



- (51) **International Patent Classification:**
C07D 311/58 (2006.01) *C07D 407/04* (2006.01)
- (21) **International Application Number:**
PCT/IB2012/053956
- (22) **International Filing Date:**
2 August 2012 (02.08.2012)
- (25) **Filing Language:** Italian
- (26) **Publication Language:** English
- (30) **Priority Data:**
RM2011A000418 2 August 2011 (02.08.2011) IT
- (71) **Applicant (for all designated States except US):** Menarini International Operations Luxembourg S.A. [LU/LU]; 1, Avenue de la Gare, L-1611 Luxembourg (LU).
- (72) **Inventors; and**
- (75) **Inventors/Applicants (for US only):** CIPOLLONE, Amalia [IT/IT]; Viale dei Primati Sportivi 86, I-00144 Roma RM (IT). D'ANDREA, Piero [IT/IT]; Via Orlando Ferrazza 29, I-00045 Genzano RM (IT). FATTORI, Daniela [IT/IT]; Via Appia Antica 3, I-00049 Velletri RM (IT).
- (74) **Agents:** GERMINARIO, Claudio et al.; Società Italiana Brevetti S.p.A., Piazza di Pietra 39, I-00186 Roma (IT).

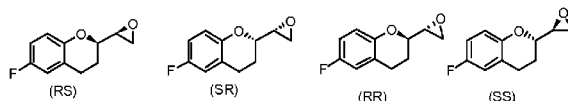
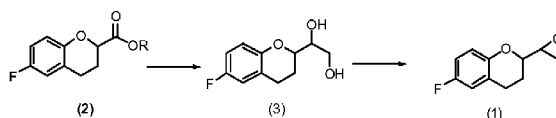
(81) **Designated States** (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) **Designated States** (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

(54) **Title:** PROCESS FOR THE PREPARATION OF EPOXIDES AS INTERMEDIATES FOR THE SYNTHESIS OF NEBIVOLOL

**Figure (1)****Scheme (1)**

(57) **Abstract:** The present invention relates to a novel process of synthesis of epoxides, 6-fluoro-2-(oxiran-2-yl)chroman (Figure 1), intermediates for the synthesis of neбиволol, depicted in Scheme (1), enabling to obtain the above-mentioned epoxides in a racemic or semichiral form.

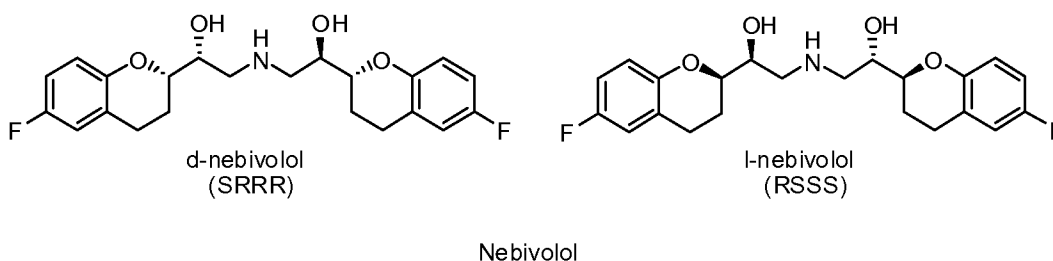
- 1 -

PROCESS FOR THE PREPARATION OF EPOXIDES AS INTERMEDIATES FOR THE SYNTHESIS OF NEBIVOLOL

FIELD OF THE INVENTION

The present invention relates to a novel process for the synthesis of 6-fluoro-2-(oxiran-2-yl)chroman epoxides (**1**), intermediates for the synthesis of nebivolol.

Nebivolol is a racemic mixture of the two enantiomers [2S[2R[R[R]]]] α,α' -[imino-bis (methylene)] bis[6-fluoro-chroman-2-methanol] and [2R[2S[S[S]]]] α,α' -[imino-bis (methylene)] bis[6-fluoro-chroman-2-methanol] (Scheme 2).



Scheme (2)

The 6-fluorochroman-2-carboxylate ester (**2**), by treatment at temperatures lower than -90°C with the organometallic compound LiCH_2Br , followed by low-temperature quenching with an aqueous solution and by treatment with a reducing agent, generates the diol (**3**) which, through tosylation and intramolecular substitution, leads to the epoxide (**1**) without alteration of the starting diastereoisomeric composition.

This method is applicable to a racemate ester (**2**) to obtain the mixture of epoxides (**1**), or to an optically active ester to obtain the semichiral epoxides.

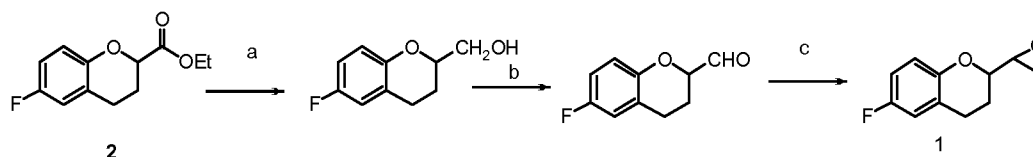
STATE OF THE ART

US Patent No. 4,654,362 (and its counterpart EP 0145067) reports the reduction of the ester (**2**) to alcohol with Red-Al ($\text{NaAlH}_2(\text{OC}_2\text{H}_4\text{OCH}_3)_2$), followed by

- 2 -

oxidation to obtain the corresponding aldehyde, and by treatment with $(\text{Me}_3)_3\text{SO}^+\text{I}^-$ to have the epoxides (**1**) (Scheme 3).

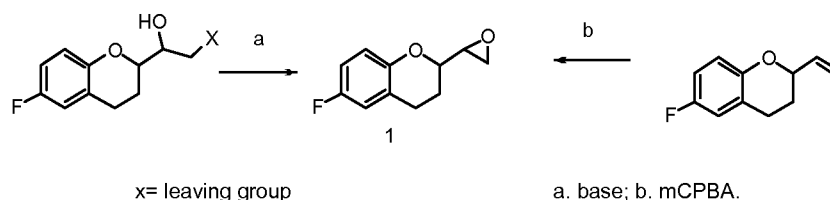
The same fundamental synthetic scheme, with ameliorative modifications in terms of yield and purity, is reported in WO 2010/089764 (Dr. Reddy's).



a. Red-Al; b. $(\text{COCl})_2$, DMSO, CH_2Cl_2 ; c. $(\text{CH}_3)_3\text{SO}^+\text{I}^-$, NaH, DMSO.

Scheme (3)

Always in US No. 4,654,362, as generic possibilities for this class of compounds, are reported that of obtaining the epoxides (**1**) by elimination from alpha-substituted alcohols with a good leaving group (X) or by epoxidation of the corresponding olefin with base and metachloroperbenzoic acid (Scheme 4).



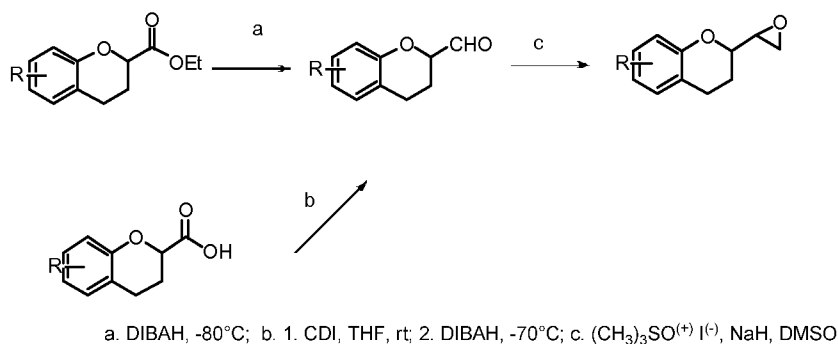
Scheme (4)

Other methods for preparing the aldehyde and then the epoxides of type (**1**) are reported in Scheme 5.

The aldehyde may be obtained by low-temperature reduction of the imidazolidine of the corresponding acid or of the same ester (**2**) with diisobutyl aluminium hydride. The aldehyde is then converted into the epoxide (**1**) by reaction with sodium hydride and trimethyl sulfoxonium

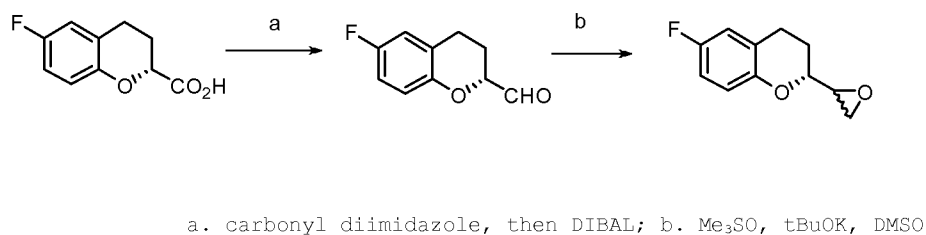
- 3 -

iodide in dimethylsulfoxide, as already described in the foregoing.



