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Reaction of caesium 4-chlorophenate and chlorohydrins from threonines: synthesis of clofibrate analogues

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Abstract—Clofibrate is a well-known peroxisome proliferator-activated receptor-α (PPARα) agonist, used in the treatment of hyperlipaemias and atherosclerosis and to prevent heart failure. Herein, the preparation of the four enantiomerically pure stereoisomers of ethyl 2-(4-chlorophenoxy)-3-hydroxybutanoate as clofibrate analogues is described. Biological evaluation of these new compounds was performed by a transactivation assay in a transiently transfected monkey kidney fibroblast cell line. All four diastereomers were inactive even at 300 μM, where clofibrate showed an evident activity, suggesting that the designed clofibrate molecular structural modifications in the analogues caused the loss of peroxisome proliferator-activated receptor-α (PPARα) activity.

1. Introduction

Clofibrate **1** (Fig. 1) and other fibrates are well-known drugs used in the treatment of dyslipidemias,[1,2] even though clofibrate was withdrawn from the market due to severe adverse side effects.[3–13] Discovery of peroxisome proliferator-activated receptors, particularly the subtype α (PPARα), as the biological target of clofibrate has renewed interest in this class of compounds.[2] As an attempt to improve the pharmacological profile of clofibrate **1**, a lot of new analogues have been synthesized and biologically evaluated.[14–26]

Recently, we reported the synthesis of new racemic ethyl 2-(4-chlorophenoxy)alkanoates **2** (Fig. 1) and their biological activity, evaluated in a transactivation assay, with respect to clofibrate and WY-14,643. However, they were found to be inactive.[27] One of the reasons of this behaviour could be that the compounds were assayed by using a mixture of the four possible stereoisomers of each new compound **2**. This prompted us to develop the synthesis of the four stereoisomers of at least the simplest compound of the set **2a** (R = CH_3) to separately evaluate their biological activity.

(2*R*,3*S*)-**2a** was prepared with ee = 94% and 97% respectively by Baker's yeast- and *Kluyveromyces marxianus*-mediated bioreduction of ethyl 2-(4-chlorophenoxy)-3-oxobutanoate, the direct precursor of **2a**.[28,29] Whereas, (2*S*,3*S*)-**2a** was prepared with ee >99% by performing the same reaction in the presence of whole cells of *Saccharomyces cerevisiae* CBS 7336 and *Trigonopsis variabilis* DSM 70714.[29] Herein, we describe the chemical asymmetric synthesis of the four stereoisomers of ethyl 2-(4-chlorophenoxy)-3-hydroxybutanoate **2a** and of the corresponding four acids **3**, whose activity as potential peroxisome proliferators is reported.

2. Results and discussion

As previously described, racemic 2-(4-chlorophenoxy)-3-hydroxybutanoic acid **3** was prepared, as a part of a larger study,[27] by hydrolyzing **2a** obtained by $NaBH_4$ reduction of ethyl 2-(4-chlorophenoxy)-3-oxobutanoate. This in turn was prepared by reacting caesium 4-chlorophenate and ethyl 2-chloro-3-oxobutanoate.

As far as the synthesis of the four optically active 2-(4-chlorophenoxy)-3-hydroxybutanoic acids **3** is concerned, (2*R*,3*S*)-D- and (2*S*,3*R*)-L-threonine and, (2*R*,3*R*)-D- and (2*S*,3*S*)-L-allothreonine were chosen as the starting materials (Fig. 2 and Scheme 1).

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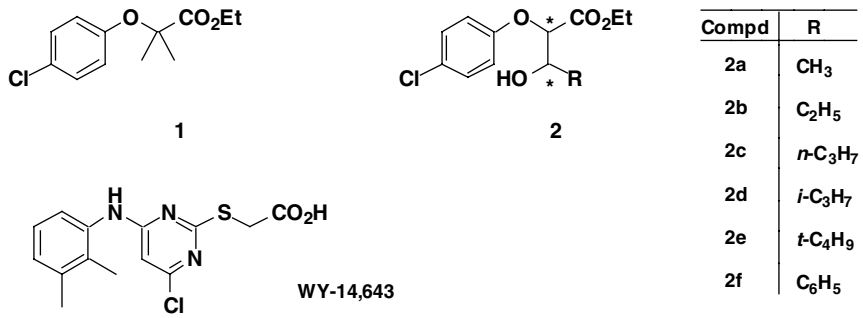


Compd	R
2a	CH_3
2b	C_2H_5
2c	n-C_3H_7
2d	i-C_3H_7
2e	t-C_4H_9
2f	C_6H_5

Figure 1. Structure of clofibrate **1** and its analogues **2a–f** and PPARα-ligand WY-14,643.

As expected, in all cases, preliminary conversion to the corresponding 2-chloro-derivatives with retention of configuration is observed.[30] Nucleophilic displacement of dinitrogen from diazotized α-amino acids by chloride[31] is known to proceed with retention of configuration[30,32,33] through anchimeric assistance by carboxylic group, via a (protonated) α-lactone,[34] and, in the case of threonines, with participation also of the hydroxy group as a neighbouring group, giving rise to the intermediate formation of a (protonated) epoxide.[35–37]

The expected products were also obtained by transforming 2-chloro-3-hydroxybutanoic acids **4** into the corresponding ethyl 2-chloro-3-hydroxybutanoates **5**.

However, noteworthy and partially unexpected results were instead obtained in the subsequent conversion of chloro- to 4-chlorophenoxy-derivatives. Reaction of chloro-derivatives **5** with 4-chlorophenoxide ion, in fact, is not a direct nucleophilic substitution of chloride.

Formation in all cases (Scheme 2 and 3 and Table 1), together with the expected 2-(4-chlorophenoxy)-derivative **2a**, also of the structural isomer **6** (in a constant ratio 1:4) indicates, in fact, a preliminary intramolecular reaction of the starting chlorohydrin **5** affording an epoxide intermediate **7**. Subsequent reaction of the epoxide generates **2a** and **6**, as observed.

In addition, the absolute configurations at C_2 and C_3 of **2a** and **6** formed from each chloro-derivative, definitively established in the case of (2*S*,3*S*)-**2a** and (2*R*,3*R*)-**2a** by X-ray analysis of the corresponding acids **3** (Figs. 3 and 4)[38–42] indicate a *trans* geometry of the epoxides [(2*R*,3*S*)-**7** or (2*S*,3*R*)-**7**]. In particular, (2*R*,3*S*)-epoxide **7** should be formed from both

