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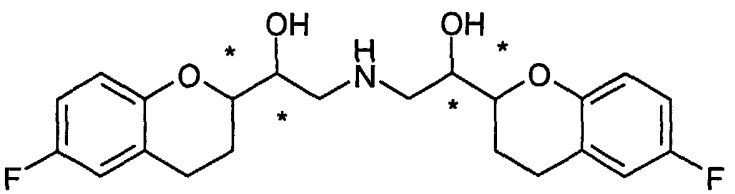
(54) Title: NEW PROCESS FOR THE PREPARATION OF RACEMIC ([2S[2R*[R[R*]]]] and ([2R[2S*[S[S*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluorochroman-2-methanol] AND ITS PURE [2S[2R*[R[R*]&



(I)

(57) Abstract: Process for the preparation of racemic ([2S[2R*[R[R*]]]]- and ([2R[2S*[S[S*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluorochroman-2-methanol] of the compound of the formula (I) and its pure ([2S[2R*[R[R*]]]]- and ([2R[2S*[S[S*]]]]-enantiomer compounds characterized in that the products are prepared from 4-fluoro-phenole or 4-fluoro-anisole via crystalline, optically active intermediates.

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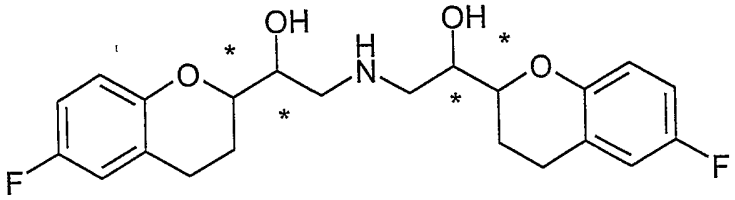
New process for the preparation of racemic ([2S[2R*[R[R*]]]] and ([2R[2S*[S[S*]]]]-(±)-α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] and its pure [2*S*[2*R**[*R*[*R**]]]]-, and [2*R*[2*S**[*S*[*S**]]]] enantiomers

TECHNICAL FIELD OF THE INVENTION

The invention relates to a new process for the preparation of ([2S[2R*[R[R*]]]] and ([2R[2S*[S[S*]]]]-(±)-α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the formula



I

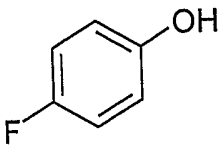
(whereafter nebivolol) and its pure [2*S*[2*R**[*R*[*R**]]]]-, and [2*R*[2*S**[*S*[*S**]]]] enantiomers.

Nebivolol is in the market as a practically side-effect free vasodilatation drug, which has β_1-adrenerg receptor blocking and vasodilatation properties with very favourable effect on the endogen formation of nitrogen monoxide.

Although the compound can have 16 stereoisomer forms theoretically because of four asymmetric centres in the structure, but the compound is symmetrical about an axis, which contains the nitrogen atom of the compound, therefore only 10 different stereoisomer forms exist.

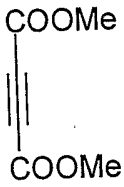
STATE OF THE ART

Preparation of nebivolol is described in the patent description US-4,654,362. 4-fluor-phenol of the formula



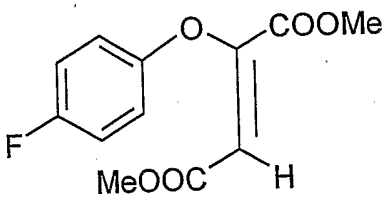
II

is the starting compound of the synthesis. It is reacted with dimethyl acethylenedicarboxylate of the formula



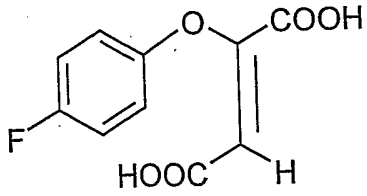
XXVIII

according to the description of the patent application No. EP 331078 obtained the compound of a phenoxy-ethylene compound of the formula