Scheme (5)

The method of Scheme (5), envisaging the reduction of the ester to aldehyde, is explicitly reported for the 6-fluoro derivative by EP 0334429 using the chiral ester, and is directed to prepare separately the single optical isomers (*R,S*; *S,S*) and (*S,R*; *R,R*) of nebivolol. In this instance, 6-fluoro-chroman carboxylic acid is resolved into single enantiomers by treatment with (+)-dehydroabiethylamine. Said enantiomers are separately converted into their corresponding epoxides, resulting in mixtures of two diastereoisomers. The following synthetic scheme (Scheme 6) describes the conversion of the *R*-acid.

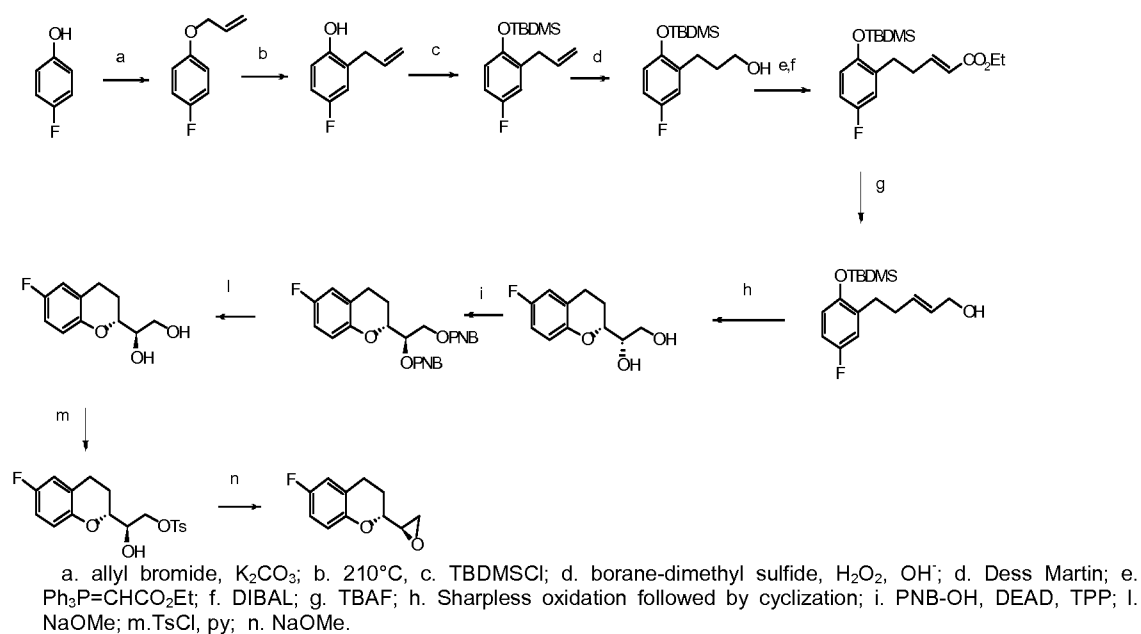


Scheme (6)

The aldehyde of the chroman is not particularly stable and is prone to racemation when it is prepared in an optically active form.

- 4 -

In Tetrahedron (2000), 56, 6339-6344 a synthesis of the above-mentioned epoxides in chiral form is reported which, starting from 4-fluorophenol, through a sequence rather rich in steps, provides the glycols of type (3) which are then transformed into epoxides via tosylates (Scheme 7).

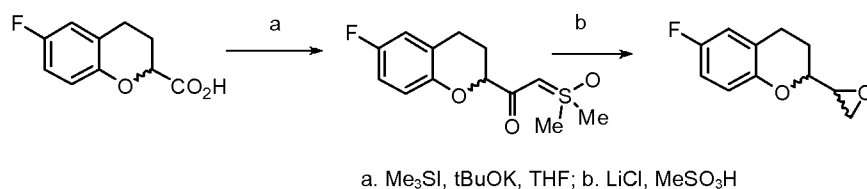


Scheme (7)

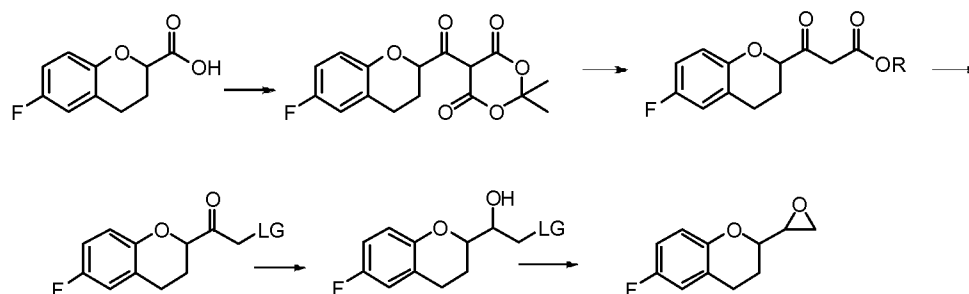
This method, despite allowing to obtain the epoxides in an optically pure form, is very lengthy and toilsome.

WO 2008/040528 (Zach System) reports the conversion of an ester of 6-fluoro-3,4-dehydro-2H-chromen-2-carboxylate into 2-halo-1-(6-fluoro-3,4-dehydro-2H-chromen-2-yl) ethanone (alpha-haloketone) via sulfoxonium ylide; the reduction of the alpha-haloketone, followed by cyclization in the presence of a base, to yield the mixture of the four epoxide diastereoisomers (Scheme 8).

- 5 -

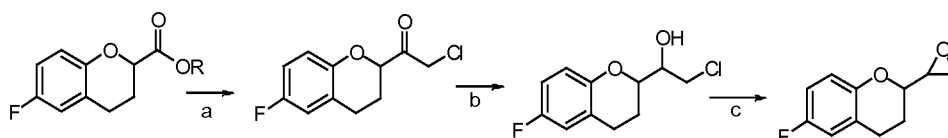
**Scheme (8)**

WO 2008/010022 (Zach System) reports a synthesis (Scheme 9) in which the acid deriving from ester (2) is reacted with dimedone to then produce in two steps the corresponding alpha-chloro or alpha-bromo ketone, which is reduced and cyclized to epoxide. The sequence is rather lengthy and toilsome.

**Scheme (9)**

WO 2010/034927 (Zach System) reports always the preparation of alpha-halo ketones as epoxide precursors. In this instance, the alpha-halo ketones are prepared as described in Scheme 10.

The ester (2) is treated at low temperature with LiCH_2Cl to obtain, after quenching with acetic acid, the corresponding alpha-chloro ketone which is then reduced to alpha-chloro alcohol and cyclized to epoxide.



a. BuLi, CHBrCl, -80°C, then AcOH; b. NaBH₄, EtOH, 0°C; c. i-PrOH, NaOH

Scheme (10)

This method, though being rather short, entails the drawback of not eliminating the apolar reaction byproducts deriving from the organometallic species used, until the end stage of epoxide. These byproducts are of aliphatic type, numerous, of slightly different nature with each other, and are not visible under UV. For these reasons, they are difficult to quantify. In addition, some are bromo- or chloro-alkyls which may then invalidate the yields of the reactions subsequently used for the preparation of nebivolol, as well as the purity of products obtained. It is not possible to carry out a purification of the intermediate product, the alcohol, by extraction or partition.

SUMMARY OF THE INVENTION

We have now, surprisingly, found a more efficient process of synthesis of epoxide intermediates (**1**), racemates or semichiral ones, which is summarized in Scheme 1. Such a process allows to eliminate the drawbacks already highlighted for the previously known synthesis pathways, i.e.:

- length and complexity of synthetic pathways
- need of chromatographic purifications to eliminate apolar aliphatic residues of secondary reactions yielded by reagents used.

According to this process, the alkyl 6-fluorochroman-2-carboxylate (**2**), for treatment at a temperature lower than -90°C with the organometallic compound LiCH₂Br, optionally generated *in situ*, followed by quenching, carried out always at a temperature lower

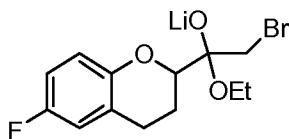
- 7 -

than -90°C with an aqueous solution, followed by treatment with a reducing agent such as NaBH_4 , generates the diol (**3**) which, by tosylation and intramolecular nucleophilic substitution, generates the epoxide (**1**) without alteration of the starting diastereoisomeric composition.

