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6 - Chloro - 2, 3 - Dihydro - 4H - 1 - Benzopyran Carboxylic Acids : Synthesis, Optical Resolution and Absolute Configuration

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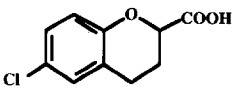
Abstract: 6-Chloro-2,3-dihydro-4H-1-benzopyran-2-carboxylic acid, a rigid analogue of clofibric acid, the active metabolite of the antilipidemic drug clofibrate, has been prepared together with two isomers, 6-chloro-2,3-dihydro-4H-1-benzopyran-3- and 4-carboxylic acids. The three acids have been resolved into their optical antipodes and the absolute configuration established by chemical correlation.

Clofibrate is an antilipidemic drug which is still on the market in spite of the adverse effects on skeletal muscle (myalgias and myotonias)[1-5] and on liver (carcinogenicity)[6,7].

In our previous work on some chiral derivatives of clofibric acid, the active metabolite of clofibrate, we demonstrated that the two enantiomers of 2-(4-chloro-phenoxy)-propionic and butyric acids present a favourable dissociation of their pharmacological properties. In fact R-isomers show the same antilipidemic effect with respect to the S-isomers and clofibric acid, but they have higher antiaggregatory activity [8] and lower myotonic [9] and hepatocarcinogenicity inducing effects[10-12].

In order to obtain more information on the receptorial site and improve the pharmacological profile of these lead compounds, three 6-chloro-2,3-dihydro-4H-1-benzopyran-carboxylic acids have been synthesized and resolved into their optical antipodes; the absolute configuration has been also established by chemical correlation.



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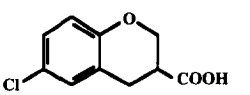

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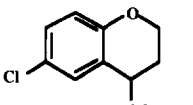
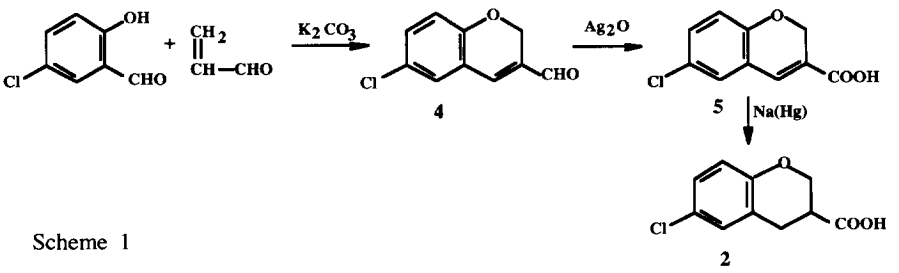


3

Compound **1** can be considered as a chiral rigid analogue of clofibric acid; compounds **2** and **3** are two isomers in which the carboxylic group and, consequently, the chiral centre are differently located.

Racemic compounds **1** and **3** were known in literature.[13,14] Compound **2** was synthesized starting from 5-chloro-salicylaldehyde and acrolein; the condensation product **4** [15] was then oxidized by silver (I) oxide to give the corresponding acid **5** which was finally reduced by sodium amalgam (scheme 1).



Scheme 1

The optical resolution of the three acids has been achieved by crystallization of the diastereomeric salts with chiral amines as reported in table 1.

Table 1. Experimental Data on Diastereomer Separation

Compound	Amine	Solvent
(+)-1	Cinchonidine	AcOEt
(+)-2	(-)-Amphetamine	EtOH/H_2O
(-)-2	(+)-2-Amino-1-(4-nitro-phenyl)-1,3-propanediol	EtOH
(+)-3	(+)-1-Phenylethylamine	EtOH
(-)-3	(-)-1-Phenylethylamine	EtOH

The *levo*-isomer of compound **1** was obtained by crystallizing from chloroform a partially resolved mixture of the two optical antipodes. In this way, the pure isomer could be obtained from the mother liquors (see Experimental). The enantiomeric excess of the optical antipodes, which has been determined by HPLC analyses on chiral stationary phase, is always > 95%.

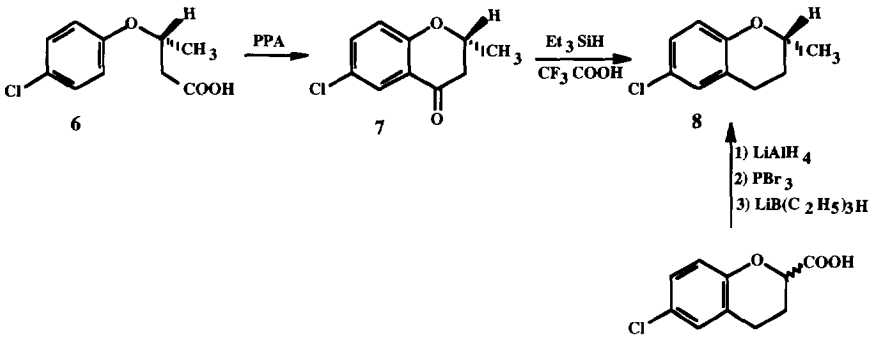
Compound **3** has been directly resolved on CHIRALCEL OD as underivatized form using n-hexane/2-propanol as mobile phase containing a small amount of trifluoroacetic acid.[16]

Compounds **1** and **2** have been resolved on SUPELCOSIL LC-(R)-Urea after conversion to suitable amides according with a standard procedure which does not involve any appreciable racemization.[17,18]

In the case of compound **2**, the 1-naphtalenemethylamide derivative was prepared and the resolution achieved using n-hexane/ethyl acetate as mobile phase containing a small amount of methanol.[19] To obtain the resolution of compound **1**, it has been necessary to synthesize a diastereomeric amide, using the 1-(1-naphthyl)-ethylamine as derivatizing agent and a n-hexane/2-propanol mixture as mobile phase.[20]

The absolute configuration has been established by chemical correlation.