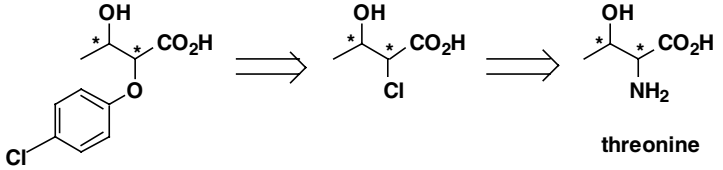
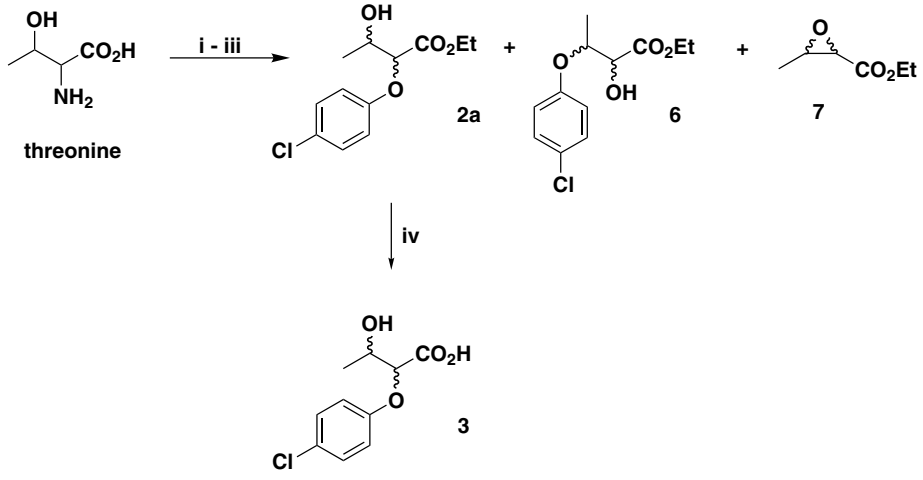
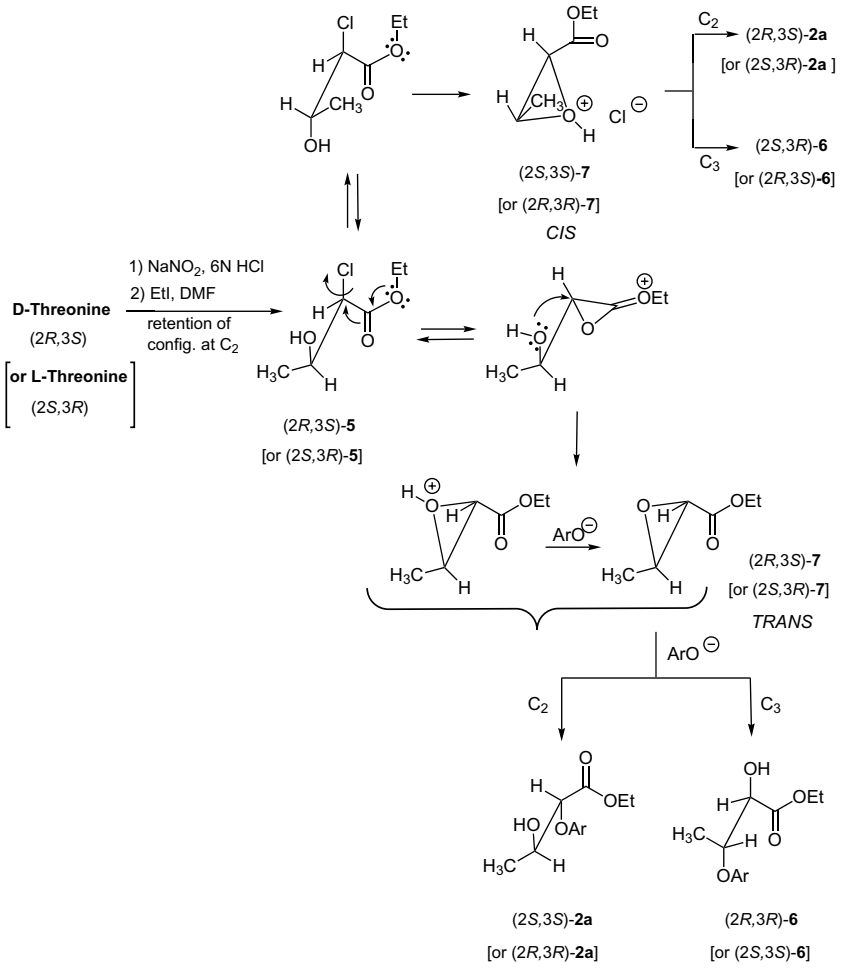


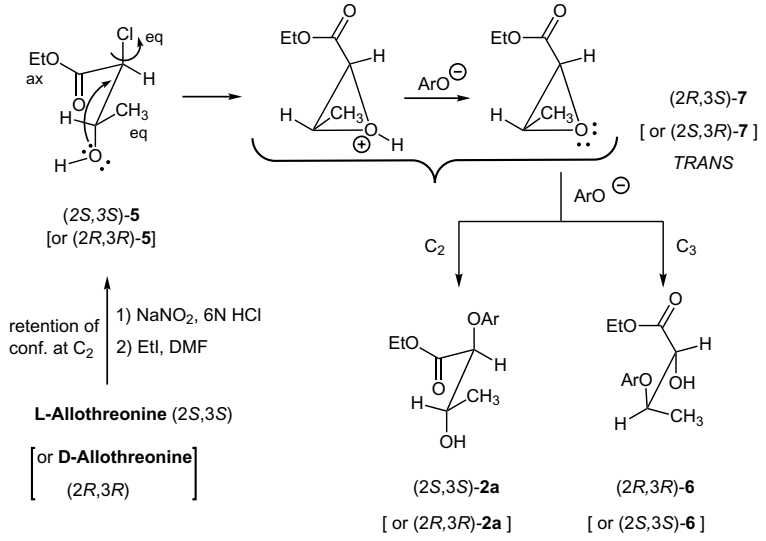
Figure 2. Retrosynthesis of 2-(4-chlorophenoxy)-3-hydroxybutanoic acid **3** starting from threonines.



Scheme 1. Reagents and conditions: (i) $NaNO_2$, HCl, −15 °C; (ii) EtI, $NaHCO_3$, anhydrous DMF, rt; (iii) caesium 4-chlorophenate, 50 °C; (iv) KOH, THF/H_2O, rt.



Scheme 2. Transformation of D-threonine [or L-threonine] into the chlorohydrin, and its reaction with caesium 4-chlorophenate.



Scheme 3. Transformation of L-allothreonine [or D-allothreonine] into the chlorohydrin, and its reaction with caesium 4-chlorophenate.

(2*R*,3*S*)- and (2*S*,3*S*)-chlorohydrin **5**, while (2*S*,3*R*)-epoxide **7** should originate from both (2*S*,3*R*)- and (2*S*,3*S*)-stereoisomers **5**.

It should be noticed that, only in the case of the chlorohydrins deriving from (2*R*,3*S*)-D- and (2*S*,3*R*)-L-threonine, small amounts (up to 12%) of *cis* (2*S*,3*S*)-**7** and

Table 1. Summary of the results of the reactions of chlorohydrins and caesium 4-chlorophenate (Schemes 2 and 3)

Threonine	Chlorohydrin [**4** (acid), **5** (ethyl ester)]	**2a**	**6**	**7**
(2*R*,3*S*)-D-Threonine	(2*R*,3*S*)	(2*S*,3*S*)/(2*R*,3*S*), dr = 89:11[a] (2*R*,3*R*)/(2*S*,3*R*), de = 78%[a] $Ee_{(2S,3S)/(2R,3R)}$ = 99%[b] $Ee_{(2R,3S)/(2S,3R)}$ = 97%[b] 34%[c]	(2*R*,3*R*)/(2*S*,3*R*), dr = 58:42[a] (2*S*,3*S*)/(2*R*,3*S*), de = 16%[a] $Ee_{(2R,3R)/(2S,3S)}$ = 99%[b] $Ee_{(2S,3R)/(2R,3S)}$ = 97%[b] 23%[c]	(2*S*,3*S*)[d]/(2*R*,3*S*),[d] dr = 50:50 (2*R*,3*R*)/(2*S*,3*R*) ND ND 30%[c]
(2*S*,3*S*)-L-Allothreonine	(2*S*,3*S*)	(2*S*,3*S*)/(2*R*,3*S*), dr >99:1[a] (2*R*,3*R*)/(2*S*,3*R*), de >99%[a] $Ee_{(2S,3S)/(2R,3R)}$ >99%[b] 25%[e]	(2*R*,3*R*)/(2*S*,3*R*), dr >99:1[a] (2*S*,3*S*)/(2*R*,3*S*), de >99%[a] $Ee_{(2R,3R)/(2S,3S)}$ >99%[b] 24%[e]	(2*R*,3*S*)/(2*S*,3*S*), dr >99:1 (2*S*,3*R*)/(2*R*,3*R*), de >99% $Ee_{(2R,3S)/(2S,3R)}$ >99%[b] 41%[e]
(2*S*,3*R*)-L-Threonine	(2*S*,3*R*)	(2*R*,3*R*)/(2*S*,3*R*), dr = 88:12[a] (2*S*,3*S*)/(2*R*,3*S*), de = 77%[a] $Ee_{(2R,3R)/(2S,3S)}$ >99%[b] $Ee_{(2S,3R)/(2R,3S)}$ >99%[b] 44%[f]	(2*S*,3*S*)/(2*R*,3*S*), dr = 57:43[a] (2*R*,3*R*)/(2*S*,3*R*), de = 14%[a] $Ee_{(2S,3S)/(2R,3R)}$ = 97%[b] $Ee_{(2R,3S)/(2S,3R)}$ >99%[b] 35%[f]	(2*S*,3*R*)[d]/(2*R*,3*R*),[d] dr = 54:46 (2*R*,3*S*)/(2*S*,3*S*), de = 8% ND ND 13%[f]
(2*R*,3*R*)-D-Allothreonine	(2*R*,3*R*)	(2*R*,3*R*)/(2*R*,3*S*), dr >99:1[a] (2*S*,3*S*)/(2*S*,3*R*), de >99%[a] $Ee_{(2R,3R)/(2S,3S)}$ >99%[b] 32%[g]	(2*S*,3*S*)/(2*S*,3*R*), dr >99:1[a] (2*R*,3*R*)/(2*R*,3*S*), de >99%[a] $Ee_{(2S,3S)/(2R,3R)}$ >99%[b] 26%[g]	(2*S*,3*R*)/(2*S*,3*S*), dr >99:1[a] (2*R*,3*S*)/(2*R*,3*R*), de >99%[a] $Ee_{(2S,3R)/(2R,3S)}$ >99%[b] 41%[g]