In a single step we go from the ester (**2**) to the diol (**3**), from the crude reaction material of which the apolar aliphatic species produced during the reaction can be eliminated by simple washings: a solution of the crude material in a polar organic solvent is treated with an apolar solvent immiscible with the former, in which diols are scarcely soluble. This method therefore proves more suitable for a large-scale synthesis process.

Such a synthesis allows to obtain the above-mentioned epoxides (**1**) in a racemate or semichiral form, where by "racemate form" a mixture of the 4 epoxides indicated in Figure 1 is meant, and by "semichiral form" a mixture of only two diastereomeric epoxides of RS + RR or SR + SS type is meant, in which the asymmetric center on the six-member ring of the pyrane has the same stereochemistry.

The mechanism of such a reaction is not clear, but it ought not be the classic one reported in the literature for the treatment of an ester with an organometallic compound, and preferably with an organolithium. In that case one would expect the intermediate initially formed, of type:

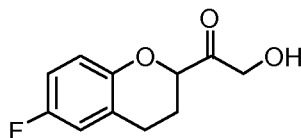


to evolve into alpha-bromo ketone, stable under reaction conditions.

What instead is observed after low-temperature

- 8 -

(lower than -90°C) quenching with a 0.1M NaHSO_4 solution is alpha hydroxy-ketone (**4**), isolated and characterized by the present Inventors, which by reduction with NaBH_4 yields the diol (**3**).



(4)

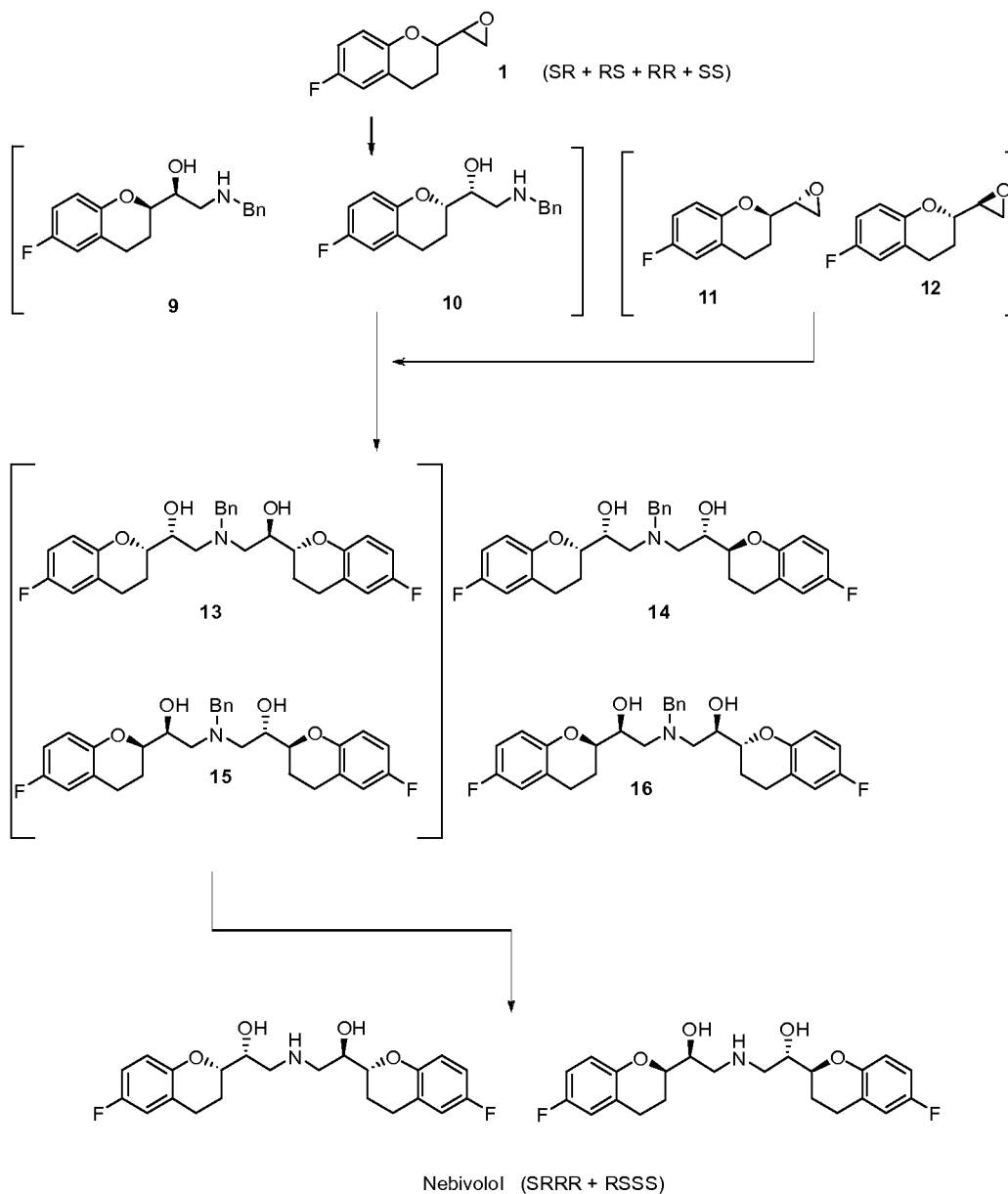
Therefore, object of the present invention is a process for the preparation of epoxides as intermediates in the synthesis of nebivolol, comprising:

- a. synthesizing the diols of type (**3**) starting from a chroman ester (**2**), both racemate and optically active, for treatment with LiCH_2Br at a temperature lower than -90°C , aqueous quenching at a low temperature and subsequent treatment with a reducing agent such as NaBH_4 ;
- b. purifying the diols thus obtained by partitioning between a polar organic solvent and an apolar solvent, immiscible with each other;
- c. transforming the diols (**3**) into epoxides (**1**), by tosylation or mesylation, and intramolecular nucleophilic substitution without alteration of the ratio between diastereoisomers.

The epoxides thus obtained can be used for the preparation of nebivolol according to methods already well-known in the art.

By way of example, the synthesis described in Scheme 11 can be used to obtain nebivolol (WO2011/098474).

- 9 -



Scheme 11

This synthesis provides for the treatment of the mixture of epoxides (**1**) with benzylamine in a solvent represented by a sterically hindered alcohol, alone or in a mixture with an apolar solvent, to obtain a mixture of four compounds (**9**, **10**, **11**, and **12**), from which the pair **9/10** is separated from the pair **11/12** by crystallization or chromatography. There follows the reaction of amines **9/10** with the epoxides **11/12** to obtain a mixture of four

- 10 -

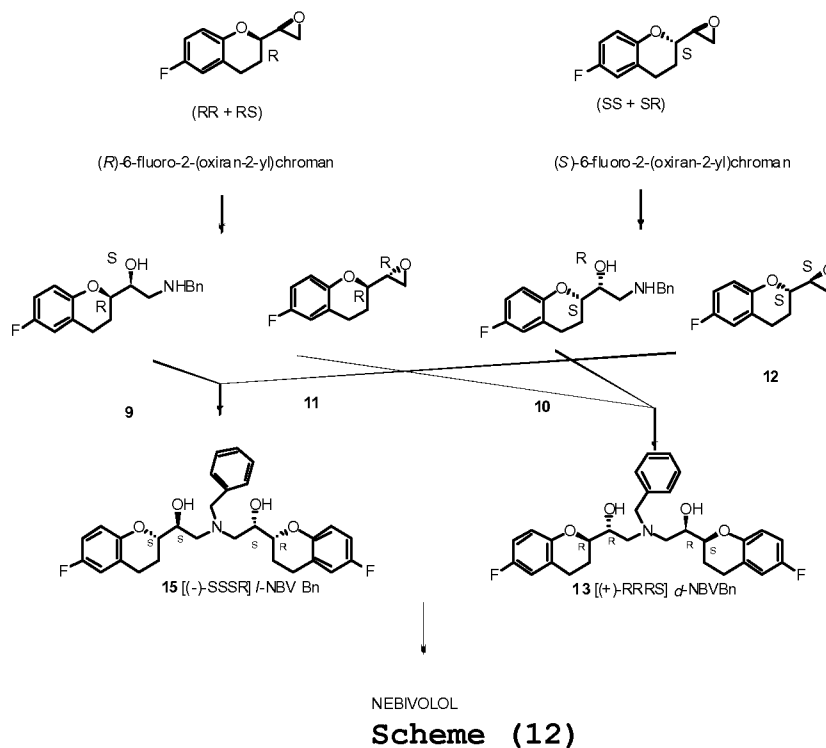
compounds (**13**, **14**, **15** and **16**). From this mixture, the compounds **13** and **15** (RSSS + SRRR) in mixture are separated from **14** and **16** by fractionated crystallization with a suitable solvent. A reaction of catalytic hydrogenation of the mixture **13/15** provides nebivolol.