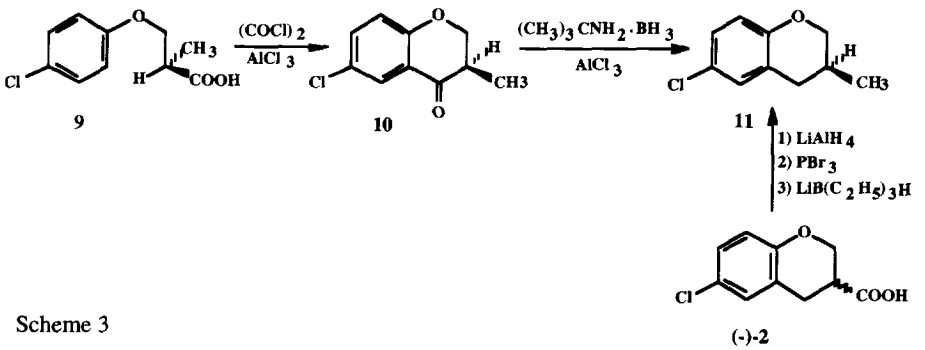
Compound (+)-**1** was transformed, by standard procedure, into the (+)-6-chloro-2-methyl-2,3-dihydro-4H-1-benzopyran **8** as reported in scheme 2.



Scheme 2

Compound **8**, also, was prepared starting from R-3-(4-chloro-phenoxy)-butyric acid **6** [21] which was cyclized by polyphosphoric acid and then reduced with Et3SiH/CF3COOH. This correlation indicates that the *dextro*-isomer of compound **1** has the S configuration.

In the same way, compound (-)-**2** was transformed into the (+)-6-chloro-3-methyl-2,3-dihydro-4H-1-benzopyran **11** as reported in scheme 3.

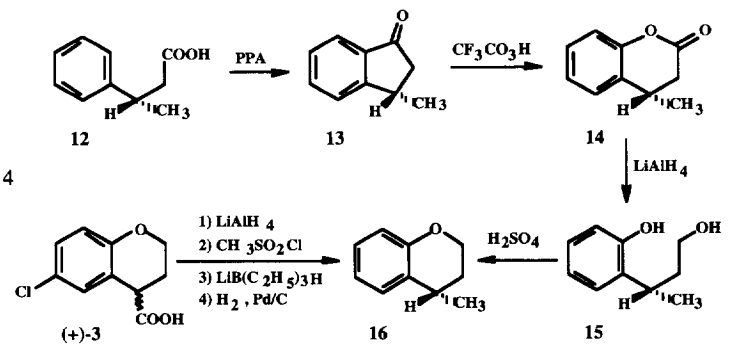


Scheme 3

The synthesis of **11** was also accomplished starting from R-2-methyl-3-(4-chloro-phenoxy)-propionic acid **9** [21], but different reaction conditions were necessary to avoid racemization. So, the cyclization was carried out with $(COCl)_2/AlCl_3$ and the subsequent reduction by t-butylaminoborane/$AlCl_3$.[22] This correlation indicates that the *levo*-isomer of compound **2** has the S configuration.

The absolute configuration of compound **3** was the most difficult to be determined. After many useless attempts, at last, we could correlate it to 3-phenyl-butyric acid as reported in scheme 4.

Scheme 4



The carboxylic group of compound **(+)-3** was still transformed into the methyl group and the chlorine atom moved away by catalytic hydrogenation obtaining, in this way, compound (-)-**16**.

The same compound (-)-**16** was synthesized starting from the S-enantiomer of 3-phenyl-butyric acid **12**, obtained by optical resolution of the racemic mixture according with the procedure known in literature.[23] This enantiomer was first cyclized by polyphosphoric acid to give S-3-methyl-1-indanone **13** as previously described;[23] the ketone was oxidized, according to literature,[24] by a Baeyer-Villiger reaction to the lactone **14** which was reduced with $LiAlH_4$ to the diol **15**. Finally, the ring closure with H_2SO_4 led to the desired compound. This chemical correlation allowed us to assign the S configuration to the *dextro*-isomer of compound **3**. The chiroptical properties of compounds **1**, **2** and **3** have been also determined. The ORD curves are reported in fig. 1.