[a] Diastereomeric ratio and excess (dr, de) were determined by ^{1}H NMR.
[b] Enantiomeric excesses (ee) were determined by HPLC.
[c] Percentage of product in the reaction crude determined by GC–mass quantitative analysis. Remaining unreacted chlorohydrin was 21%.
[d] Predominant enantiomer.
[e] Percentage of product in the reaction crude determined by GC–mass quantitative analysis. Remaining unreacted chlorohydrin was 2%.
[f] Percentage of product in the reaction crude determined by GC–mass quantitative analysis. Remaining unreacted chlorohydrin was 8%.
[g] Percentage of product in the reaction crude determined by GC–mass quantitative analysis. Remaining unreacted chlorohydrin was 1%.

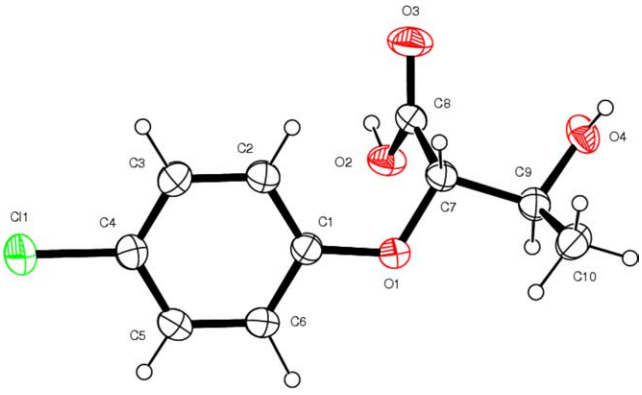


Figure 3. ORTEP view of the asymmetric unit with the atomic numbering scheme of (2*S*,3*S*)-2-(4-chlorophenoxy)-3-hydroxybutanoic acid **3**. Thermal ellipsoids probability level at 30%.

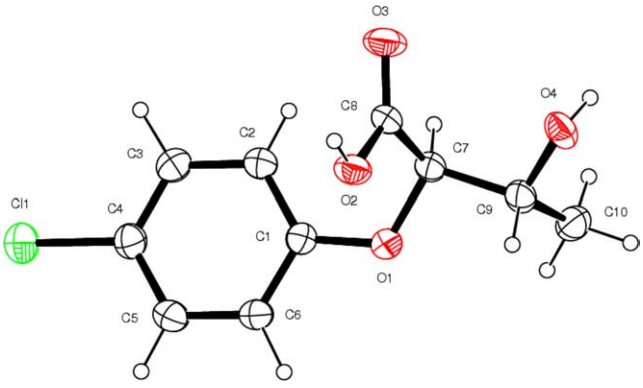
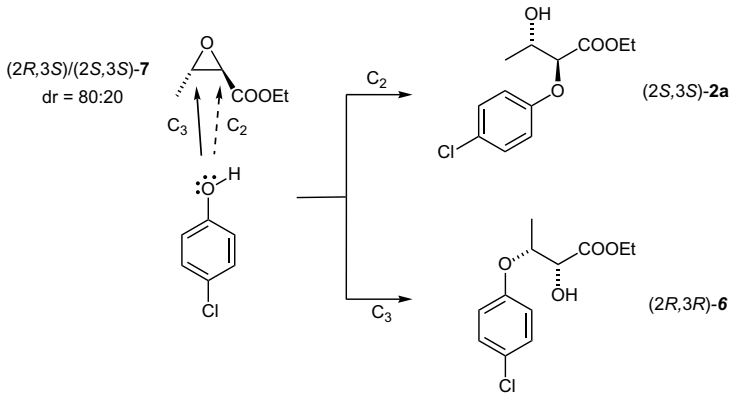


Figure 4. ORTEP view of the asymmetric unit with the atomic numbering scheme of (2*R*,3*R*)-2-(4-chlorophenoxy)-3-hydroxybutanoic acid **3**. Thermal ellipsoids probability level at 30%.

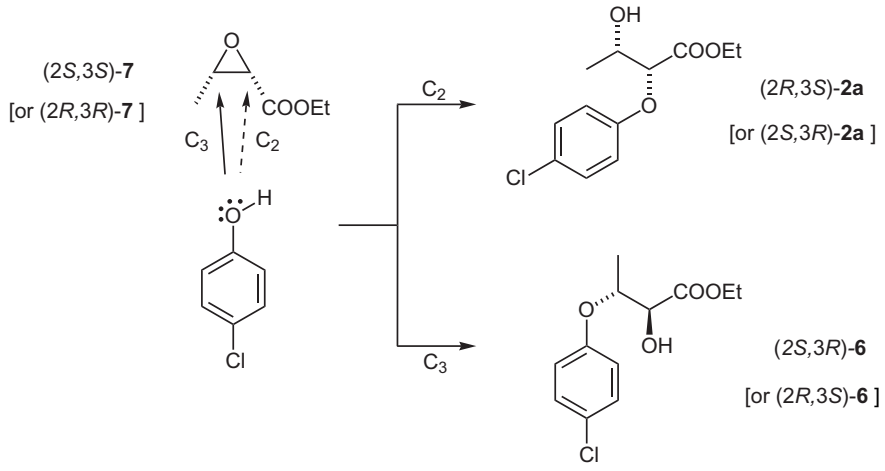
cis (2*R*,3*R*)-**7**, respectively, were formed. In the presence of 4-chlorophenoxide ion, these were converted into (2*R*,3*S*)-**2a** and (2*S*,3*R*)-**6** in the case of (2*S*,3*S*)-**7**, or (2*S*,3*R*)-**2a** and (2*R*,3*S*)-**6** in the case of (2*R*,3*R*)-**7** (Scheme 2 and Table 1).

The above conclusions are confirmed by separately reacting (2*R*,3*S*)-**7**, prepared according to Akita's procedure,[36] and the commercially available (2*S*,3*S*)-**7** and (2*R*,3*R*)-**7**, and isolating both **2a** and **6** with the expected absolute configurations and same ratio (Schemes 4 and 5).

On the other hand, formation of the same epoxide from two different chloro-derivatives [(2*R*,3*S*)-**5** and (2*S*,3*S*)-**5**, or (2*S*,3*R*)-**5** and (2*R*,3*R*)-**5**] deserves some comment. Formation of the epoxide by intramolecular reaction of adjacent hydroxy group should in fact take place with inversion of configuration at C_2, as the reaction presumably follows an S_N2 mechanism. Thus, while the *trans*-epoxide is the expected result in the case of (2*S*,3*S*)- and (2*R*,3*R*)-chloro-derivative, the same result seems to be anomalous for both (2*R*,3*S*)-**5** and (2*S*,3*R*)-**5**, for which a retention of configuration at C_2 carbon should instead take place (Schemes 2 and 3). A possible explanation could once again be found



Scheme 4. Reaction of *trans*-epoxide **7** with 4-chlorophenol.



