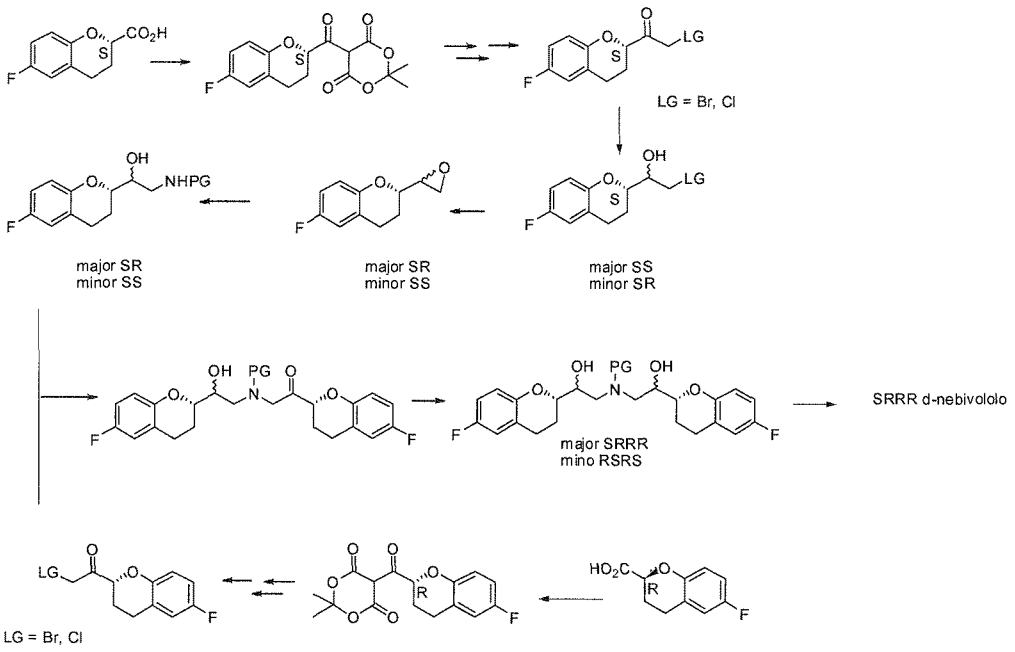
to the need to remove unwanted diastereoisomers.

WO 2007~~4~~/041805 (Egis Gyógyszergyár) describes a process for the preparation of [2S*[R*[R*[R*]]]] and [2R*[S*[S*[S*]]]]-(±)-α,α'-[iminobis(methylene)] bis[6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] and its individual pure [2S*[R*[R*[R*]]]] and [2R*[S*[S*[S*]]]] enantiomers starting from very different compounds. The steps used for Nebivolol synthesis as mixture of enantiomers are about thirty, making the synthesis very lengthy and uneconomic~~ (Scheme 5)~~.



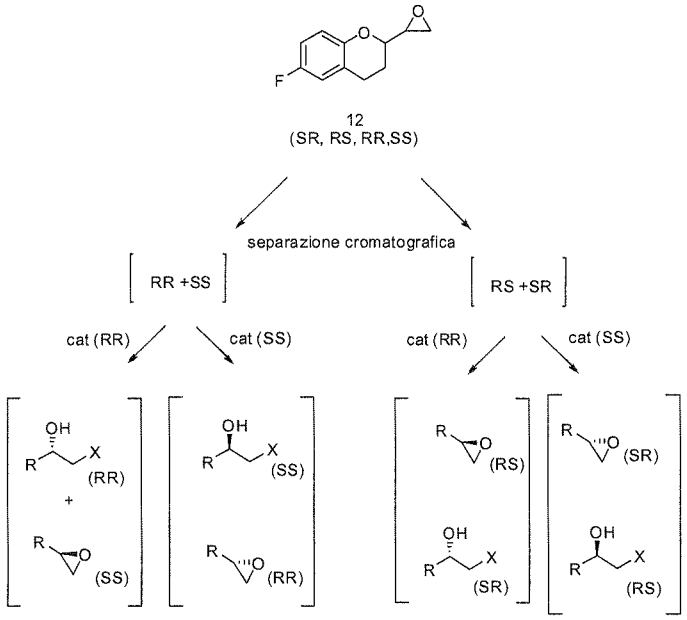
Scheme 5

In WO 2008/010022 (Cimex Pharma) a route is reported that, starting from 6-fluoro chroman carboxylic acids resolved according to processes in the literature, leads to the synthesis of the two Nebivolol enantiomers according to two separate sequences (Scheme ~~6~~5, for d-Nebivolol).