Methods for separating the enantiomers of an alkyl 6-fluorochroman-2-carboxylate are known, for instance as described in EP334429 by amide formation with (+)-dehydroabiethylamine, or, as reported in the Italian Patent Application RM2010A000622 of 11/30/2010, by enzymatic hydrolysis by a fungal esterase.

When the starting alkyl 6-fluorochroman-2-carboxylate (**2**) is a definite isomer, the present synthesis gives rise to the semichiral epoxides, specifically to the RS/RR mixture or to the SS/SR mixture, depending on whether the starting ethyl carboxylate is the R isomer or the S isomer.

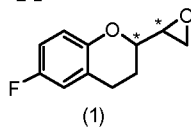
From the mixtures of semichiral epoxides it is possible to carry out nebivolol synthesis according to methods known in the art, e.g., the semichiral (RR + RS) and (SS + SR) epoxides are reacted separately with benzylamines under the conditions described in the foregoing, to obtain the separated compounds (**9**), (**10**), (**11**) and (**12**). Then, the amine (**9**) is reacted with the epoxide (**12**) to obtain solely the enantiomer (**15**), whereas the amine (**10**) is reacted with the epoxide (**11**) to obtain solely the enantiomer (**13**). The two benzylated derivatives (**13**) and (**15**) of nebivolol are united in equal parts and subjected to catalytic hydrogenation in order to have nebivolol (Scheme 12).

- 11 -

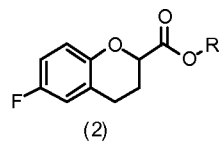


DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, the racemate or semichiral epoxides of type **(1)**,

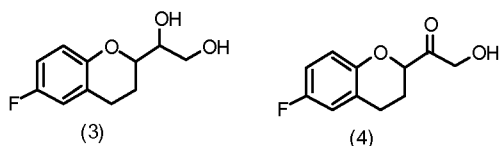


are obtained with the method described in Scheme 1 from an ester **(2)** of 6-fluorochroman 2-carboxyl acid, both in a racemic mixture and as an isolated enantiomer, wherein R is a C₁-C₆ alkyl group, preferentially an ethyl group.



This conversion provides the transformation of the ester **(2)** into the diol **(3)** via alpha-hydroxy ketone **(4)**.

- 12 -



Alpha-hydroxy ketone **(4)** is obtained by treatment of **(2)** with LiCH_2Br , at low temperatures and in an inert organic solvent, and subsequent quenching at low temperatures.

The organometallic compound LiCH_2Br may be preferentially obtained *in situ* by adding a BuLi solution to a solution containing the ester **(2)** and the CH_2Br_2 in an inert organic solvent. The temperature is lower than -90°C , preferentially comprised between -130°C e -95° , and even more preferentially between -105°C and -95°C .

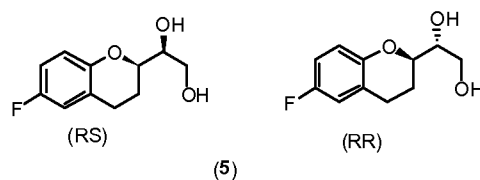
The solvent belongs to the family of hydrocarbons or of ethers, alone or in mixture, preferably tetrahydrofuran alone or in mixture.

At completion of the reaction, keeping the mixture at the initial temperature, an aqueous solution is added; said solution may be neutral or acidic, but anyhow used in an amount such as to maintain the environment under alkalinity conditions, and preferably 0.1 M NaHSO_4 , and temperature is let rise to values comprised between -50 and -10°C , preferably -30°C .

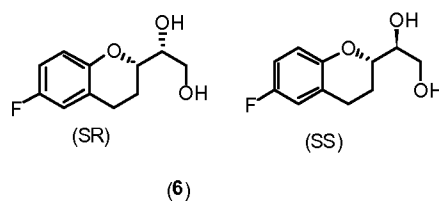
Then, a reducing agent (LiBH_4 , NaBH_4), and preferentially NaBH_4 , is added, and it is kept under stirring until complete disappearance of the alpha-hydroxy ketone intermediate **(4)** to obtain the diol **(3)**.

An aspect of the present invention relates to the procedure from the enantiopure chroman ester **(2)** according to which: under the same conditions described for the racemate ester **(2)**, the ester **(2)** as R isomer or, alternatively, as S isomer, is reacted until providing a mixture of diols **(5)** comprised of RS + RR isomers

- 13 -



or, alternatively, of a mixture of diols (6) comprised of SR + SS isomers



Another characteristic aspect of the present invention is the procedure enabling purification of the diols (3) or of the semichiral mixtures (5) or (6) obtained with the preceding method. This procedure envisages the dissolution of the crude product, obtained from the synthesis of diols as described above, into an organic polar solvent, such as methanol, ethanol, acetonitrile, DMF, DMI, NMP, and preferentially methanol, and the subsequent washing of the solution thus obtained with a C₅-C₁₀ alkane, immiscible with the former, and preferentially heptane. This washing enables to remove aliphatic apolar byproducts generated during the reaction with the organometallic compound, since the diol (3) or the corresponding mixtures of semichiral diols (5) and (6) are scarcely soluble in apolar organic solvents.

Another characteristic aspect of the present invention is represented by the reaction of formation of the epoxides (1), from the neighbouring diols (3), conducted by tosylation or mesylation and subsequent intramolecular nucleophilic substitution, two-stage or one-pot, carried out so as not to alter the initial diastereomeric ratio.

- 14 -

In this case it has surprisingly been found that treating the diol (**3**) with a base (selected from LiH, NaH, KH, tBuOK and preferentially NaH), in an organic solvent (selected from DMF, DMSO, NMP (N-methylpyrrolidone) and DMI (dimethylimidazolidone), preferentially DMF, and leaving the system under stirring for times higher than 1 hour, followed by addition of a mesylating or tosylating agent such as tosyl chloride, tosyl imidazole or mesyl chloride, and preferably tosyl chloride, results in the conversion *in situ* into epoxide without alteration of the initial ratio between the diastereoisomers.

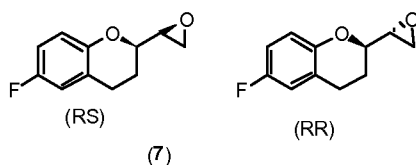
Alternatively, it has surprisingly been discovered that by treating the diol (**3**) with a preformed solution of DMSO and NaH, or of imidazole and NaH in an organic solvent, followed by addition of a tosylating agent, selected from tosyl chloride or tosyl imidazole, preferably tosyl chloride, the conversion *in situ* into epoxide is obtained without alteration of the initial ratio between the diastereoisomers. Alternatively, the same result is obtained by treatment of the diols dissolved into an organic solvent non-miscible with water, with a tosylating agent selected from tosyl chloride or tosyl imidazole, preferably tosyl chloride, under Schotten-Baumann conditions.

A further alternative is the treatment of a solution of the diol (**3**) into an organic solvent non-miscible with water and containing an organic base, preferentially diisopropylethylamine, cooled and maintained at a temperature lower than 25°C, preferentially lower than 4°C, with a solution of tosyl chloride in organic solvent, followed by addition of a 50% aqueous NaOH solution.

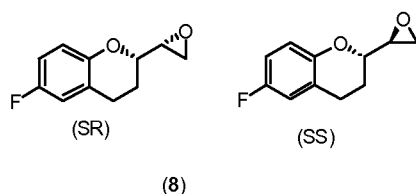
Likewise, it has been demonstrated and is therefore an object of the present invention that, treating with the hereto-described methods the 'semichiral' mixture of

- 15 -

RS + RR diols (**5**) or, alternatively, the 'semichiral' mixture of SR + SS diols (**6**), yields the 'semichiral' mixture of RS + RR epoxides (**7**),



or, alternatively, the 'semichiral' mixture of SR + SS epoxides (**8**)

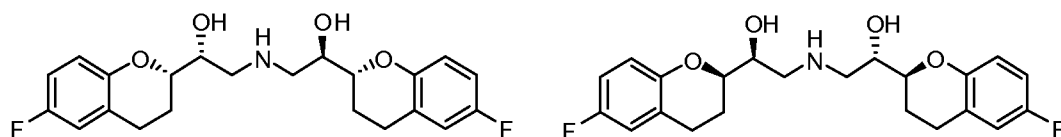


without alteration of the diastereoisomeric ratios.