Scheme 5. Reaction of *cis*-epoxide (2*S*,3*S*)-**7** [or (2*R*,3*R*)-**7**] with 4-chlorophenol.

in the anchimeric assistance by the adjacent carbethoxy group, similar to that above mentioned as responsible for C_2 retention of configuration in conversion of aminoacids into 2-chloro-derivatives **4**,[32] and hence **5**, only in the case of (2*R*,3*S*)-**5** and (2*S*,3*R*)-**5**, and could possibly be caused by the formation of the more stable *trans*-epoxides.

It must be pointed out, however, that the anchimerically assisted reaction although prevailing, is not the only one observed in the latter cases. Some unassisted epoxide formation (*cis*-epoxide) may in fact also compete, as revealed by formation in minor amounts of different stereoisomers **2a** and **6**.

Finally, acids **3**, obtained in quantitative yields by reacting **2a** with KOH (Scheme 1), were biologically evaluated by using a transactivated assay in eukaryotic cells, transiently expressing the fusion protein between the yeast GAL4 transactivation factor DNA-binding domain (DBD) and murine PPARα-ligand-binding domain (LBD), to establish their ability to activate PPARα. They were compared to WY-14,643 and clofibrate,[27] however they proved inactive. This could be ascribed either to the presence of the hydroxy group which probably does not allow suitable interactions between the compounds and the receptor LBD, or to the higher size of the moiety linked to the C_2 of **3** than the two hydrogens of WY-14,643 and the two methyls of clofibrate.

3. Conclusion

The results reported above support the proposed mechanism, that the reaction between chlorohydrins and caesium 4-chlorophenate occurs through the epoxide-intermediate **7**. In particular, (2*S*,3*S*)-**2a** is formed starting from both D-threonine and L-allothreonine via the common intermediate ethyl (2*R*,3*S*)-3-methyloxirane-2-carboxylate **7**. On the other hand, (2*R*,3*R*)-**2a** is obtained from both L-threonine and D-allothreonine, via ethyl (2*S*,3*R*)-3-methyloxirane-2-carboxylate as the common epoxide intermediate. Unfortunately, acids **3**, obtained in quantitative yields on treating **2a** with KOH, proved inactive towards mouse PPARα. However, it is worth noting that the reported data do not exclude the possibility that they could be endowed with antagonist activity.

4. Experimental

4.1. General methods

Melting points were taken on an electrothermal apparatus and are uncorrected. Reaction progress was monitored by GC analysis. Column chromatography was conducted using silica gel Merck 60 (0.040–0.063 mm).

GC analyses were performed by using a HP-5MS column (5% phenyl methyl siloxane; 30 m × 0.321 mm × 0.25 μm) on an Agilent 6850 Series GC System. GC–MS analyses were performed on a Hewlett–Packard 6890-5793MSD. LC–MS spectra were recorded by direct infusion of their solution (c = 0.01 mg/mL) in methanol/5 mM aq ammonium formate = 9:1 in a LC–MSD trap; MS–MS spectra are also reported.

^{1}H NMR spectra were recorded in $CDCl_3$ or CD_3OD on a Varian Mercury 300 MHz or Bruker Aspect 500 MHz spectrometer and chemical shifts are reported in parts per million (δ). Absolute values of the coupling constants (J) in hertz are reported. IR spectra were recorded on a Perkin–Elmer 681 spectrometer.

Ee values of the reaction products **2a** and **6** were determined by HPLC analysis performed on a Perkin–Elmer 200 series with a UV/vis detector 785A by the commercially available Chiralcel OD (Daicel) in isocratic conditions employing n-hexane–2-propanol = 98:2, flow rate = 1 mL/min and λ = 230 nm. Racemic **2a** and **6** were used as reference compounds for the HPLC analysis. Their chromatograms are shown in Figures 5 and 6.

Absolute configurations of (2*S*,3*S*)-**3** and (2*R*,3*R*)-**3** were established by single crystal X-ray analyses. As far as (2*R*,3*S*)-**3** absolute configuration by X-ray analysis is concerned, crystallographic data have been already reported.[29] Absolute configuration of (2*S*,3*R*)-**3** was assigned by HPLC under the conditions used to determine the ee values. Optical rotations were measured on a Perkin–Elmer polarimeter.

4.2. Materials

D-Allo- and L-allo-threonine were from Bachem Chemicals, CH. Ethyl (2*S*,3*S*)-3-methyloxirane-2-carboxylate and ethyl (2*R*,3*R*)-3-methyloxirane-2-carboxylate were from Acros Organics BE. D- and L-Threonine and all other chemicals and solvents were from Aldrich Chemical Co. Hydrochloric acid was obtained by distillation (bp = 108–109 °C) of a 50 vol % aqueous solution of 37% hydrochloric acid. Anhydrous *N*,*N*-dimethylformamide was distilled from calcium hydride, under nitrogen atmosphere, immediately prior to use. EtI was distilled immediately prior to use.

4.2.1. Preparation of 2-chloro-3-hydroxybutanoic acid 4: general procedure. To a solution of threonine (209.9 mmol) in hydrochloric acid (262 mL) cooled at −15 °C, $NaNO_2$ (335.8 mmol) was carefully added in small aliquots. The reaction was stirred for 5 h at −15 °C. Then, the reaction mixture was extracted three times with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. A yellow oil was obtained.

4.2.1.1. (2*S*,3*R*)-4.[30,37] Yield 57%; $[\alpha]_D^{20} = -8.3$ (c 1.0, $CHCl_3$). IR (neat): 3600–2500, 2985, 1733, 1635, 1381, 1288, 1194, 1126, 1090, 1037, 948, 863, 815, 703 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40–5.80 (br s, 2H, O*H* and COO*H*: exchange with D_2O); 4.42–4.35 (qd partially overlapped to a d, J = 6.32 and 3.71 Hz, 2H, C*H*OH and C*H*Cl); 1.37–1.35 (d, J = 6.32 Hz, 3H, CH_3). ^{13}C NMR (76 MHz, $CDCl_3$): δ 172.22 (1C, *C*OOH); 68.63 (1C, *C*HOH); 63.16 (1C,

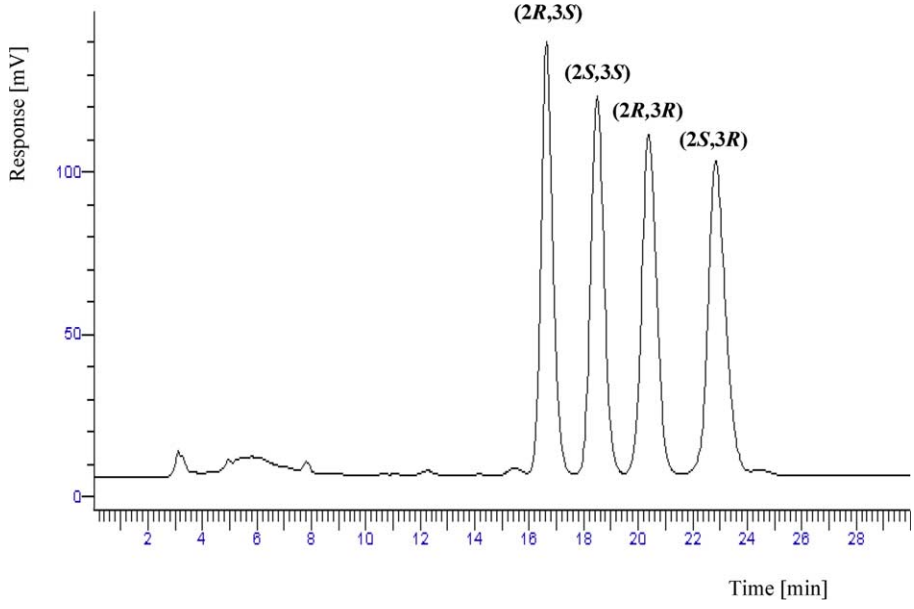


Figure 5. HPLC chromatogram of racemic ethyl 2-(4-chlorophenoxy)-3-hydroxybutanoate **2a**.