In the opening of epoxides by a benzylamine, a

single opening product crystallizes from the reaction mixture, but the other diastereoisomer is removed with the mother liquors, leading in this case as well to the elimination of a considerable fraction of material in an already quite advanced stage of the synthetic sequence. In addition, the last chiral centre is added at the penultimate step by reduction of a ketone, quite a sensitive reaction, which in order to obtain optimal results envisages the use of KBH_4 and titanium isopropoxide.

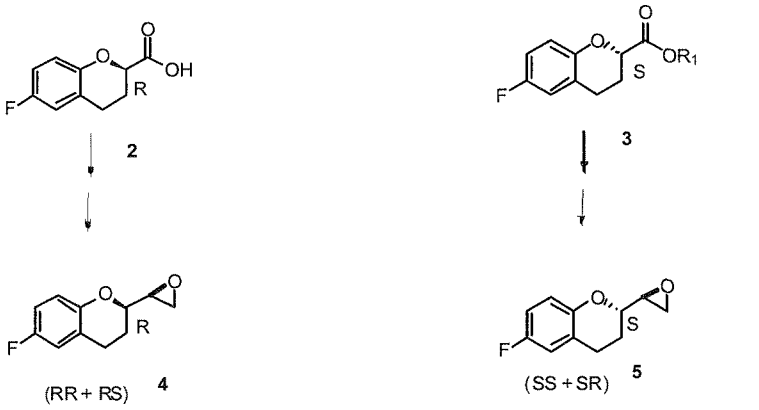
WO2008/064826 (Zach System) reports a process for the resolution of epoxides, once the pairs of diastereoisomers (RS/SR and RR/SS) have been separated chromatographically, through the enantioselective opening of the same epoxides mediated by chiral complexes of cobalt II (Scheme 76). In this case a chromatographic separation step is necessary, less than practical from the standpoint of the process, while cobalt complexes require caution in manipulation and disposal.



Scheme 6

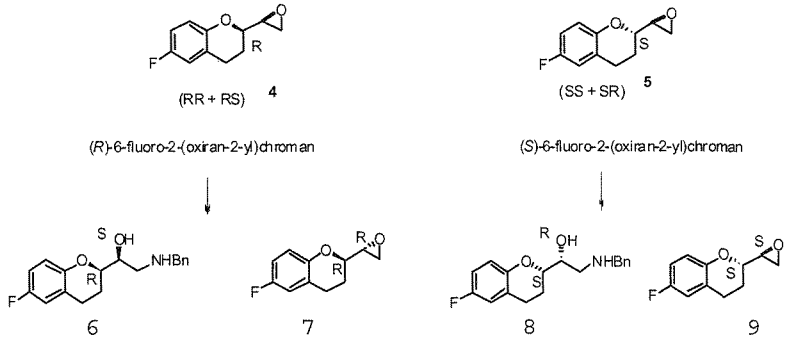
WO 2008/064827 (Zach System) describes the separate

Through processes known to a person skilled in the art (by way of a non-limiting example, analogously to that described in ~~WO2007041805~~ WO 2008/010022) the acid (**2**) is transformed into the mixture of epoxides (RS) and (RR) (**4**), diastereoisomeric therebetween, while the ester (**3**) is converted into the mixture of epoxides (SR) + (SS)



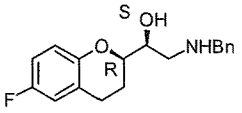
(**5**).

By performing the reaction of opening of the mixture of epoxides (**4**) with benzylamine in a sterically hindered alcoholic solvent (such as isopropanol, sec-Butanol, tert-butanol, 2-methyl-2-butanol, isoamyl alcohol, 2-methyl-2-pentanol) it is had a kinetic resolution with formation of the sole amino alcohol RS (**6**), while the epoxide RR (**7**) is recovered as unchanged.

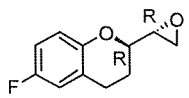


The same procedure, applied to mixture (**5**), produces amino alcohol SR (**8**) and epoxide SS (**9**).