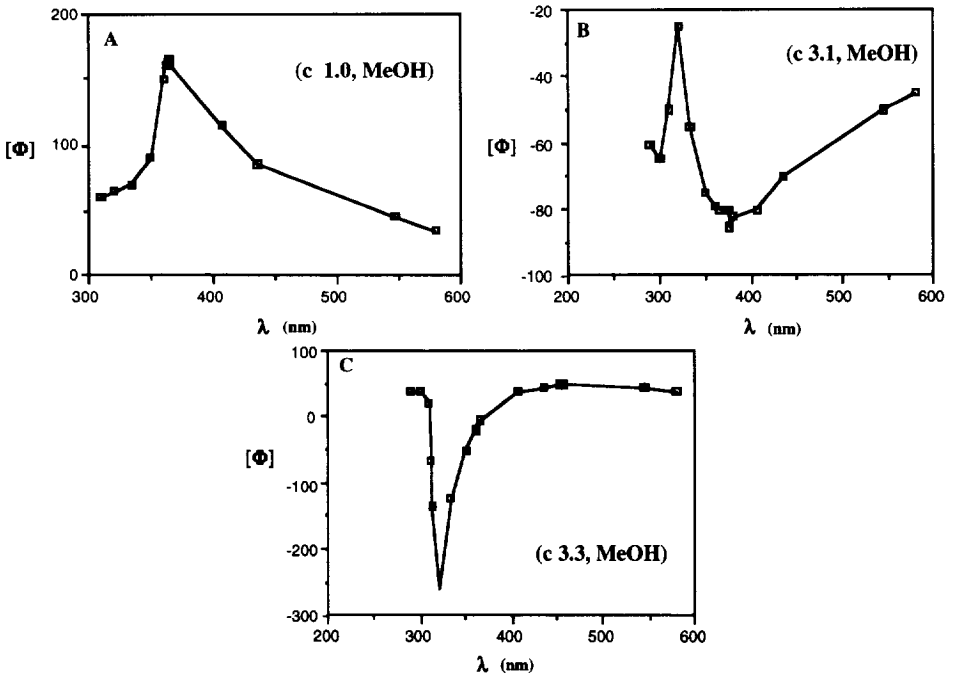


Fig 1. ORD curves of compounds (S)-1 (A), (S)-2 (B) and (S)-3 (C), respectively

In the CD curves (fig. 2), compounds **(S)-1** and **(S)-2** present a positive Cotton effect in the aromatic absorption region, whereas compound **(S)-3** show a negative Cotton effect in the same region.

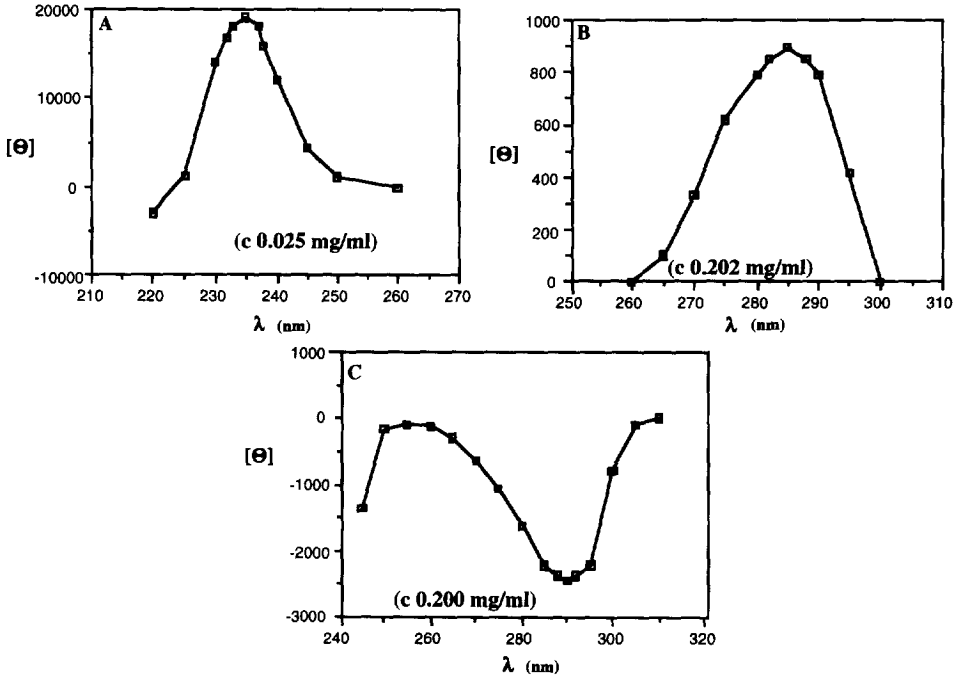


Fig 2. CD curves of compounds (S)-1 (A), (S)-2 (B) and (S)-3 (C), respectively

EXPERIMENTAL

Chemistry - Melting points were taken on a Gallenkamp apparatus and are uncorrected. Mass and IR spectra were determined with a Kratos MS 80 spectrometer and a Perkin-Elmer 283 spectrophotometer, respectively. ^{1}H- NMR spectra were recorded on a Varian EM390 spectrometer using Me_4Si as internal standard (chemical shifts are expressed in δ). Optical rotations at different wavelengths were measured with a Perkin-Elmer 241 MC polarimeter. CD curves were measured in MeOH with a Cary 61 dichrograph using a 10 mm cell. Microanalyses were carried out with a HP Model 185 CHN analyzer (the analytical results are within 0.4 % of the theoretical values).

6-Chloro-2,3-dihydro-4H-1-benzopyran-2-carboxylic acid (1) - This compound was prepared according to a known procedure.[13] However, the last step of this synthetic pathway was modified as follows.

To a solution of 15 g (0.066 mol) of 6-chloro-4-chromanon-2-carboxylic acid[13] in 110 ml of CF_3COOH, 45 ml of Et_3SiH (32.76 g, 0.282 mol) was added with stirring under N_2. The solution was refluxed for 2h. After cooling to room temperature, the solution was made basic by addition of NaOH and washed with Et_2O (3 x 200 ml). The aqueous phase was acidified with 6N HCl and extracted with Et_2O (3 x 400 ml). The Et_2O solution was washed with brine (3 x 200 ml), dried over Na_2SO_4 and the solvent was removed under reduced pressure. Crystallization from $CHCl_3$ afforded 12.9 g (91.7 %) of white crystals; mp 161-2°C (lit.[13] 152-5°C).