By way of a non-limiting example, starting from the diol (**3**) (RS+SR:RR+SS mixture in a 1:1 ratio) obtained from the racemate ester (**2**) by the organometallic reaction described, it is obtained, by tosylation or mesylation and base-catalyzed nucleophilic intramolecular substitution according to any one of the above-described methods, the mixture (RS+SR:RR+SS) of epoxides (**1**) in a 1:1 diastereoisomeric ratio.

A further object of the present invention is the synthesis of nebivolol in the form of racemic mixture of the two enantiomers [2S[2R[R[R]]] α , α' -[imino-bis (methylene)] bis[6-fluoro-chroman-2-methanol] and [2R[2S[S[S]]] α , α' -[imino-bis (methylene)] bis[6-fluoro-chroman-2-methanol], having the following formulas

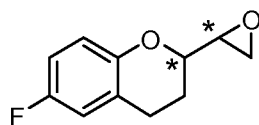
- 16 -



Nebivololol (SRRR + RSSS)

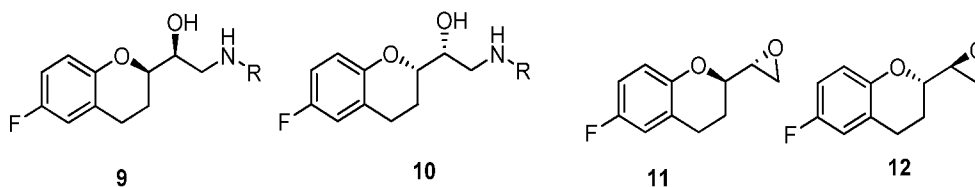
comprising the following steps:

a) a mixture of the four SR, RS, RR and SS isomers of the epoxide (1)



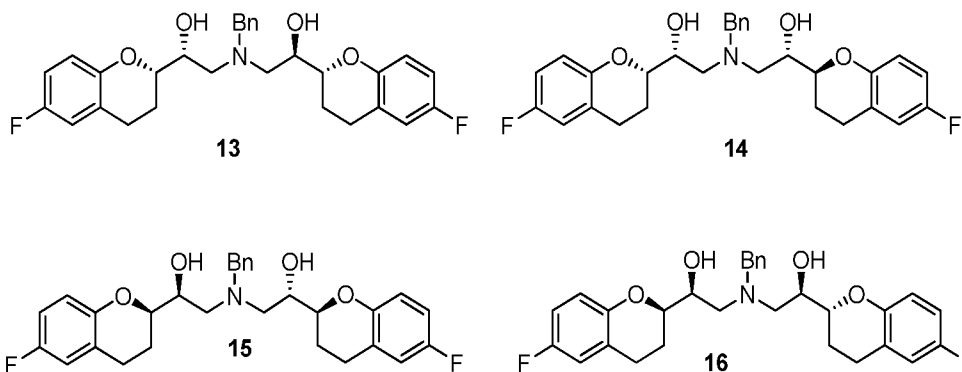
(1)

obtained according to one of the methods described hereto starting from the racemate ester (2), is reacted with benzylamine in a solvent represented by a sterically hindered alcohol selected from tert-BuOH, 2-methyl-2-butanol, 2-methyl-2-pentanol, used alone or in mixture with an apolar solvent, preferably cyclohexane, to obtain a mixture of the four compounds **9**, **10**, **11** and **12**, from which the pair **9/10** is separated from the pair **11/12**;



b) the amines **9** and **10**, in mixture, are reacted with the pair of epoxides **11** and **12**, in mixture, to obtain a mixture of four compounds (**13**, **14**, **15** and **16**);

- 17 -



c) the compounds **13** and **15** (RSSS + SRRR), in mixture, are separated from **14** and **16** by fractionated crystallization from 2-methyl-2-butanol, and subsequently from an ethyl acetate/cyclohexane mixture,

d) the protecting group benzyl is removed from mixture **13** and **15**, and the hydrochloride salt is optionally subsequently formed, to obtain the final product Nebivolol or Nebivolol hydrochloride.

Another aspect of the present invention consists in the synthesis of nebivolol, comprising the following steps:

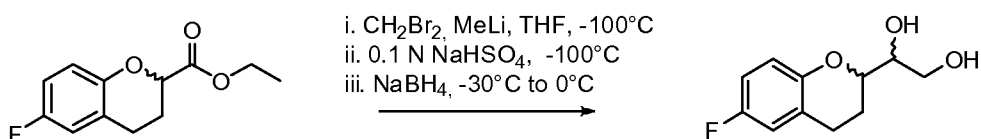
a) kinetically resolving the 'semichiral' mixture of epoxides (**7**), and/or separately the 'semichiral' mixture of epoxides (**8**), obtained according to the above-described methods starting respectively from the R or S chroman ester, by reacting them with benzylamine in a sterically hindered alcohol selected from tert-BuOH, 2-methyl-2-butanol, 2-methyl-2-pentanol, to obtain the compounds (**9**) and (**11**) and/or respectively the compounds (**10**) and (**12**).

b) reacting the amino alcohol (**9**) with the epoxide (**12**) to obtain the l-benzyl nebivolol (**15**) and/or the amino alcohol (**10**) with the epoxide (**11**), to obtain the d-benzyl nebivolol (**13**)

c) removing the protecting group benzyl with forming of D- and/or L-nebivolol.

EXAMPLES

EXAMPLE 1: Synthesis of
1-(6-fluorochroman-2-yl)ethane-1,2-diol **racemate**
diols



To a solution of racemate ethyl 6-fluorochroman-2-carboxylate (2.2 g, 10 mmol) and dibromomethane (1.35 mL) in anhydrous THF (40 mL) cooled to -100°C under nitrogen atmosphere, a solution of 1.6M MeLi in diethyl ether (11.2 mL), cooled beforehand to -78°C , was added dropwise, in a time of about 30 min. Stirring was maintained at -100°C for about 1.0 h in total, until disappearance of ester substrate (TLC control). Then, a 0.1N NaHSO_4 solution (5 mL) was added at the same temperature. At the end of the addition the temperature was slowly brought to $-30/-20^\circ\text{C}$ and the mixture stirred for 30 min. Then, NaBH_4 (0.3 g) was added and the resulting mixture mixed, after having removed the cooling bath, until complete reduction of the intermediate alpha-hydroxy ketone to diol (about 0.5 h). 1N NaHSO_4 was added to the mixture up to pH 5, the organic phase was separated and the aqueous phase extracted with EtOAc. The reunited organic extracts were washed with water, dried over Na_2SO_4 , filtered and concentrated at reduced pressure to obtain a yellow and viscous fluid (2.05 g). HPLC analysis indicated a 97% purity of the two diastereoisomeric pairs of diols (in a substantially 1:1 ratio).

For characterization purposes, the two diastereoisomeric pairs of diols were separated by flash chromatography on silica (eluent EtOAc/petroleum ether 1:1).

- 19 -

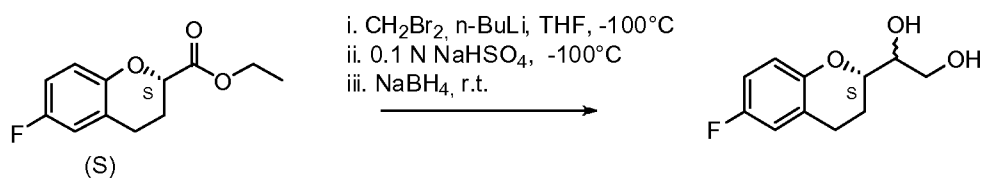
(RS/SR) isomer

¹H NMR (400 MHz, DMSO-d₆) δ 6.98-6.82 (m, 2H); 6.75-6.67 (m, 1H), 4.92-4.90 (d, 1H, J = 6.0 Hz); 4.57 (t, 1H, J = 6.0 Hz); 3.95-3.88 (m, 1H); 3.60-3.50 (m, 2H); 3.50-3.40 (m, 1H); 2.80-2.60 (m, 2H); 2.10-1.98 (m, 1H); 1.76-1.63 (m, 1H).

(SS/RR) isomer:

¹H NMR (400 MHz, DMSO-d₆) δ 6.98-6.80 (m, 2H); 6.75-6.67 (m, 1H), 4.80-4.76 (d, 1H, J = 6.0 Hz); 4.60 (t, 1H, J = 6.0 Hz); 4.00-3.94 (d, 1H, J = 14.0 Hz); 3.60-3.50 (m, 2H); 3.50-3.40 (m, 1H); 2.90-2.70 (m, 2H); 1.95-1.85 (m, 1H); 1.85-1.70 (m, 1H).