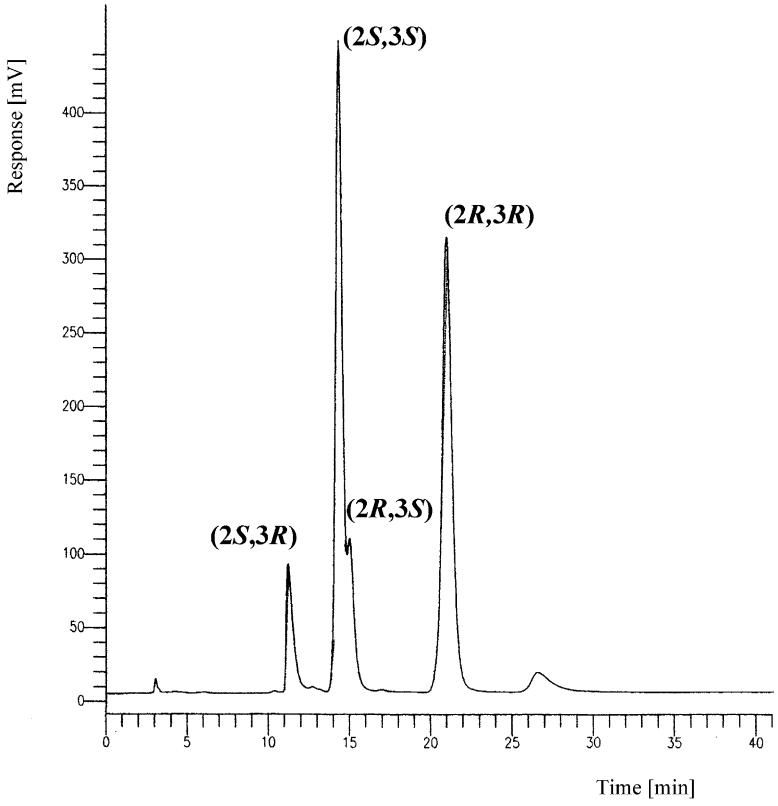


Figure 6. HPLC chromatogram of racemic ethyl 3-(4-chlorophenoxy)-2-hydroxybutanoate **6**.

*C*HCl); 19.87 (1C, *C*H_3). LC–MS (*m*/*z*) (rel. int.): 139 [M(^{37}Cl)$^-$, 16], 137 [M(^{35}Cl)$^-$, 41]. MS–MS (137) (*m*/*z*) (rel. int.): 101 (100), 83 (9), 57 (47).

4.2.1.2. (2*R*,3*S*)-4.[30,37] Yield 47%; $[\alpha]_D^{20} = +8.5$ (*c* 1.0, $CHCl_3$). Analytical and spectroscopic data were identical to those ones of its enantiomer (2*S*,3*R*)-**4**.

4.2.1.3. (2*S*,3*S*)-4.[30,37] Yield 87%; $[\alpha]_D^{20} = +4.3$ (*c* 1.0, $CHCl_3$). IR (neat): 3600–2400, 2986, 1732, 1669, 1381, 1299, 1195, 1122, 1091, 1045, 953, 880, 822, 696 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03–7.70 (br s, 2H, O*H* and COO*H*: exchange with D_2O); 4.31–4.20 (m, 2H, C*H*OH and C*H*Cl); 1.37–1.35 (d, $J = 5.82$ Hz, 3H, CH_3). ^{13}C NMR (76 MHz, $CDCl_3$): δ 173.40 (1C, *C*OOH); 69.64 (1C, *C*HOH); 61.49 (1C, *C*HCl); 19.08 (1C, *C*H_3).

4.2.1.4. (2*R*,3*R*)-4.[30,37] Yield 62%; $[\alpha]_D^{20} = -4.0$ (*c* 1.0, $CHCl_3$). Analytical and spectroscopic data were identical to those ones of its enantiomer (2*S*,3*S*)-**4**.

4.2.2. Preparation of ethyl 2-chloro-3-hydroxybutanoate 5: general procedure.[37] To a solution of **4** (116.4 mmol) in anhydrous *N*,*N*-dimethylformamide (104 mL), $NaHCO_3$ (232.8 mmol) was added under a nitrogen stream. The reaction was stirred at room temperature for 10 min. A solution of iodoethane (232.8 mmol) in anhydrous *N*,*N*-dimethylformamide (104 mL) was dropwise added. The reaction was stirred for 22 h at room temperature. Then, water was added and the reaction mixture extracted three times with ethyl acetate. The combined extracts were washed with a solution of $Na_2S_2O_3$, a saturated solution of $NaHCO_3$ and with brine. The organic layer was dried over anhydrous Na_2SO_4 and the solvent evaporated under reduced pressure. A yellow oil was obtained.

4.2.2.1. (2*S*,3*R*)-5.[36] Yield 57%; $[\alpha]_D^{20} = -14.2$ (*c* 1.0, $CHCl_3$). IR (neat): 3600–3200, 2984, 2939, 2904, 1744, 1448, 1373, 1301, 1183, 1127, 1095, 1024, 944, 878, 850 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.28–4.15 (m, 4H, C*H*OH, C*H*Cl and CH_2O); 2.80–2.65 (br s, 1H, O*H*: exchanges with D_2O); 1.31–1.26 (m, formed from a triplet and a doublet, $J = 7.14$ and 6.18 Hz, 6H, CH_3CH$_2$O and CH_3CHOH). ^{13}C NMR (76 MHz, $CDCl_3$): δ 168.78 (1C, *C*O); 68.63 (1C, *C*HOH); 63.39 (1C, *C*HCl); 62.64 (1C, *C*H$_2$CH$_3$); 19.88 (1C, *C*H$_3$CHOH); 14.35 (1C, *C*H$_3$CH$_2$). GC–MS (70 eV) (*m*/*z*) (rel. int.): 151 ($M^+ - 15$, 2), 124 (25), 123 (12), 122 (70), 96 (38), 94 (100), 85 (17), 78 (12), 76 (31), 45 (29), 43 (12).

4.2.2.2. (2*R*,3*S*)-5.[36] Yield 65%; $[\alpha]_D^{20} = +14.0$ (*c* 1.0, $CHCl_3$). Analytical and spectroscopic data were identical to those of its enantiomer (2*S*,3*R*)-**5**.

4.2.2.3. (2*S*,3*S*)-5.[36] Yield 64%; $[\alpha]_D^{20} = +4.8$ (*c* 1.1, $CHCl_3$). IR (neat): 3600–3200, 2984, 2939, 2909, 2878, 1741, 1448, 1395, 1373, 1304, 1277, 1216, 1182, 1095, 1024, 953, 882 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.27–4.18 (m, 4H *C*H$_2$O, *C*HOH and *C*HCl); 3.18–2.99 (br s, 1H, O*H*: exchanges with D_2O); 1.32–1.25 (m, 6H, CH_3CHOH and CH_3CH$_2$). ^{13}C NMR

(76 MHz, $CDCl_3$): δ 168.92 (1C, *C*O); 69.10 (1C, *C*HOH); 62.47 (1C, *C*HCl); 61.26 (1C, *C*H_2CH$_3$); 19.35 (1C, *C*H_3CHOH); 14.18 (1C, *C*H_3CH$_2$). GC–MS (70 eV) (*m*/*z*) (rel. int.): 151 (M^+-15, 2), 124 (19), 122 (56), 96 (33), 94 (100), 85 (17), 78 (10), 76 (28), 45 (32), 43 (12).

4.2.2.4. (2*R*,3*R*)-5.[36] Yield 75%; $[\alpha]_D^{20} = -4.9$ (*c* 1.2, $CHCl_3$). Analytical and spectroscopic data were identical to those ones of its enantiomer (2*S*,3*S*)-**5**.

4.2.3. Preparation of ethyl 2-(4-chlorophenoxy)-3-hydroxybutanoate 2a: general procedure. A mixture of **5** (51.9 mmol) and caesium 4-chlorophenate (57.1 mmol) was stirred at 50 °C for 5 days, monitoring the reaction progress by GC analysis. Water was added and the reaction mixture extracted three times with ethyl acetate. The combined extracts were dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. A red oil was obtained. Products were separated by flash chromatography (silica gel; mobile phase: petroleum ether/ethyl acetate = 8:2).