Resolution of (R,S)-1 - 10.65 g of racemic acid (0.05 mol) and 14.77 g of cinchonidine (0.05 mol) were mixed and crystallized from AcOEt. After three crystallizations the salt had $[\alpha]_D$ = -33.0 (c 2.1, dioxane). This salt was treated with 6N HCl and extracted with Et_2O, affording the (+)-acid which was crystallized from $CHCl_3$; mp 133-6 °C; $[\alpha]_D$ = +16.3 (c 2.1, MeOH).

The mother liquors from the first crystallization of the cinchonidine salt were concentrated and crystallized twice. At this point the mother liquors were evaporated to dryness and the residue treated with 6N HCl and extracted with Et_2O. Evaporation of the solvent afforded the acid which was crystallized from $CHCl_3$. The mother liquors were concentrated and white crystals with $[\alpha]_D$: -12.0 separated. Finally, the (-)-isomer, with $[\alpha]_D$ = -16.4 (c 2.1, MeOH) was obtained from the evaporation of the mother liquors.

3-Formyl-6-chloro-2H-1-benzopyran (4) - To a solution of 53 g (0.34 mol) of 5-chlorosalicylaldehyde in 250 ml of dioxane, 46.8 g (0.34 mol) of K_2CO_3 and 25 ml of acrolein (21 g, 0.37 mol) were added. The mixture was refluxed for 2h, then was poured into H_2O and extracted three times with toluene. The organic phase was washed with 2N NaOH, water and dried over Na_2SO_4 . The solvent was removed under reduced pressure affording a yellow solid which was crystallized from $CHCl_3$/hexane. Yield: 40 g (60 %); mp 93-5°C (lit.[15] mp 91°C). NMR ($CDCl_3$): 5.00 (s, 2H, CH_2), 6.70-7.30 (m, 4H, aromatic + vinylic), 9.60 (s, 1H , aldehydic); IR (nujol): 1670 cm^{-1} (C=O); MS: m/z 194 (M, 43), 165 (100).

6-Chloro-2H-1-benzopyran-3-carboxylic Acid (5) - To a suspension of Ag_2O in 1000 ml of 50% aqueous EtOH, prepared *in situ* from 72 g of $AgNO_3$ (0.42 mol) and 32 g of NaOH (0.8 mol), 40 g (0.2 mol) of **4** was added. The mixture was refluxed for 45 min, then was filtered and the precipitate washed several times with hot water. The filtrate was acidified with 6N HCl and extracted with Et_2O. The organic phase was extracted with satd. $NaHCO_3$, the aqueous layer acidified with 6N HCl and extracted with Et_2O; the ether layer was washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure. The solid obtained (35 g) was crystallized from EtOH yielding 30 g (70 %) of yellow crystals; mp 243-5°C. NMR (DMSO-d_6): 4.93 (d, 2H, CH_2), 6.80-7.56 (m, 4H, aromatic + vinylic); IR (nujol): 1680 cm^{-1} (C=O); MS: m/z 210 (M, 33), 165 (100).

6-Chloro-2,3-dihydro-4H-1-benzopyran-3-carboxylic Acid (2) - 30 g of **5** (0.14 mol) was added to 750 ml of 10% NaOH; a sparingly soluble Na salt precipitated. Sodium amalgam (prepared from 360 g of Hg and 12 g of sodium) was added in small portions with mechanical stirring during 30 minutes. The mixture was stirred at room temperature for 24 h, the Hg was separated, the aqueous phase acidified with 6N HCl and extracted with Et_2O; the organic phase was extracted with 5% $NaHCO_3$, the alkaline solution acidified with 6N HCl and extracted with Et_2O. The ether layer was washed with water, dried over Na_2SO_4 and the solvent removed under reduced pressure. Crystallization from $CHCl_3$/hexane afforded 19.8 g of white crystals (65%); mp 144-5°C. NMR ($CDCl_3$): 3.08 (d, 3H, $ArCH_2CH$), 4.07-4.55 (m, 2H, OCH_2), 6.70-7.25 (m, 3H, aromatic), 8.37 (s, 1H, COOH); IR (nujol): 1705 cm^{-1} (C=O); MS: m/z 212 (M, 63), 166 (100).

Resolution of (R,S)-2 - 24 g of racemic acid (0.113 mol) and 16.1 g of (R)-(-)-amphetamine (0.119 mol) were mixed and crystallized from EtOH/H_2O (1:1). After three crystallizations the salt had $[\alpha]_D$ = -35 (c = 2.0, MeOH). This salt was treated with 6N HCl and extracted with $CHCl_3$, affording the (+)-acid, which was crystallized from $CHCl_3$/hexane; mp 147-9°C; $[\alpha]_D$ = + 18.3 (c 2.7, MeOH). The mother liquors from the first crystallization of the amphetamine salt were evaporated to dryness; the residue was treated with 6N HCl and extracted with $CHCl_3$ obtaining a partially enriched mixture of the *levo*-acid which was mixed with an equivalent amount of L-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol and crystallized from EtOH. After three crystallizations the salt had $[\alpha]_D$ = +35 (c 1.5, MeOH). This salt was treated with 6N HCl and extracted

with $CHCl_3$, affording the (-)-isomer, which was crystallized from $CHCl_3$/hexane; mp 147-9°; $[\alpha]_D$ = - 18.4 (c 3.0, MeOH).

6-Chloro-2,3-dihydro-4H-1-benzopyran-4-carboxylic acid (3) - This compound was prepared according to J. L. Belletire[14] .

