic phase was washed twice with water, dried over sodium sulfate and evaporated to dryness in vacuo. The residue 12.3 g (0.39 mole) was dissolved in a few milliliters of absolute ethanol and 2.53 ml (39 mmole) of methanesulfonic acid in 2 ml of absolute ethanol were added. The solution was diluted with diethyl ether and allowed to stand for 48 hr. After filtration 10.87 g (53%) of crystalline product was obtained; m.p. 100-102°, $[\alpha]_D^{20}$ = +21.89° (C 1.0, 95% ethanol). Analogously, starting from D(-) mandelic acid, the enantiomer (-)-(2R,3R) Ia was obtained.

Method b) from (-) 9a.
The procedure was the same as for compound (±) Ia; the enantiomer (+)-(2S,3S) Ia was obtained in 65% yield and was found identical to the product from method a); m.p. 100-102°, $[\alpha]_D^{20}$= +21,81° (C 1.0, 95% ethanol), IR (KBr) cm^{-1} 3000-2400 ($\overset{+}{N}H_2$), 1590, 1495, (arom. C=C), 1250 (Ar-O-Alk), 1205 (Alk-O-Alk), 1190, 1040 (SO_3).

(2RS,3SR)-2-[α-(-Ethoxyphenoxy)benzyl]morpholine methanesulfonate Ib.
This compound was obtained in 68% yield in the same reaction conditions as for Ia; m.p. 156-157°. (Found; C, 58.48; H, 6.80; N 3.30; S, 7.44%. $C_{20}H_{27}NO_6S$ requires C, 58.65; H, 6.55; N, 3.42; S, 7.83%). ^{1}H-NMR ($CDCl_3$)δ 1.43 (3H, t, CH_2-CH_3), 2.68 (3H, s, CH_3S), 2.90-4.30 (7H, m, CH_2-N-CH_2, CH_2-O-CH), 4.04 (2H, q, CH_2-CH_3), 5.10 (1H, d, Ph-CH), 6.60-6.90 (4H, m, Ar-O), 7.30 (5H, m, Ph-C); IR (KBr) cm^{-1} 3000-2400 ($\overset{+}{N}H_2$), 1590-1500 (arom. C=C), 1250 (Ar-O-Alk), 1210 (Alk-O-Alk), 1190-1035 (SO_3H).

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