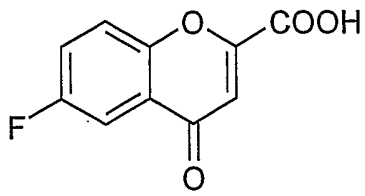
XXIX

This compound is hydrolysed in an alkali media to the compound of dicarboxylic acid compound of the formula



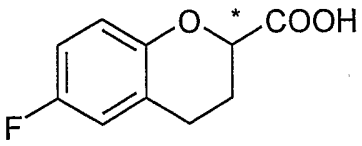
XXX

which is converted to the compound of chromanone compound of the formula



XXXI

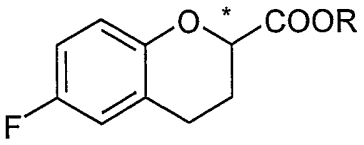
by reacting with sulphuric acid. This compound is transferred to the compound of racemic 6-fluoro-chroman-carbocilyc acid of the formula



XXXII

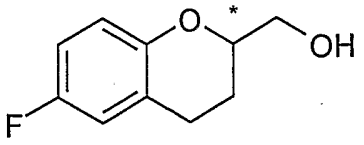
by catalytic hydrogenation.

Racemic 6-fluoro-chroman-carboxylic acid of the formula XXXII is esterified to the compound of the formula



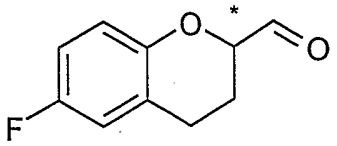
XXXIII

wherein R represents lower alkyl, which is reduced with sodium dihydro bis(2-methoxyethoxy) aluminate to the racemic methanol compound of the formula



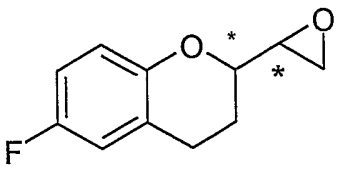
XXXIV

The product is reacted with oxalyl chloride and then triethylamine at -60 °C produced the racemic aldehyde of the formula



XXXV

The racemic aldehyde of the formula XXXV is reacted with sodium hydride, then trimethyl sulfoxonium iodide in a solution of dimethyl sulfoxide. A mixture of racemic RS and SR epoxides of the formula

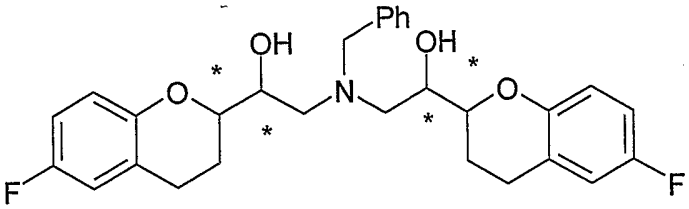


XXXVI-A racemate

XXXVI-B racemate

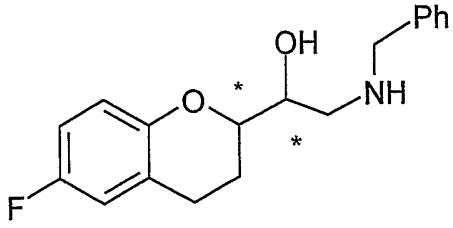
and of racemic SS and RR epoxides of the formula XXXVI-B are obtained. The mixture is separated by column chromatography, thus the oily A-isomer racemate of the formula XXXVI-A and the oily B-isomer racemate of the formula XXXVI-B are obtained.

The mixture of "A"-"B" isomer racemates of the formula



XXXVIII

can be prepared by reacting the compound of the formula XXXVI-A isomer racemate with benzylamine, the given racemic products of the formula



XXXVII-A racemate

XXXVII-B racemate

subsequently reacted with the compound of the formula XXXVI-B isomer racemate. The order of reactions can be changed. Thus, the compound of the formula XXXVI-B isomer racemate could be reacted with benzylamine. The given racemic product of the formula XXXVII-

B is reacted with the compound of the formula XXXVI-A isomer racemate.