Resolution of (R,S)-3 - 10 g of racemic acid (0.047 mol) and 5.83 g of (S)-(-)-1-phenylethylamine (0.048 mol) were mixed and crystallized from EtOH. After three crystallizations the salt had $[\alpha]_D$ = - 4 (c 2.0, MeOH). This salt was treated with 2N HCl and extracted with $CHCl_3$ affording the (-)-acid, which was crystallized from hexane; mp 114-5°C; $[\alpha]_D$ = -17.1 (c 3.0, MeOH).

The acid obtained from the mother liquors of the first crystallization of the phenylethylamine salt, was mixed with an equivalent amount of (R)-(+)-1-phenylethylamine and crystallized from EtOH. After three crystallizations the salt was treated with 2N HCl and extracted with $CHCl_3$ affording the (+)-isomer which was cristallyzed from hexane; mp 114-5°C; $[\alpha]_D$ = + 16.5 (c 2.0, MeOH).

Preparation of R-(+)-6-chloro-2-methyl-2,3-dihydro-4H-1-benzopyran (8) starting from R-(-)-6

R-(+)-6-Chloro-2-methyl-2,3-dihydro-4H-1-benzopyran-4-one (7) - 1.8 g of R-(-)-3-(4-chlorophenoxy)-butyric acid **6** (0.0084 mol) with $[\alpha]_D$ = - 11.4 (MeOH) [21] was mixed with 25 ml of polyphosphoric acid. The mixture was kept at 70-80°C for 90 min, then poured into ice and extracted with $CHCl_3$; the organic phase was washed with water, 5% $NaHCO_3$, water again and dried over Na_2SO_4 . The solvent was removed under reduced pressure affording 1.52 g of a yellow solid which was crystallized from hexane yielding 1.26 g of light yellow crystals (77%); mp 105-7°C, $[\alpha]_D$ = + 32 (c 2.7, MeOH). NMR ($CDCl_3$): 1.53 (d, 3H, CH_3), 2.77-2.58 (m, 2H, CH_2), 4.35-4.85 (m, 1H, CH), 6.87-7.95 (m, 3H aromatic); IR (nujol): 1685 cm^{-1} (C=O); MS: m/z 196 (M, 49), 154 (100).

R-(+)-6-Chloro-2-methyl-2,3-dihydro-4H-1-benzopyran (8) - To a solution of 1.16 g of **7** (0.0059 mol) in 8 ml of CF_3COOH, 5 ml of Et_3SiH was added with stirring under N_2 . The mixture was refluxed for 5h; after cooling was made basic with 3N NaOH and extracted with Et_2O. The organic phase was washed with water, dried over Na_2SO_4 , evaporated under reduced pressure affording 3.6 g of a pale yellow oil which was purified by distillation. The fraction (1.85 g) which distilled at 90-4°C (2 mmHg) was chromatographed on a silica gel column (pet. ether/AcOEt 95:5) affording 0.446 g (41.5%) of white crystals; mp 38-9°C, $[\alpha]_D$ = + 43.3 (c 1.5, MeOH). NMR ($CDCl_3$): 1.37 (d, 3H, CH_3), 1.45-2.18 (m, 2H, CH_2-C-O), 2.60-2.88 (m, 2H, CH_2Ar), 3.90-4.30 (m, 1H, CH), 6.60-7.15 (m, 3H, aromatic); MS: m/z 182 (M, 69), 141 (100).

Preparation of R-(+)-6-chloro-2-methyl-2,3-dihydro-4H-1-benzopyran (8) starting from (+)-1

(+)-6-Chloro-2-hydroxymethyl-2,3-dihydro-4H-1-benzopyran - To a suspension of 0.200 g (0.0053 mol) of $LiAlH_4$ in 15 ml of dry THF, 1.16 g (0.0054 mol) of **(+)-1** (for this purpose the *dextro*-acid with $[\alpha]_D$ = + 8.2 was used) in 15 ml of dry THF was added dropwise within 15 min. The suspension was stirred at room temperature for 5h, was poured into ice and acidified with 2N HCl; after removing the organic solvent under reduced pressure, the aqueous phase was extracted with Et_2O, the ether layer washed with 5% $NaHCO_3$, water and dried over Na_2SO_4 . The solvent was removed under reduced pressure affording 0.98 g of a yellow oil (90%), $[\alpha]_D$ = + 51 (c 2.5, MeOH). NMR ($CDCl_3$): 1.75-2.05 (m, 2H, C-CH_2-C), 2.17 (s, 1H, OH), 2.65-2.95 (m, 2H, $ArCH_2$), 3.73-3.85 (m, 2H, CH_2O), 3.90-4.25 (m, 1H, CH), 6.68-7.25 (m, 3H, aromatic); IR (neat): 3400 cm^{-1} (OH); MS: m/z 198 (M, 60), 167 (100).