The configuration of the two diastereoisomeric pairs of diols was attributed on the basis of the pair of enantiomeric epoxides produced by each of them.

EXAMPLE 2: Synthesis of**(S)-1-(6-fluorochroman-2-yl)ethane-1,2-diol
semichiral diols**

To a solution of (S)-ethyl 6-fluorochroman-2-carboxylate) (18 g, 80.3 mmol) and dibromomethane (12.6 mL) in anhydrous THF (360 mL) cooled to -100°C under nitrogen atmosphere, a solution of 1.6M BuLi in hexane (101 mL), cooled beforehand to -78°C, was added dropwise, in a time of 30 min. Stirring was maintained at -100°C for 1.5 h in total, until disappearance of the ester substrate (TLC control). Then, a 0.1N NaHSO₄ solution (40 mL) was added at the same temperature. At the end of the addition, temperature was slowly brought to -30/-20°C and it was stirred for 30-50 min. Then, NaBH₄ (2.5 g) was added and the resulting mixture mixed until complete

- 20 -

reduction of the intermediate alpha-hydroxy ketone to diol (about 0.5 h). 1N NaHSO₄ was added to the mixture, up to pH 5, the organic phase was separated and the aqueous phase extracted with EtOAc. The reunited organic extracts were washed with water, dried over Na₂SO₄, filtered and concentrated under reduced pressure to obtain a yellow and viscous fluid (18 g). HPLC analysis showed a 1.1:1.0 ratio of the two (SR:SS) diastereoisomeric diols (**6**).

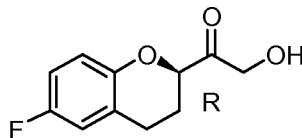
Analogously to what described in example 2, the (RS:RR) diols **5** were obtained starting from (R)-ethyl 6-fluorochroman-2-carboxylate).

Example 3: diol purification

The residue containing the diols from Example 2 (18 g) was dissolved in CH₃OH (2 volumes). The resulting solution was shaken with heptane (10 volumes). After phase separation, the methanol solution was concentrated under reduced pressure, obtaining a viscous residue (15 g). ¹H-NMR analysis indicated the absence of signals related to aliphatic impurities produced in the reaction of formation of the same diols. Following this purification step, the ratio of the two (RS:SS) diastereoisomeric diols remained unchanged.

Example 4: Isolation and characterization of intermediate alpha-hydroxy ketone

In order to demonstrate a possible reaction mechanism for the reaction described in Examples 1 and 2, the Inventors tried to isolate the intermediate alpha-hydroxy ketone (**4**) of the synthesis of RS:RR diols described by analogy in Example 2



(4)

The reaction solution, still at -20°C after

- 21 -

quenching with NaHSO₄ and before addition of the reducing agent, was quickly deposited on a 2.5 mm-thick preparative silica plate and run using EtOAc/hexane 1:1 as eluent; R_f = 0.4, UV detection. The product was recovered by cutting of the corresponding silica strip, subsequent washing with acetonitrile followed by solvent removal.

¹H NMR (400 MHz, CD₃CN) δ 6.95-6.70 (m, 3H); 4.75-4.70 (m, 1H); 4.60-4.38 (AB system, 2H, J = 17 Hz); 2.90-2.60 (m, 2H); 2.20-2.00 (m, 1H); 1.90-1.60 (m, 1H).

Alpha-hydroxy ketone (**4**) reduction with NaBH₄ produces the pair of diols RS:RR.

Example 5: Synthesis of epoxides (1) from diols (3)

Use of NaH and tosyl chloride in DMF.

To a solution of diols obtained according to Example 1 in a 1.1/1.0 diastereoisomeric ratio (200 mg, 0.80 mmol) in anhydrous DMF (6 mL, 30 volumes) NaH (48 mg, 2.0 mmol, 2.5 eq) was added. The mixture was left to equilibrate (1 hour), then tosyl chloride (305 mg, 1.60 mmol, 2 eq) was added. At the end of the reaction (8 hours), the mixture was diluted with MTBE (15 mL) and treated with 1M NaHSO₄ (10 mL). The organic phase was shaken with H₂O, dried over Na₂SO₄ and concentrated to dryness, giving a viscous residue. HPLC analysis showed the presence of epoxides (**1**) (75% purity) in a 1.1/1.0 diastereoisomeric ratio.

Example 6: Synthesis of epoxides (1) from diols (3)

Use of NaH and DMSO in methyl t-butyl eter and TsCl

To a NaH suspension (2.70 g, 0.07 mol, 4 eq) in MTBE (75 mL), anhydrous DMSO (10 mL, 0.14 mol, 8 eq) was added under N₂ atmosphere at 50°C. After 5-10 min, a solution of the diols (**3**) (5.00 g, 0.017 mol) in MTBE (75 mL) was added and the mixture was stirred at 50°C for 1 hour. After this period, a solution of tosyl chloride (5.00 g, 0.026 mol, 1.5 eq) in MTBE (50 mL) was added dropwise and the mixture was maintained under stirring for 1 hour,

- 22 -

controlling the pattern by HPLC. At the end of the reaction the mixture was filtered, the filtrate washed with MTBE (50 mL x 2) and the reunited filtrates washed with NaHSO₄ 1M (100 mL), NaHCO₃ (2x50 mL), and water (50 mL) and dried over Na₂SO₄. Solvent was removed under reduced pressure to yield a viscous residue (yield: 90%, HPLC purity: 95.5%, diastereomeric ratio between epoxides: unchanged).

Example 7: Synthesis of epoxides (1) from diols (3)

Use of NaH and imidazole

To a suspension of imidazole (190.6 mg, 2.80 mmol, 3.5 eq) and NaH (58 mg, 2.4 mmol, 3.0 eq) in a solvent such as DMF, DCM, THF, MTBE (3 mL) left under stirring for 10-15 min, the diols (200 mg, 0.80 mmol) (diastereoisomeric ratio: 1.0:1.0) dissolved in the solvent used (3 mL) were added, and after about 10 min tosyl chloride (213 mg, 1.10 mmol, 1.4 eq) was added. At the end of the reaction (2-3 hours), the mixture was diluted with MTBE (15 mL) and treated with 1M NaHSO₄ (10 mL). Organic phase was shaken with H₂O, dried over Na₂SO₄ and concentrated to dryness, giving a viscous residue. HPLC analysis showed the presence of diastereoisomeric epoxides in a 1.0/1.0 ratio (purity: 90%).

Example 8: Synthesis of epoxides (8) from diols (6)

Use of Schotten Baumann conditions

A biphasic system comprised of the diols (6, SR/SS, diastereoisomeric ratio: 1.1/1.0) (100 mg, 0.40 mmol) in DCM (2.0 mL, 20 vol) and of an aqueous solution of 50% NaOH (0.5 mL, 5 vol), was maintained under vigorous stirring for 1 hour. A solution of tosyl imidazole (115.6 mg, 0.52 mmol, 1.3 eq) in DCM (2.5 mL, 25 vol) was added dropwise to the suspension in 15 min at room temperature. At the end of the reaction (14 hours) the mixture was poured in water (2 mL), organic phase was separated, washed with water and dried over Na₂SO₄. Solvent was removed under reduced pressure, giving a viscous residue.

- 23 -

HPLC analysis showed the presence of diastereoisomeric epoxides (8) (73% purity) in a 1.1/1.0 ratio.

Example 9: Synthesis of epoxides (8) from diols (6)

Use of diisopropylethylamine and tosyl chloride at low temperature

To a solution containing the SR/SS diols (10.15 g, 47.87 mmol) (1.1/1.0), diisopropylethylamine (10.65 mL, 61.11 mmol, 1.3 eq) and dimethylaminopyridine (0.17 g, 1.43 mmol, 0.03 eq) in DCM (250 mL), tosyl chloride (10.9 g, 57.17 mmol, 1.2 eq) was added, at 0°C. The mixture was left under stirring at 4°C and, at the end of the reaction (12 hours), was treated with 2-(diisopropylamino)ethylamine (2.0 mL, 11.43 mmol, 0.2 eq) for 15 minutes, then shaken with 0.1 M NaHSO₄ and water. Alternatively, the mixture can be treated with 8.5 g of (aminomethyl) polystyrene resin (1.5 mmol/g) for about 1 hour and then filtered. To the separated organic phase 50% aqueous NaOH (30 mL) was added, and it was vigorously stirred to completion of the epoxides formation reaction (30 min). The mixture was diluted with water and the organic phase separated, it was washed with 1 M NaHSO₄, with water and finally dried over Na₂SO₄. The solvent was removed under reduced pressure, giving a viscous residue (11 g, yield: 95%, diastereoisomeric ratio of the epoxides (8): 1.1/1.0).