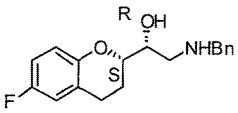
obtain respectively the compounds (**6**)+ (**7**) and (**8**) +(**9**).



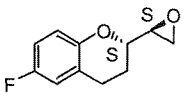
(6)



(7)

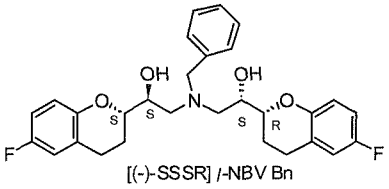


(8)

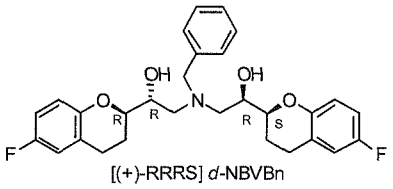


(9)

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**)



(10)



(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~~a sterically hindered alcohol.~~

~~2. The synthesis method according to claim 1~~, wherein the enzymatic hydrolysis reaction is carried out by use of an esterase obtained from ~~genus~~ *Ophiostoma*.

~~3.~~2. The synthesis method according to claim ~~2~~1, wherein the enzymatic hydrolysis reaction is carried out by use of the esterase obtained from strain AJ3 of

Ophiostoma novo-ulmi.

43. The method according to claims 2 ~~or 3~~, wherein the enzymatic hydrolysis reaction is conducted at a pH comprised between 8 and 11.

54. The method according to claim 43, wherein the enzymatic hydrolysis reaction is conducted at a pH comprised between 8.5 and 10.

65. The method according to claims 2 ~~or 3~~, wherein the enzymatic hydrolysis reaction is conducted at a temperature comprised between 10° and 35°C.

76. The method according to claim 65, wherein the enzymatic hydrolysis reaction is conducted at a temperature comprised between 20° and 25°C.

87. The method according to claims 2 ~~or 3~~, wherein the enzymatic hydrolysis reaction is conducted in an aqueous environment or in the presence of water immiscible solvents.

98. The method according to claims 2 ~~or 3~~, wherein the enzymatic hydrolysis of the mixture of esters (1) proceeds to yield a mixture of (R) acid (**2**) and (S) ester (**3**) with an enantiomeric excess of >80% or >90% in both components.

109. A method according to claim 1, 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**).

~~11. The method according to claim 1, wherein the kinetic resolution with benzylamine of the mixtures of epoxides (4) and (5) is conducted in a sterically hindered alcohol selected from isopropanol, sec-Butanol, tert-butanol, 2-methyl 2-butanol, isoamyl alcohol, 2-methyl 2-pentanol.~~

1210. . The method according to claim 119, wherein the kinetic resolution with benzylamine of the mixture of epoxides (**4**) is conducted in a sterically hindered alcohol selected from isopropanol, sec-Butanol, tert-

butanol, 2-methyl-2-butanol, isoamyl alcohol, 2-methyl-2-pentanol, obtaining only the amino alcohol RS (**6**), while the epoxide RR (**7**) is recovered as unchanged.

~~13~~11. The method according to claim ~~11~~9, wherein the kinetic resolution with benzylamine of the mixture of epoxides (**5**) is conducted in a sterically hindered alcohol selected from isopropanol, sec-Butanol, tert-butanol, 2-methyl-2-butanol, isoamyl alcohol, 2-methyl-2-pentanol, obtaining only the amino alcohol SR (**8**) while the epoxide SS (**9**) is recovered as unchanged.

~~14~~12. The method according to claims ~~12~~ 10 or ~~13~~11, wherein the sterically hindered alcohol is 2-methyl-2-butanol.

~~15~~13. The method according to any one of the claims 1 to ~~14~~12, wherein the amino alcohol RS (**6**) is reacted with the epoxide SS (**9**) to give the *l*-benzylated Nebivolol (**10**) and/or the amino alcohol SR (**8**) is reacted with the epoxide RR (**7**) to give the *d*-benzylated Nebivolol (**11**).

~~16~~14. The method according to claim ~~15~~13, wherein the compounds (**10**) and (**11**) are mixed in a 1:1 ratio, deprotected from the benzyl group to give the final product Nebivolol.

~~17~~15. The method according to any one of the claims 1-~~16~~14, wherein the final product Nebivolol is salified with hydrochloric acid, obtaining the corresponding hydrochloride.