(+)-6-Chloro-2-bromomethyl-2,3-dihydro-4H-1-benzopyran - To a cold solution (-10°C) of the above alcohol (0.98 g, 0.0049 mol) in 5 ml of dry CH_2Cl_2, 0.45 g of PBr_3 (0.0017 mol) in 5 ml of dry CH_2Cl_2 was added dropwise during 15 minutes. The mixture was allowed to warm to room temperature and stirred for 5h then poured into ice. The organic layer was separated and the aqueous phase extracted once more with CH_2Cl_2. The organic extracts were washed with brine, dried over Na_2SO_4 and the solvent removed under reduced pressure affording 1 g of a pale yellow oil . Column chromatography on silica gel (pet. ether/AcOEt 8:2) yielded 0.260 g of an oil (20 %) with $[\alpha]_D$ = + 49 (c 1.9, MeOH). NMR ($CDCl_3$): 1.70-2.30 (m, 2H, C-CH_2-C), 2.60-2.95 (m, 2H, $ArCH_2$), 3.40-3.65 (m, 2H, CH_2Br), 4.05-4.40 (m, 1H, CH), 6.70-7.20 (m, 3H, aromatic); MS: m/z 260 (M, 70), 262 (M+2, 93), 167 (100).

(+)-6-Chloro-2-methyl-2,3-dihydro-4H-1-benzopyran (8) - To a solution of 0.200 g (0.00076 mol) of the above compound in 7 ml of dry THF, 1.5 ml of 1.0 M $Li(Et)_3BH$ in THF [ALDRICH] was added dropwise under N_2. After stirring for two hours at room temperature, the mixture was quenched with water and extracted with Et_2O; the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure affording 0.200 g of an oil. After column chromatography on silica gel (pet. ether/AcOEt 98:2) 0.058 g of solid was collected (42 %); $[\alpha]_D$ = +56.5 (c 1.7, MeOH).

Preparation of S-(+)-6-chloro-3-methyl-2,3-dihydro-4H-1-benzopyran (11) starting from R-(-)-9

R-(+)-6-Chloro-3-methy-2,3-dihydro-4H-1-benzopyran-4-one (10) - To a solution of 0.5 g (0.0023 mol) of R-(-)-2-methyl-3-(4-chlorophenoxy)-propionic acid **9**, with $[\alpha]_D$ = -8 [21], in 10 ml of CH_2Cl_2, 0.05 ml of DMF and 0.23 ml of oxalyl chloride (0.0026 mol) were added at 0°C under N_2. The mixture was allowed to warm to room temperature with stirring and after 1.5 h was cooled at -15° C and added with 0.66 g (0.005 mol) of $AlCl_3$; the stirring was continued at -15°C for 1h. The solution was quenched with cold 1N HCl (10 ml) and diluted with cold water (5 ml); the phases were separated and the organic layer washed successively with cold 1N HCl (2 x10 ml), water (5 ml) and satd. $NaHCO_3$ (2 x 10 ml). It was dried over Na_2SO_4 and the solvent removed under reduced pressure affording 0.400 g of a solid which was crystallized from hexane to yield 0.27 g (59%) of white crystals; mp 90-92.5°C, $[\alpha]_D$ = + 57.7 (c 1.65, MeOH) (lit.[22] $[\alpha]_D$: + 48, $CHCl_3$); NMR ($CDCl_3$): 1.25 (d, 3H, CH_3), 2.70-3.10 (m, 1H, CH), 4.00-4.70 (m, 2H, CH_2), 6.88-8.10 (m, 3H, aromatic); IR (nujol): 1700 cm^{-1} (C=O); MS: m/z 196 (M, 34), 154 (100).

S-(+)-6-Chloro-3-methyl-2,3-dihydro-4H-1-benzopyran (11) - 0.407 g of $AlCl_3$ (0.003 mol) was suspended at 0°C in 10 ml of CH_2Cl_2 then 0.531 g of *t* -butylaminoborane (0.006 mol) was added and the mixture stirred at 0°C for 10 minutes. The solution so obtained was added with 0.200 g of R-(+)-**10** (0.001 mol) dissolved in 2 ml of CH_2Cl_2. The mixture was stirred for 1.5 h at 0°C and for 3h at room temperature. It was quenched with cold 0.1N HCl (5 ml); the phases were separated and the organic layer washed twice with cold 0.1N HCl, with brine and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded 0.170 g of a white solid which was purified by column chromatography on silica gel (pet. ether/AcOEt 98:2) yielding 0.100 g of a product which was crystallized from EtOH to yield 0.057 g of white crystals (31 %); mp 57.5-59.5°C, $[\alpha]_D$ = + 66.9 (c 1.6, $CHCl_3$); NMR ($CDCl_3$): 1.05 (d, 3H, CH_3), 1.90-3.00 (m, 3H, CH + $ArCH_2$), 3.45-4.38 (m, 2H, CH_2), 6.70-7.23 (m, 3H, aromatic); MS: m/z 182 (M, 100).

Preparation of S-(+)-6-chloro-3-methyl-2,3-dihydro-4H-1-benzopyran (11) starting from (-)-2

(+)-6-Chloro-3-hydroxymethyl-2,3-dihydro-4H-1-benzopyran - To a suspension of 0.50 g (0.013 mol) of $LiAlH_4$ in 15 ml of dry THF, 1.5 g (0.007 mol) of **(-)-2** dissolved in 10 ml of dry THF was added dropwise

during 15 min (for this purpose the *levo*-acid with $[\alpha]_D$: -12.4 was used). The suspension was stirred at room temperature for 1.5 h, then was poured into ice and acidified with 2N HCl ; after removing the organic solvent under reduced pressure, the aqueous phase was extracted with Et_2O; the ether layer was washed with satd. $NaHCO_3$, water and dried over Na_2SO_4. The solvent was removed under reduced pressure affording 1.3 g of a solid which was crystallized from $CHCl_3$/hexane to yield 0.67 g (48 %) of white crystals; mp 80-3°C, $[\alpha]_D$ = + 13 (c 1.5, MeOH); NMR ($CDCl_3$): 1.80 (s, 1H, OH), 2.10-3.05 (m, 3H, CH + CH_2Ar), 3.70 (d, 2H, $\underline{CH_2}$OH), 3.85-4.50 (m, 2H, CH_2-OAr), 6.67-7.27 (m, 3H, aromatic); IR (nujol): 3300 cm^{-1} (OH); MS: m/z 198 (M, 100).