EXAMPLE 10: Kinetic resolution on the mixture of (SS + SR) epoxides.

A solution of the mixture of (SS +SR) epoxides (4.50 g, 22.5 mmol) and benzylamine (3.8 mL, 35 mmol) in 2-methyl-2-butanol (38 mL) was mixed at room temperature for 12 hours. At the end of the reaction, the amine (10, SR) formed was filtered under vacuum and dried (1.90 g, 6.30 mmol). The filtered solution was poured in cyclohexane (250 mL) and the solution thus obtained was washed with 1M NaHSO₄ (100 mL) and H₂O (50 mL x 2) and then concentrated under reduced pressure to obtain 1.30 g

- 24 -

(6.00 mmol) of (SS) epoxide (**12**).

Kinetic resolution on the mixture of (RS + RR) epoxides was conducted likewise what described in the above example.

EXAMPLE 11: Synthesis of (SSSR) benzyl l-nebivolol

The compound (RS)-2-benzylamino-1-(6-fluorochroman-2-yl) (**9**), coethanol and the epoxide (**12**, SS) were dissolved in absolute ethanol (6 mL) and maintained under reflux until disappearance of the starting reagents. At the end of the reaction the mixture was left to reach room temperature and the solvent was removed under reduced pressure.

EXAMPLE 12: Synthesis of (RRRS) d-benzyl nebivolol

The compound (SR)-2-benzylamino-1-(6-fluorochroman-2-yl) (**10**), ethanol and the epoxide (**11**, RR) were treated as in Example 11, to obtain d-benzyl nebivolol.

EXAMPLE 13: Synthesis of d,l-benzyl nebivolol

L-benzyl nebivolol described in example 11 (3.00 g) and d-benzyl nebivolol described in example 12 (3.00 g) were reunited and the mixture thus obtained (6.0 g) was collected again in 2-methyl-2-butanol (36 mL), heated to dissolution (80°C) and left at room temperature for 24h under light stirring. The obtained solid was filtered, collecting it again with 2-methyl-2-butanol (5 mL). It was dried on filter. 4.20 g of crystalline mixture having a 99.6% purity were obtained.

EXAMPLE 14: Synthesis of nebivolol hydrochloride

The compound d,l-benzyl nebivolol (2.0 g, 4.0 mmol) was dissolved in methanol (160 mL) along with 20% (1% b/w) Pd(OH)₂/C. The mixture was maintained under stirring, under hydrogen atmosphere. At the end of the reaction the catalyst was filtered on a porous septum, and concentrated HCl (0.52 mL) was added to the filtrate. The solution was concentrated under reduced pressure and the obtained residue was heat-treated with absolute

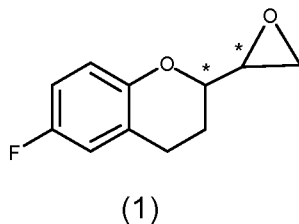
- 25 -

ethanol (20 mL). The obtained solid was filtered and dried under vacuum (1.7 g).

- 26 -

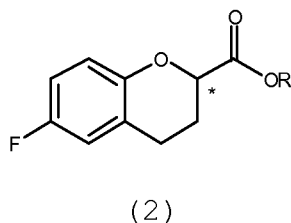
CLAIMS

1. A process for the preparation of a mixture of epoxides **(1)**, through the intermediate diol (3),

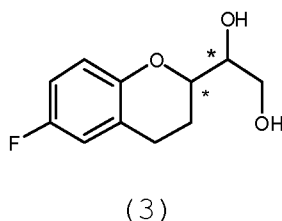


as intermediates in the synthesis of nebivolol, comprising the following synthetic steps:

a) reacting the ester **(2)**, wherein R is a C₁-C₆ alkyl group



with LiCH₂Br, at a temperature lower than -90°C in an inert solvent, subsequently adding an aqueous means at the same temperature, and thereafter treating the aqueous mixture with a reducing agent to obtain the mixture of the diol **(3)**;



b) transforming the mixture of the diol (3) thus obtained into the mixture of epoxides **(1)**.

2. The process according to claim 1, wherein step (b) comprises the following synthetic steps:

1. treating the mixture of the diol (3) with a mesylating or tosylating agent, and subsequently, by an intramolecular substitution, generating the

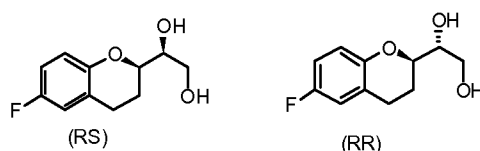
- 27 -

mixture of epoxides (1).

3. The process according to claim 1 or 2, wherein the diols (3) obtained at step (a) are purified by partitioning between a polar organic solvent and an apolar solvent immiscible with each other, the diol thus purified is then subjected to step (b).

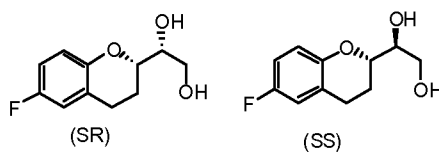
4. The process according to any one of the claims 1 to 3, wherein in step (a):

the ester (2) is reacted as R isomer or, alternatively, as S isomer, obtaining a mixture of diols (5) comprised of RS + RR isomers



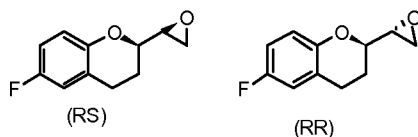
(5)

or, alternatively, of a mixture of diols (6) comprised of SR + SS isomers



(6)

b) treating the mixture of RS + RR diols (5) or, alternatively, the mixture of SR + SS diols (6), with a mesylating or tosylating agent to yield the 'semichiral' mixture of RS + RR epoxides (7)

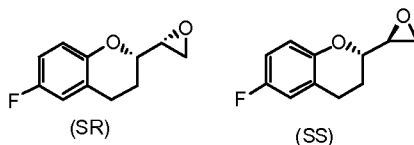


(7)

or, alternatively, the 'semichiral' mixture of SR +

- 28 -

SS epoxides (8) .



(8)

5. The process according to any one of the claims 1 to 4, wherein the synthetic step a) is conducted at a temperature comprised between -130°C and -95°C .

6. The process according to claim 5, wherein the temperature is comprised between -105°C and -95°C .

7. The process according to any one of the claims 1 to 6, wherein in synthetic step a) the aqueous solution used for the treatment may be neutral or acidic but anyhow used an amount such as to maintain the environment under alkalinity conditions.

8. The process according to any one of the claims 1 to 7, wherein group R represents an ethyl.

9. The process according to any one of the claims 1 to 8, wherein the organometallic compound LiCH_2Br is generated *in situ* by adding a BuLi solution to a solution containing the ester (2) and the CH_2Br_2 in an inert organic solvent at a temperature lower than -90° .

10. The process according to any one of the claims 1 to 9, wherein the reducing agent in synthetic step a) is selected from NaBH_4 or LiBH_4 , preferentially NaBH_4 .

11. The process according to any one of the claims 3 to 10 wherein, in the diol purification step, the polar organic solvent is selected from methanol, ethanol, acetonitrile, DMF (dimethylformamide), DMI (dimethylimidazolidinone), NMP (N-methylpyrrolidone), and preferentially methanol, and the apolar solvent immiscible with the former is a $\text{C}_5\text{-C}_{10}$ alkane or a mixture of $\text{C}_5\text{-C}_{10}$ alkanes, preferentially heptane.

12. The process according to any one of the claims 2 to 11, wherein in step (b) the mixture of the diols is

- 29 -

reacted in an organic solvent selected from dichloromethane, methyl tert-butyl ether, tetrahydrofuran, DMF, DMSO, NMP and DMI, and preferentially DMF, with a base selected from LiH, NaH, KH, tBuOK and preferentially NaH, optionally in the presence of a salt of lithium, potassium or cesium, and subsequently with a mesylating or tosylating agent selected from tosyl chloride (TsCl), tosyl imidazole and mesyl chloride, and preferentially TsCl.

13. The process according to any one of the claims 2 to 11, wherein, alternatively to what described in claim 12, the mixture of the diols is reacted with a system comprised of a preformed solution in an organic solvent, selected from DMSO/NaH, or of imidazole/NaH and a tosylating agent selected from tosyl chloride (TsCl), tosyl imidazole and preferentially TsCl.