4.2.3.1. (2*R*,3*R*)-2a. Yield 5%; $[\alpha]_D^{20} = +29.0$ (*c* 1.1, $CHCl_3$). Dr = 88:12, de = 77%, ee >99%. IR (neat): 3700–3100, 3050, 2984, 2939, 1737, 1659, 1596, 1584, 1492, 1447, 1375, 1281, 1238, 1201, 1095, 1063, 1023, 826 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23–7.17 (m, 2H, aromatic protons); 6.84–6.79 (m, 2H, aromatic protons); 4.55–4.53 (d, J = 4.39 Hz, 1H, *CH*OC_6H_4Cl); 4.32–4.17 (qd, J = 6.59 and 4.39 Hz, 1H, C*H*OH, partially overlapped to a quartet of doublets, J = 7.14 and 1.38 Hz, 2H, CH_2CH$_3$); 3.80–3.00 (br s, 1H, O*H*: exchanges with D_2O); 1.34–1.32 (d, J = 6.59 Hz, 3H, CH_3CHOH); 1.24–1.20 (t, J = 7.14 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (76 MHz, $CDCl_3$): δ 169.59 (1C, *C*O); 156.48 (1C, aromatic carbon); 129.68 (2C, aromatic carbons); 127.13 (1C, aromatic carbon); 116.91 (2C, aromatic carbons); 81.12 (1C, *C*HOC_6H_4Cl) 68.57 (1C, *C*HOH); 61.86 (1C, *C*H_2CH$_3$); 18.58 (1C, *C*H_3CHOH); 14.33 (1C, *C*H_3CH$_2$). GC–MS (70 eV) (*m*/*z*) (rel. int.): 260 [M(^{37}Cl)$^+$, 7], 258 [M(^{35}Cl)$^+$, 19], 216 (10), 214 (20), 168 (10), 167 (11), 143 (32), 142 (10), 141 (100), 139 (16), 130 (18), 129 (10), 128 (52), 111 (11), 99 (10), 75 (11), 45 (10), 43 (11).

4.2.3.2. (2*S*,3*R*)-2a. $[\alpha]_D^{20} = -36.0$ (*c* 1.4, $CHCl_3$). Ee >99%. IR (neat): 3600–3200, 3056, 2985, 2932, 2855, 1748, 1596, 1491, 1376, 1266, 1236, 1199, 1137, 1095, 1076, 1025, 1009, 826, 738 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.25–7.20 (m, 2H, aromatic protons); 6.86–6.83 (m, 2H, aromatic protons); 4.43–4.42 (d, J = 4.94 Hz, 1H, C*H*OC_6H_4Cl); 4.32–4.17 (qd, J = 7.15 and 1.64 Hz, 2H of CH_2CH$_3$ completely overlapped to the signal of C*H*OH); 2.60–2.20 (br s, 1H, O*H*: exchanges with D_2O); 1.35–1.34 (d, J = 6.45 Hz, 3H, CH_3CHOH); 1.27–1.24 (t, J = 7.15 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (76 MHz, $CDCl_3$): δ 169.74 (1C, *C*O); 156.44 (1C, aromatic carbon); 129.68 (2C, aromatic carbons); 127.13 (1C, aromatic carbon); 116.91 (2C, aromatic carbons); 81.12 (1C, *C*HOC_6H_4Cl) 68.57 (1C, *C*HOH); 61.86 (1C, *C*H_2CH$_3$); 18.58 (1C, *C*H_3CHOH); 14.33 (1C, *C*H_3CH$_2$). GC–MS (70 eV) (*m*/*z*) (rel. int.): 260 [M(^{37}Cl)$^+$, 6], 258 [M(^{35}Cl)$^+$, 19], 214 (19), 168 (9), 167 (8), 143 (32), 142 (8), 141 (100), 139 (15), 130 (16), 129 (10), 128 (49), 111 (10), 99 (7), 75 (10), 45 (7), 43 (9).

4.2.3.3. (2*S*,3*S*)-2a. Yield 5%; $[\alpha]_D^{20} = -29.0$ (*c* 1.1 $CHCl_3$). Dr = 89:11, de = 78%, ee = 99%. Analytical and spectroscopic data were identical to those of its enantiomer (2*R*,3*R*)-**2a**.

4.2.3.4. (2*R*,3*S*)-2a. $[\alpha]_D^{20} = +36.5$ (*c* 1.4, $CHCl_3$). Ee = 97%. Analytical and spectroscopic data were identical to those of its enantiomer (2*S*,3*R*)-**2a**.

4.2.4. Preparation of ethyl 3-(4-chlorophenoxy)-2-hydroxybutanoate 6: general procedure. A mixture of **7** (3.86 mmol), 4-chlorophenol (3.86 mmol) and caesium 4-chlorophenate (0.39 mmol) was stirred at 50 °C for 5 days. Reaction progress was monitored by GC analysis. Then, water was added and the reaction mixture extracted three times with ethyl acetate. The extracts were combined and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and a colourless oil was obtained. Products were isolated by flash chromatography (silica gel; mobile phase: petroleum ether/ethyl acetate = 8:2).

4.2.4.1. (2*S*,3*R*)-6. $[\alpha]_D^{20} = +20.9$ (*c* 1.0, $CHCl_3$). White solid, mp 47–50 °C. De >99%, ee >99%. IR (KBr): 3750–3250, 3030, 2985, 2936, 1740, 1594, 1580, 1491, 1409, 1393, 1378, 1281, 1241, 1157, 1120, 1092, 1062, 1008, 968, 882, 867, 823, 648 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.23–7.18 (m, 2H, aromatic protons); 6.84–6.79 (m, 2H, aromatic protons); 4.73–4.66 (qd, J = 6.33 and 2.20 Hz, 1H, C*H*CH$_3$); 4.19–4.12 (m, 3H, C*H*OH and CH_2CH$_3$); 3.20–3.00 (br s, 1H, O*H*: exchanges with D_2O); 1.42–1.40 (d, J = 6.33 Hz, 3H, CH_3CH); 1.17–1.12 (t, J = 7.15 Hz, 3H, CH_3CH$_2$). ^{13}C NMR (76 MHz, $CDCl_3$): δ 172.59 (1C, *C*O); 156.23 (1C, aromatic carbon); 129.65 (2C, aromatic carbons); 126.58 (1C, aromatic carbon); 117.73 (2C, aromatic carbons); 75.76 (1C, *C*HCH$_3$); 73.88 (1C, *C*HOH); 62.19 (1C, *C*H_2CH$_3$); 15.73 (1C, *C*H_3CH); 14.37 (1C *C*H_3CH$_2$). GC–MS (70 eV) (*m*/*z*) (rel. int.): 260 [M(^{37}Cl)$^+$, 10], 258 [M(^{35}Cl)$^+$, 29], 214 (5), 167 (5), 157 (25), 155 (69), 141 (19), 130 (38), 129 (12), 128 (100), 111 (10), 75 (8), 57 (12).

4.2.4.2. (2*R*,3*S*)-6. $[\alpha]_D^{20} = -15.9$ (*c* 0.74, $CHCl_3$). White solid, mp 57–58 °C. De >99%, ee >99%. Analytical and spectroscopic data were identical to those of its enantiomer (2*S*,3*R*)-**6**.

4.2.4.3. (2*R*,3*R*)-6. Oil; $[\alpha]_D^{20} = -19.9$ (*c* 1.0, $CHCl_3$). De = 73%, $ee_{(2R,3R)}$ = 82%, $ee_{(2S,3R)}$ = 93%. IR (neat): 3700–3200, 3099, 3073, 2983, 2937, 2874, 1736, 1595, 1582, 1490, 1447, 1381, 1282, 1239, 1150, 1093, 1076, 1022, 940, 826 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ 7.22–7.20 (m, 2H, aromatic protons); 6.87–6.85 (m, 2H, aromatic protons); 4.64–4.59 (qd, J = 6.42 and 3.01 Hz, 1H, C*H*CH$_3$); 4.40–4.39 (d, J = 3.01 Hz, 1H, C*H*OH); 4.33–4.24 (m, 2H, CH_2CH$_3$); 3.30–3.15 (br s, 1H, O*H*: exchanges with D_2O); 1.32–1.31 (d, J = 6.41 Hz, 3H,

CH_3CH); 1.32–1.29 (t, J = 7.14 Hz, 3H, CH_3CH_2). ^{13}C NMR (76 MHz, $CDCl_3$): δ 172.35 (1C, *C*O); 156.22 (1C, aromatic carbon); 129.70 (2C, aromatic carbons); 126.62 (1C, aromatic carbon); 117.82 (2C, aromatic carbons); 76.25 (1C, $CHCH_3$); 72.96 (1C, *C*HOH); 62.41 (1C, CH_2CH_3); 14.74 (1C, CH_3CH); 14.45 (1C, CH_3CH_2). GC–MS (70 eV) (*m*/*z*) (rel. int.): 260 [M(^{37}Cl)$^+$, 10], 258 [M(^{35}Cl)$^+$, 28], 167 (4), 157 (26), 155 (70), 130 (40), 129 (12), 128 (100), 111 (10), 75 (7), 57 (12).