(+)-6-Chloro-3-bromomethyl-2,3-dihydro-4H-1-benzopyran - To 1.035 g (0.0052 mol) of the above alcohol in 10 ml of dry CH_2Cl_2 , 0.58 g (0.0021 mol) of PBr_3 in 5 ml of dry CH_2Cl_2 was added dropwise at 0°C during 15 min. The solution was allowed to warm to room temperature and stirred for 5h, then poured into ice. The organic layer was separated and the aqueous phase extracted once more with CH_2Cl_2. The organic extracts were washed with brine and dried over Na_2SO_4. Evaporation *in vacuo* gave a yellow oil which was purified by column chromatography on silica gel (pet. ether/AcOEt 95:5) affording 0.3 g of a white solid which was crystallized from EtOH to yield 0.100 g (8%) of white crystals ; mp 54-6°C, $[\alpha]_D$ = + 1.6 (c 1.7, CH_2Cl_2); NMR ($CDCl_3$): 2.20-3.15 (m, 3H, CH + CH_2Ar), 3.43 (d, 2H, CH_2Br), 3.80-4.43 (m, 2H, CH_2O), 6.67-7.25 (m, 3H, aromatic); MS: m/z 260 (M, 64), 262 (M+2, 100).

(+)-6-Chloro-3-methyl-2,3-dihydro-4H-1-benzopyran (11) - 2 ml of 1.0 M $Li(Et)_3BH$ in THF [ALDRICH] was added dropwise, under N_2 , to a solution of 0.25 g (0.00096 mol) of the above compound in 8 ml of dry THF. After stirring for 2.5h at room temperature, the mixture was concentrated *in vacuo* , quenched with water and extracted with Et_2O; the organic phase was dried over Na_2SO_4 and evaporated under reduced pressure affording 0.185 g of a white solid which was purified successively by column chromatography on silica gel (pet. ether/AcOEt 95:5) and by crystallization from aqueous EtOH to yield 0.035 g (20 %) of white crystals; mp 57-58.5°C, $[\alpha]_D$ = + 43.9 (c 1.4, $CHCl_3$).

Preparation of S-(-)-4-methyl-2,3-dihydro-4H-1-benzopyran (16) starting from S-(+)-12

S-(+)-3-Methyl-1-indanone (13) - 7.3 g of S-3-phenylbutyric acid **12** with $[\alpha]_D$ = + 55.3 [23] was mixed with 25 g of polyphosphoric acid. The mixture was kept at 90-5°C for 1.5h, poured into ice and extracted with $CHCl_3$. The organic solution was washed with NaOH, brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure affording an oil (4.9 g) which distilled at 79-81°C (0.5 mmHg). 4.0 g of a colourless oil was obtained (61.5 %) with $[\alpha]_D$ = + 16.5 (c 2.0, Me_2CO) (lit.[23] $[\alpha]_D$ = + 16.0, Me_2CO). NMR ($CDCl_3$): 1.43 (d, 3H, CH_3), 2.10-3.17 (m, 2H, CH_2), 3.20-3.70 (m, 1H, CH), 7.20-8.00 (m, 4H, aromatic); IR (neat): 1710 cm^{-1} (C=O); MS: m/z 146 (M, 66), 131 (100).

S-(-)-4-Methyl-3,4-dihydrocoumarine (14) - This compound was prepared according to lit.[24] adding a mixture of 53.2 g of $(CF_3CO)_2O$ (0.253 mol), 5 ml of 35% H_2O_2 and 50 ml of CH_2Cl_2 to a solution of 3.7 g of **13** (0.0253 mol) in 50 ml of CH_2Cl_2 . After work-up, an oil was obtained (3.5 g) which distilled at 92-4°C (1 mmHg); 2.80 g of a colourless oil was collected (68 %) with $[\alpha]_D$ = - 40.5 (c 2.0, C_6H_6) (lit.[24] $[\alpha]_D$ = - 34, C_6H_6); NMR ($CDCl_3$): 1.35 (d, 3H, CH_3), 2.35-3.40 (m, 3H, CH + CH_2), 6.90-7.60 (m, 4H, aromatic); IR (neat): 1765 cm^{-1} (C=O); MS: m/z 162 (M, 79), 91(100).

S-(+)-3-(2-Hydroxyphenyl)-1-butanol (15) - 1 g of **14** (0.0062 mol) in 30 ml of dry THF was added dropwise to an ice-bath cold suspension of 0.500 g of $LiAlH_4$ (0.013 mol) in 30 ml of dry THF during 15 min. Stirring and cooling were continued for 1h then the mixture was poured into ice and acidified with 2N HCl.

The organic solvent was removed under reduced pressure and the aqueous phase extracted with CH_2Cl_2 ; the organic solution was washed with water, dried over Na_2SO_4 . Evaporation of the solvent gave 1 g (98 %) of a pale yellow oil with $[\alpha]_D$ = + 16.0 (c 2.5, Me_2CO). NMR ($CDCl_3$): 1.10-2.25 (d, 3H, CH_3 + m, 2H, C-CH_2-C), 3.15-3.95 (m, 3H, CH + CH_2O), 4.80 (broad, 2H, 2OH), 6.70-7.50 (m, 4H, aromatic); IR (neat): 3300 cm^{-1} (broad, OH); MS: m/z 166 (M, 27), 121(100).