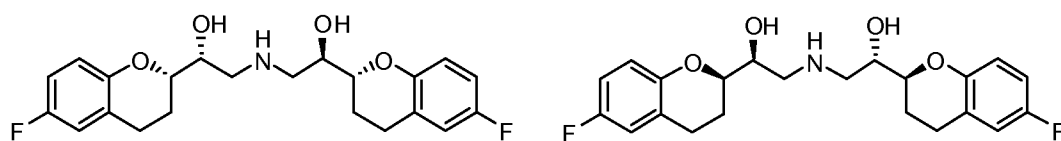
14. The process according to any one of the claims 2 a 11, wherein, alternatively to what described in claims 12 and 13, the mixture of the diols is reacted in an organic solvent non-miscible with water, with a tosylating agent selected from tosyl chloride or tosyl imidazole, preferably tosyl chloride, with 50% NaOH in water, under conditions provided for the Schotten-Baumann reaction.

15. The process according to any one of the claims 2 to 11, wherein, alternatively to what described in claim 12, 13 and 14, the mixture of the diols is reacted in an organic solvent non-miscible with water, and containing an organic base, preferentially diisopropylethylamine, cooled and maintained at a temperature lower than 25°C, preferentially lower than 4°C, with a solution of tosyl chloride in organic solvent, followed by addition of an aqueous NaOH solution.

16. The process comprising all steps according to any one of the claims 1 to 3 and 5 to 15 for the synthesis of nebivolol in the form of racemic mixture of

- 30 -

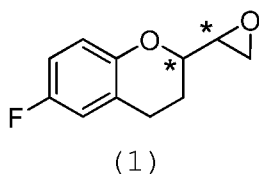
the two enantiomers [2S[2R[R[R]]] α , α' -[imino-bis (methylene)] bis[6-fluoro-chroman-2-methanol] e [2R[2S[S[S]]] α , α' -[imino-bis (methylene)] bis[6-fluoro-chroman-2-methanol], having the following formulas



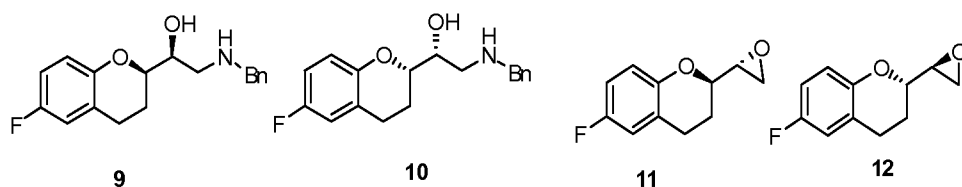
Nebivolol (SRRR + RSSS)

comprising the further steps wherein:

a) a mixture of the four SR, RS, RR and SS isomers of the epoxide of formula (1)

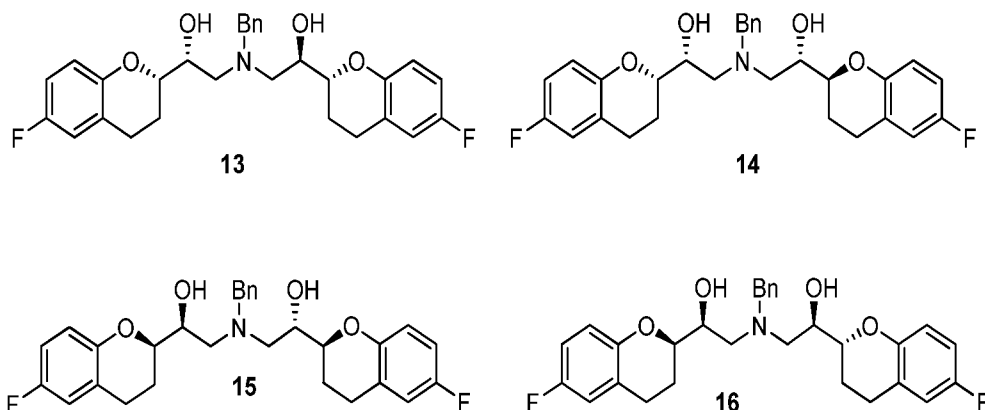


is reacted with benzylamine in a solvent represented by a sterically hindered alcohol selected from tert-BuOH, 2-methyl-2-butanol, 2-methyl-2-pentanol, used alone or in mixture with an apolar solvent, preferably cyclohexane, to obtain a mixture of the four compounds **9**, **10**, **11** and **12**, from which the pair **9/10** is separated from the pair **11/12**;



b) the amines **9** and **10**, in mixture, are reacted with the pair of epoxides **11** and **12**, in mixture, to obtain a mixture of four compounds (**13**, **14**, **15** and **16**);

- 31 -



c) the compounds **13** and **15** (RSSS + SRRR), in mixture, are separated from **14** and **16** by fractionated crystallization from 2-methyl-2-butanol, and subsequently from an ethyl acetate/cyclohexane mixture,

d) the protecting group benzyl is removed, and the hydrochloride salt is optionally subsequently formed, to obtain the final product Nebivolol or Nebivolol hydrochloride.

17. The process according to claims 4 to 15, for the synthesis of nebivolol, comprising the following steps:

a) kinetically resolving the 'semichiral' mixture of epoxides (**7**), and/or separately the 'semichiral' mixture of epoxides (**8**) by reacting them with benzylamine in a sterically hindered alcohol selected from tert-BuOH, 2-methyl-2-butanol, 2-methyl-2-pentanol, to obtain the compounds (**9**) and (**11**) and/or respectively the compounds (**10**) and (**12**);

b) reacting the amino alcohol (**9**) with the epoxide (**12**) to obtain the l-benzyl nebivolol (**15**) and/or the amino alcohol (**10**) with the epoxide (**11**) to obtain the d-benzyl nebivolol (**13**);

c) removing the protecting group benzyl with forming of D- and/or L-nebivolol.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/053956

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D311/58 C07D407/04
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/064827 A2 (ZACH SYSTEM SPA [IT]; VOLPICELLI RAFFAELLA [IT]; MARAGNI PAOLO [IT]; C) 5 June 2008 (2008-06-05) *see pp 9-10, 18-19 -----	1-17
A	WO 2010/034927 A1 (ZACH SYSTEM [FR]; DERRIEN YVON [FR]; CHENARD ERIC [FR]; BURGOS ALAIN []) 1 April 2010 (2010-04-01) cited in the application pages 6-11 -----	1-17
A	WO 2008/040528 A2 (ZACH SYSTEM SPA [IT]; VOLPICELLI RAFFAELLA [IT]; MARAGNI PAOLO [IT]; C) 10 April 2008 (2008-04-10) pages 7-8 ----- -/-	1-17

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 October 2012

Date of mailing of the international search report

17/10/2012

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Lauro, Paola

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2012/053956

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/041805 A1 (EGYT GYOGYSZERVEGYESZETI GYAR [HU]; TRINKA PETER [HU]; REITER JOZSEF [] 21 May 2004 (2004-05-21) pages 23-28; example 16 -----	1-17

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2012/053956

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008064827	A2	05-06-2008	AT 473224 T 15-07-2010
		AU 2007324896 A1	05-06-2008
		CA 2667919 A1	05-06-2008
		CN 101553485 A	07-10-2009
		EP 2099790 A2	16-09-2009
		EP 2228374 A1	15-09-2010
		ES 2346371 T3	14-10-2010
		HR P20100420 T1	30-09-2010
		JP 2010510969 A	08-04-2010
		SI 2099790 T1	30-09-2010
		US 2010056813 A1	04-03-2010
		US 2011201831 A1	18-08-2011
		WO 2008064827 A2	05-06-2008

WO 2010034927	A1	01-04-2010	AU 2009295730 A1 01-04-2010
		CA 2736600 A1	01-04-2010
		CN 102164906 A	24-08-2011
		EP 2328883 A1	08-06-2011
		JP 2012503636 A	09-02-2012
		US 2011237808 A1	29-09-2011
		WO 2010034927 A1	01-04-2010

WO 2008040528	A2	10-04-2008	AU 2007304419 A1 10-04-2008
		CA 2663339 A1	10-04-2008
		CN 101522656 A	02-09-2009
		EP 2078005 A2	15-07-2009
		JP 2010505779 A	25-02-2010
		US 2010069652 A1	18-03-2010
		WO 2008040528 A2	10-04-2008

WO 2004041805	A1	21-05-2004	AU 2003301857 A1 07-06-2004
		HU 0203810 A2	28-09-2004
		WO 2004041805 A1	21-05-2004