4.2.5. Preparation of 2-(4-chlorophenoxy)-3-hydroxybutanoic acid 3: general procedure. To **1** (1.357 mmol) in THF (18 mL) a solution of KOH (152 mg, 2.713 mmol, in 6 mL water) was added. The resulting mixture was stirred at room temperature for 1 h. Reaction progress was monitored by GC analysis. Then, THF was removed under reduced pressure and the alkaline reaction mixture was washed three times with ethyl ether, acidified with 2 N HCl and extracted three times with ethyl ether. The second extracts were combined and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure and a colourless oil was obtained. The crude product was purified by crystallization (chloroform/hexane).

4.2.5.1. (2*S*,3*S*)-3. Yield 59%; $[\alpha]_D^{20} = -41.5$ (*c* 0.56, CH_3OH). Mp 128.2–129.4 °C ($CHCl_3$/hexane). De >99%. IR (KBr): 3700–3200, 3035, 2985, 2937, 2818, 1717, 1594, 1586, 1494, 1460, 1374, 1346, 1274, 1233, 1176, 1146, 1106, 1082, 1058, 1010, 970, 827 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 7.26–7.23 (m, 2H, aromatic protons); 6.93–6.90 (m, 2H, aromatic protons); 5.10–4.91 (br s, 2H, COO*H* and O*H*: exchange with D_2O); 4.61–4.59 (d, J = 4.25 Hz, 1H, $CHOC_6H_4Cl$); 4.25–4.18 (qd, J = 6.45 and 4.25 Hz, 1H, C*H*OH); 1.34–1.31 (d, J = 6.45 Hz, 3H, CH_3CHOH). ^{13}C NMR (76 MHz, CD_3OD): δ 171.75 (1C, *C*O); 157.15 (1C, aromatic carbon); 129.15 (2C, aromatic carbons); 126.26 (1C, aromatic carbon); 116.71 (2C, aromatic carbons); 81.21 (1C, $CHOC_6H_4Cl$) 67.90 (1C, *C*HOH); 17.27 (1C, CH_3CHOH). Anal. Calcd for $C_{10}H_{11}ClO_4$: C, 52.07; H, 4.81. Found: C, 52.05; H, 4.84.

4.2.5.2. (2*R*,3*R*)-3. Yield 60%; $[\alpha]_D^{20} = +41.8$ (*c* 0.46, CH_3OH). Mp 127.3–128.5 °C ($CHCl_3$/hexane). De >99%. Analytical and spectroscopic data were identical to those of its enantiomer (2*S*,3*S*)-**3**.

4.2.5.3. (2*S*,3*R*)-3. Quantitative yield. Oil. $[\alpha]_D^{20} = -12.4$ (*c* 1.0, $CHCl_3$). D.e. >99% IR (neat): 3700–3200, 3014, 2926, 2855, 1732, 1596, 1585, 1490, 1456, 1407, 1380, 1281, 1236, 1173, 1139, 1089, 1075, 1009, 879, 824 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.24–7.21 (m, 2H, aromatic protons); 6.83–6.80 (m, 2H, aromatic protons); 5.70–5.00 (br s, 2H, COO*H* and O*H*: exchange with D_2O); 4.48–4.47 (d, J = 3.58 Hz, 1H, $CHOC_6H_4Cl$); 4.37–4.29 (qd, J = 6.33 and 3.58 Hz, 1H, C*H*OH); 1.38–1.36 (d, J = 6.33 Hz, 3H, CH_3CHOH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.38 (1C, *C*O); 156.04 (1C, aromatic carbon); 129.61 (2C, aromatic carbons); 127.33 (1C, aromatic carbon); 116.57 (2C, aromatic carbons); 80.33 (1C, $CHOC_6H_4Cl$) 68.54 (1C, *C*HOH); 19.09 (1C, CH_3CHOH). Anal. Calcd for $C_{10}H_{11}ClO_4$: C, 52.07; H, 4.81. Found: C, 52.09; H, 4.85.

4.2.5.4. (2*R*,3*S*)-3. Quantitative yield. $[\alpha]_D^{20} = +12.4$ (*c* 1.0, $CHCl_3$). Mp 105–106 °C ($CHCl_3$/hexane). Analytical and spectroscopic data were identical to those ones of its enantiomer (2*S*,3*R*)-**3**.

4.3. X-ray crystallography

To establish the absolute configuration at C(7) and C(9) (Figs. 3 and 4) in an unambiguous manner, suitable crystals were grown and subjected to a single crystal X-ray analysis, using a Nonius Kappa CCD area detector diffractometer equipped with a fine focus sealed graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Data for (2*S*,3*S*)-2-(4-chlorophenoxy)-3-hydroxybutanoic acid **3** and (2*R*,3*R*)-2-(4-chlorophenoxy)-3-hydroxybutanoic acid **3** were collected at 293(2) K. Data collection was carried out with the program COLLECT.[38] Cell refinement and data reduction were carried out with the program DENZO.[39] The structures were solved by the direct methods procedure of SIR97,[40] while the refinement processes were carried on full matrix least squares technique using SHELXL-97.[41] Detailed crystal data and geometrical parameters were deposited in the Supporting Information (cif files).[42] The asymmetric units of (2*S*,3*S*)-**3** and (2*R*,3*R*)-**3** with the atomic numbering schemes are depicted in Figures 3 and 4.

4.3.1. Pertinent crystallographic data for (2*S*,3*S*)-3. $C_{10}H_{11}ClO_4$, Mr = 230.64 g mol^{-1}, orthorhombic, space group: $P2_12_12_1$, a = 5.2267(1), b = 6.7172(1), c = 30.2782(7) Å, cell volume = 1063.03(4) Å^3, Z = 4, T = 293(2) K, ρ_c = 1.441 g cm^{-3}, μ = 0.350 mm^{-1}, Θrange = 3.96–27.51°, *hkl* indices: $-6 \leqslant h \leqslant 6$, $-8 \leqslant k \leqslant 8$, $-38 \leqslant l \leqslant 39$, reflections (measured) = 2334, reflections (unique) = 2334, reflections (unique [$F_o > 2\sigma\{|F_o|\}$]): 1934, R_{int} = 0, 180 parameters, R_1/wR_2 (all data): 0.0477/0.0892, R_1/wR_2 ($I > 2\sigma(I)$): 0.0346/0.0826, Flack parameter = −0.06(7), largest diff. peak/hole: 0.169/−0.154 e Å^{-3}.

4.3.2. Pertinent crystallographic data for (2*R*,3*R*)-3. $C_{10}H_{11}ClO_4$, Mr = 230.64 g mol^{-1}, orthorhombic, space group: $P2_12_12_1$, a = 5.2273(1), b = 6.7201(1), c = 30.2906(7) Å, cell volume = 1064.05(3) Å^3, Z = 4, T = 293(2) K, ρ_c = 1.440 g cm^{-3}, μ = 0.350 mm^{-1}, Θrange = 3.11°–27.47°, *hkl* indices: $-6 \leqslant h \leqslant 6$, $-8 \leqslant k \leqslant 8$, $-38 \leqslant l \leqslant 39$, reflections (measured) = 2390, reflections (unique) = 2390, reflections (unique [$F_o > 2\sigma\{|F_o|\}$]): 2157, R_{int} = 0, 180 parameters, R_1/wR_2 (all data): 0.0405/0.0923, R_1/wR_2 ($I > 2\sigma(I)$): 0.0347/0.0888, Flack parameter = 0.01(8), largest diff. peak/hole: 0.185/−0.179 e Å^{-3}.