S-(-)-4-Methyl-2,3-dihydro-4H-1-benzopyran (16) - 0.250 g of **15** (0.0015 mol) was mixed with 3 ml of 25% H_2SO_4 and the mixture stirred and refluxed for 30 min. The suspension was extracted with Et_2O, the organic layer washed with water and dried over Na_2SO_4 . Evaporation of the solvent afforded 0.140 g of an oil which, by column chromatography on silica gel (pet.ether/AcOEt 9:1), gave 0.096 g (43 %) of a colourless oil with $[\alpha]_D$ = - 7.4 (c 1.7, C_6H_6). NMR ($CDCl_3$): 1.05-2.30 (d, 3H, CH_3 + m, 2H, C-CH_2-C), 2.75-3.15 (m, 1H, CH), 3.95-4.40 (t, 2H, CH_2O), 6.60-7.35 (m, 4H, aromatic); MS: m/z 148 (M, 46), 133 (100).

Preparation of S-(-)-4-methyl-2,3-dihydro-4H-1-benzopyran (16) starting from (+)-3

(-)-6-Chloro-4-hydroxymethyl-2,3-dihydro-4H-1-benzopyran - A solution of 0.50 g (0.0024 mol) of **(+)-3**, with $[\alpha]_D$ = + 17, in 10 ml of dry THF was added dropwise, during 15 min, to an ice-bath cold suspension of 0.500 g (0.0132 mol) of $LiAlH_4$ in 12 ml of dry THF. Stirring and cooling were continued for 5h then the mixture was poured into ice and acidified with 2N HCl. The organic solvent was removed under reduced pressure and the aqueous layer extracted with CH_2Cl_2 ; the organic phase was washed with 5% $NaHCO_3$, water and dried over Na_2SO_4 . Evaporation of the solvent gave 0.430 g of a white solid which was crystallized from hexane affording 0.380 g (81 %) of white crystals with $[\alpha]_D$ = - 9.8 (c 2.1, Me_2CO); mp 80-1°C. NMR ($CDCl_3$): 1.60-2.50 (s,1H, OH + m, 2H, C-CH_2-C), 2.75-3.20 (m, 1H, CH), 3.65-4.55 (d, 2H, CH_2OH + t, 2H, $ArOCH_2$), 6.68-7.60 (m 3H, aromatic); IR (nujol): 3300 cm^{-1} (broad, OH); MS: m/z 198 (M, 33), 167 (100).

(-)-6-Chloro-4-methanesulfoniloxymethyl-2,3-dihydro-4H-1-benzopyran - To a stirred and cold (-5°C) solution of 0.400 g (0.0020 mol) of the alcohol obtained from the previous reaction in 10 ml of CH_2Cl_2 , 0.3 g of Et_3N (0.003 mol) and then 0.250 g of methanesulfonyl chloride (0.0022 mol) were added. Stirring and cooling were continued for 1h, then the mixture was poured into ice and the phases were separated. The organic layer was washed with cold 10% HCl , with satd. $NaHCO_3$ and brine. After drying over Na_2SO_4, evaporation of the solvent gave 0.5 g of a white solid which was crystallized from $CHCl_3$/hexane affording 0.300 g of white crystals with $[\alpha]_D$ = + 15.7 (c 2.1, Me_2CO); mp 86-8°C. NMR ($CDCl_3$): 1.90-2.40 (m, 2H, C-CH_2-C), 2.80-3.50 (s, 3H, CH_3 + m, 1H, CH), 3.90-4.67 (m, 4H, CH_2OAr + CH_2OSO_2), 6.65-7.40 (m, 3H, aromatic); MS: m/z 276 (M, 30), 180 (100).

(+)-6-Chloro-4-methyl-2,3-dihydro-4H-1-benzopyran - To a solution of 0.470 g (0.0017 mol) of the above mesylate in 15 ml of dry THF, 8 ml of 1.0 M $Li(Et)_3BH$ in THF [ALDRICH] was added dropwise under N_2 . The mixture was stirred and refluxed for 30 minutes then was quenched with water and the organic solvent was evaporated under reduced pressure. The aqueous phase was extracted with CH_2Cl_2 and the organic layer washed with brine and dried over Na_2SO_4 . Evaporation of the solvent gave an oil which was purified by column chromatography on silica gel (pet. ether/AcOEt 9:1) affording 0.150 g of an oil (48 %) with $[\alpha]_D$ = + 21.8 (c 2.1, MeOH). NMR ($CDCl_3$): 1.10-2.40 (d, 3H, CH_3 + m, 2H, C-CH_2-C), 2.70-3.20 (m, 1H, CH), 4.10-4.45 (t, 2H, CH_2O), 6.65-7.60 (m, 3H, aromatic); MS: m/z 182 (M, 69), 167 (100).

(-)-4-Methyl-2,3-dihydro-4H-1-benzopyran (16) - The above oil (0.200 g, 0.0011 mol) was dissolved in EtOH (30 ml) and hydrogenated over 10% Pd/C (20 mg) under an atmospheric pressure of hydrogen overnight at room temperature. The solution was filtered through Celite, the solvent was removed under

reduced pressure and the residue chromatographed on a silica gel column (hexane) affording 0.080 g (49%) of a pale yellow oil with $[\alpha]_D$ = - 7.1 (c 1.9, C_6H_6).

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