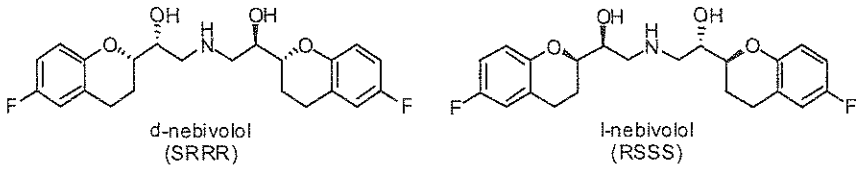
To the ends of the present invention the group R_1, defined as a linear or branched C_{1-5} alkyl group, represents a radical selected from: methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, amyl, tert-amyl; preferably it is a radical selected from methyl, ethyl, propyl, and even more preferably it is an ethyl group.

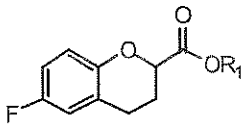
In another aspect, there is provided a method for the synthesis of *d*-Nebivolol and/or *l*-Nebivolol of the following formulas



Nebivolol

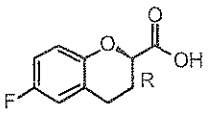
comprising the following steps:

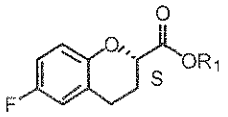
a) hydrolyzing a mixture of enantiomers of the 6-fluoro-2-carboxylic acid ester (1), wherein R_1 *is a linear or branched* C_{1-5} alkyl group



(1)

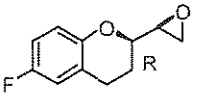
to give a mixture of acid (2) and ester (3)



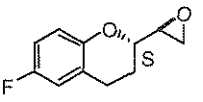


(2) (3)

b) using thus obtained acid (**2**) and ester (**3**) for the synthesis respectively of the mixtures of epoxides (**4**) and (**5**),



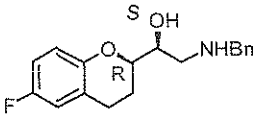
(RR + RS)

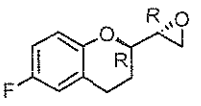


(SS + SR)

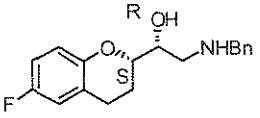
(4) (5)

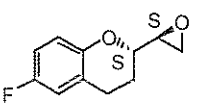
c) resolving the mixtures of epoxides (**4**) and (**5**) to obtain respectively the compounds (**6**)+ (**7**) and (**8**) +(**9**).





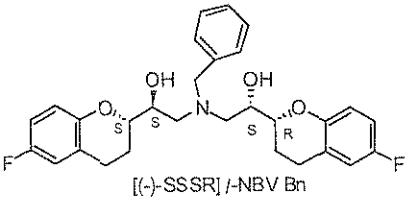
(6) (7)





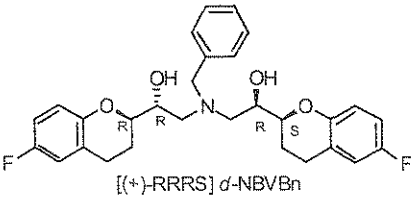
(8) (9)

d) reacting the amino alcohols (**6**) and (**8**) with the epoxides (**7**) and (**9**) to obtain *l*-benzyl Nebivolol (**10**) and *d*-benzyl Nebivolol (**11**)



[(-)-SSSR] *l*-NBV Bn

(10)



[(+)-RRRS] *d*-NBVBn

(11)

e) removing the benzyl protecting group,

characterized in that there are carried out, in step (a), hydrolizing by a stereoselective enzymatic hydrolysis reaction, to give the mixture of R acid (2) with an enantiomeric excess of >70% and of S ester (3) with an enantiomeric excess of >70%; and, in step (c), kinetically resolving the mixtures of epoxides (4) and (5), by reacting them with benzylamine in sterically hindered alcohol selected from isopropanol, sec-Butanol, tert-butanol, 2-methyl-2-butanol, isoamyl alcohol, 2-methyl-2-pentanol,
wherein the enzymatic hydrolysis reaction is carried out by use of an esterase obtained from *Ophiostoma*.

In another aspect, there is provided a method as defined herein, wherein the acid (**2**) is converted into the mixture of RR+RS epoxides (**4**), whereas the ester (**3**) is converted into the mixture of SS+SR epoxides (**5**).

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, the Nebivolol compound is obtained with the process described in Scheme 1 starting from the racemic mixture of the 6-fluorochroman-2-carboxylic acid ester (**1**).

6-fluorochroman-2-carboxylate (1) may be resolved into its two enantiomers with high stereoselectivity through enantioselective hydrolysis catalyzed by a fungal esterase (lipase) obtainable from genus *Ophiostoma*. The preferred species is esterase from *Ophiostoma novo-ulmi*, already described in the literature for its stereoselective activity on the esters of naproxen or ketoprofen compounds.

The enzyme, in the form of an isolated and crystallized expression protein, is described by M. N. Isupov et al. in *Acta Crystallographica - Biological Crystallography* Section D60, p. 1879-1882 (2004). The enzyme is also described in EP-B1-0687305 (WO94/20634), EP-0693134, US5912164, and in EP1626093.

Enzyme expression in *E coli* may be performed as described by M. N. Isupov et al. (*supra*) or in EP-B1-0687305 (WO94/20634).

This strain provides a good example of activity, however, given the rather diffused nature of activity in a wide variety of related strains, the scope of the invention is not meant to be limited only thereto. The microorganisms of genus *Ophistoma* and their enzymatic activity may be used to hydrolyze the racemic ester of 6-fluorochroman-2-carboxylated ethyl in a stereoselective