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References

1. Berger, J.; Moller, D. E. *Ann. Rev. Med.* **2002**, *53*, 409–435.
2. Staels, B.; Dallongeville, J.; Auwerx, J.; Schoonjans, K.; Leitersdorf, E.; Fruchart, J. C. *Circulation* **1998**, *98*, 2088–2093.
3. Sgro, C.; Escousse, A. *Therapie* **1991**, *46*, 351–354.
4. Gariot, P.; Barrat, E.; Mejean, L.; Pointel, J.; Drouin, P.; Debry, G. *Arch. Toxicol.* **1983**, *53*, 151–163.
5. Angelin, B.; Einarsson, K.; Leijd, B. *Eur. J. Clin. Invest.* **1984**, *14*, 73–78.
6. Evans, M.; Rees, A. *Drug Safety* **2002**, *25*, 649–663.
7. Conte-Camerino, D.; Tortorella, V.; Ferrannini, E.; Bryant, S. H. *Arch. Toxicol.* **1984**, *7*, 482–484.
8. Mastaglia, F. L. *Drugs* **1982**, *24*, 304–321.
9. Margarian, G. J.; Lucas, L. M.; Colley, C. *Arch. Intern. Med.* **1991**, *151*, 1873–1874.
10. Lavarenne, J.; Poinas-Caillaud, H. *Therapie* **1991**, *46*, 347–349.
11. London, S. F.; Gross, K. F.; Ringel, S. P. *Neurology* **1991**, *41*, 1159–1160.
12. Reddy, J. K.; Azarnoff, D. C.; Hignite, C. E. *Nature* **1980**, *283*, 397–398.
13. Vouillamoz, D.; Schaller, M. D.; Bianchi, L.; Chaubert, P.; Reinhart, W.; Armstrong, D.; Thorens, J.; Blum, A. L. *Lancet* **1991**, *338*, 581.
14. Tikkanen, M. *Curr. Opin. Lipidol.* **1992**, *3*, 29–33.
15. Zimetbaum, P.; Frishman, W.; Kahn, S. *J. Clin. Pharmacol.* **1991**, *31*, 25–37.
16. Feller, D. R.; Kamanna, V. S.; Newman, H. A. I.; Romstedt, K. J.; Witiak, D. T.; Bettoni, G.; Bryant, S. H.; Conte-Camerino, D.; Loiodice, F.; Tortorella, V. *J. Med. Chem.* **1987**, *30*, 1265–1267.
17. Bettoni, G.; Loiodice, F.; Tortorella, V.; Conte-Camerino, D.; Mambrini, M.; Ferrannini, E.; Bryant, S. H. *J. Med. Chem.* **1987**, *30*, 1267–1270.
18. Esbenshade, T. A.; Kamanna, V. S.; Newman, H. A. I.; Tortorella, V.; Witiak, D. T.; Feller, D. R. *Biochem. Pharmacol.* **1990**, *40*, 1263–1274.
19. Inomata, N.; Yoshida, H.; Aoki, Y.; Tsunoda, M.; Yamamoto, M. *Tohoku J. Exp. Med.* **1991**, *165*, 171–182.
20. Ciolek, E.; Dauca, M. *Biol. Cell* **1991**, *71*, 313–320.
21. Ferorelli, S.; Franchini, C.; Loiodice, F.; Perrone, M. G.; Scilimati, A.; Sinicropi, M. S.; Tortorella, P. *Tetrahedron: Asymmetry* **2001**, *12*, 853–862, and references cited therein.
22. Ferorelli, S.; Loiodice, F.; Tortorella, V.; Amoroso, R.; Bettoni, G.; Conte-Camerino, D.; DeLuca, A. *Farmaco* **1997**, *52*, 367–374, and references cited therein.
23. Rangwala, S. M.; O'Brien, M. L.; Tortorella, V.; Longo, A.; Loiodice, F.; Noonan, D. J.; Feller, D. R. *Chirality* **1997**, *9*, 37–47.
24. Ferorelli, S.; Loiodice, F.; Tortorella, V.; Conte-Camerino, D.; DeLuca, A. *Farmaco* **2001**, *56*, 239–246.
25. Carbonara, G.; Fracchiolla, G.; Loiodice, F.; Tortorella, P.; Conte-Camerino, D.; DeLuca, A.; Liantonio, A. *Farmaco* **2001**, *56*, 749–754.
26. Liantonio, A.; Accardi, A.; Carbonara, G.; Fracchiolla, G.; Loiodice, F.; Tortorella, P.; Traverso, S.; Guida, P.; Pierno, S.; DeLuca, A.; Conte-Camerino, D.; Push, M. *Mol. Pharmacol.* **2002**, *62*, 265–272.
27. Perrone, M. G.; Santandrea, E.; Dell'Uomo, N.; Giannessi, F.; Milazzo, F. M.; Sciarroni, A. F.; Scilimati, A.; Tortorella, V. *Eur. J. Med. Chem.* **2005**, *40*, 143–154.
28. Perrone, M. G.; Santandrea, E.; Scilimati, A.; Tortorella, V.; Capitelli, F.; Bertolasi, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3501–3510.
29. Perrone, M. G.; Santandrea, E.; Scilimati, A.; Syldatk, C.; Tortorella, V.; Capitelli, F.; Bertolasi, V. *Tetrahedron: Asymmetry* **2004**, *15*, 3511–3517.
30. Hintzer, K.; Koppenhoefer, B.; Schurig, V. *J. Org. Chem.* **1982**, *47*, 3850–3854.
31. Brewster, P.; Hiron, F.; Hughes, E. D.; Ingold, C. K.; Rao, P. A. *Nature* **1950**, *166*, 179–180.
32. It has been proved that racemization does not exceed 2.7% in the conversion (with retention of configuration) of 2-amino carboxylic acids to 2-chloro carboxylic acids: Schurig, V.; Koppenhoefer, B.; Buerkle, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *90*, 993–995.
33. Koppenhoefer, B.; Weber, R.; Schurig, V. *Synthesis* **1982**, 316–318.
34. Winstein, S.; Lucas, H. J. *J. Am. Chem. Soc.* **1939**, *61*, 1576–1581.
35. Ketola, M.; Lyytinen, M. R.; Hotokka, M.; Pihlaja, K. *Acta Chem. Scand. Sez B: Org. Chem. Biochem.* **1978**, *B32*, 743–748.
36. Akita, H.; Todoroki, R.; Endo, H.; Ikari, Y.; Oishi, T. *Synthesis* **1993**, 513–516.
37. Amoroux, R.; Gerin, B.; Chastrette, M. *Tetrahedron* **1985**, *41*, 5321–5324.
38. Nonius B. V. (COLLECT). *Nonius, 1998. KappaCCD Server Software*; Delft: The Netherland.
39. Otwinowski, Z.; Minor, W. In *Methods in Enzymology, Macromolecular Crystallography. Part A*; Carter, C. W., Sweet, R. M., Eds.; Academic: University of Texas, Southwestern Medical Centre at Dallas, HKL DENZO and Scalepack, USA, 1997; Vol. 276, p 307.
40. Altomare, A.; Burla, M. C.; Camalli, M.; Cascarano, G. L.; Giacovazzo, C.; Guagliardi, A.; Moliterni, A. G. G.; Polidori, G.; Spagna, R. *J. Appl. Crystallogr.* **1999**, *32*, 115–119.
41. Sheldrick, G. M. *SHELXL-97. Program for the Refinement of Crystal Structures*. University of Gottingen: Germany, 1997.
42. Crystallographic data (excluding structure factors) for the structures here reported have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications Nos. CCDC-261641–241642, respectively, for (2*S*,3*S*)-2-(4-chlorophenoxy)-3-hydroxybutanoic acid **3** and (2*R*,3*R*)-2-(4-chlorophenoxy)-3-hydroxybutanoic acid **3**. Copies of available material can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or email: deposit@ccdc.cam.ac.uk).