There is no teaching to separate the given mixture. The mixture can be separated by preparative HPLC supposedly. The desired nebivolol of the formula I was obtained by elimination of the benzyl group of the pure isomer racemate "A" of the formula XXXVIII-A. The reaction is carried out by catalytic hydrogenation.

The process described above has several serious disadvantages. For example the quality of dimethyl acetylenedicarboxylate is very changeable even if it was bought from same supplier. The cause is the uncertainty of the preparation method of this product. The preparation of racemic aldehyde of the formula XXXV takes place at a very low (-60 °C) temperature, which requires special equipments.

Very serious disadvantage of the process is that the racemic aldehyde of the formula XXXV is very unstable. According to our experiments, the product given by vacuum distillation can not be used after standing a night at room temperature because it is changed considerably disintegrated.

Additional very serious disadvantage is that the racemates of the epoxides of the formula XXXVI, the RS and SR = A isomer and the RR and SS = B isomer are oily products. Their separation can be carried out by chromatographic, especially column chromatographic process, which is very difficult to use in industrial scale. There is no teaching in the description of the separation of the mixture of racemates (A and B) of the formula XXXVIII. According to our experiments the separation can be carried out only by chromatographic method.

We tried to transform the racemic mixture of the compound of the formula "A" and "B" to the racemic mixture of the compound of the formula I by catalytic reduction. We expected that the separation of the desired product of the racemic compound A (nebivolol) from the other racemic compound can be carried out by crystallisation. The separation of mixture of the compounds of raceme "A" and "B" is not possible by recrystallisation nevertheless several different solvents are used.

The preparation of the compounds of SSSR and RRRS isomers of the compound nebivolol is described in the patent description EP 334-429 patent application. The substance of this invention is that the chromene-4-on-carboxylic acid compound of the formula XXXI obtained by catalytic hydrogenation (83% yield) of the 6-fluoro-chroman-2-carboxylic acid of the formula XXXII, the product is resolved than the obtained (+)-(S)-6-fluoro-chroman-carboxylic acid and the (-)-(S)-6-fluoro-chroman-carboxylic acid products are reacted separately according to reaction steps described in the US-4,654,362 patent application.

The 6-fluoro-chroman-2-carboxylic acid compound of the formula XXXII is resolved using (+)-dehydroabietylamine. The yield of the compound of (+)-(S)-6-fluoro-chroman-carboxylic acid is 11,3%, of the compound of (-)-(S)-6-fluoro-chroman-carboxylic acid is 9,2 % on the basis of the racemic compound.

The compound of (+)-(S)-6-fluoro-chroman-carboxylic acid is transferred to the aldehyde compound of the formula XXXV (S) at -70°C with 57,9% yield, then the oily compound of (+)-[S(S)]-6-fluoro-2-oxiranyl-chroman of the formula XXXVI (S) is obtained with 9,8 % yield after the separation by chromatographic method. The yield on the

basis of the 6-fluoro-chromane-4-carboxylic acid compound of the formula XXXII is 0,64%, the total yield on the basis of the compound of chromene-4-one-carboxylic acid is 0,53%.

The compound of (-)-(R)-6 -fluoro-chroman-2-carboxylic acid is transferred to the compound of methyl ester of the formula XXXIII (R) wherein R stands for a methyl group, with 82,6% yield, then it is reduced to the aldehyde compound of the formula XXXV (R) at -80°C with[bis(2-methyl-propyl)]-aluminium hydride. The compound of (-)-[R(S)]-6-gluoro-2-oxiranyl-chromanone of the formula XXXVI (R) is obtained with 24,8% yield by the reaction of the aldehyde compound with trimethyl-sulfoxonium iodide, then purified by HPLC. The yield on the basis of the 6-fluoro-chromane-4-carboxylic acid compound of the formula XXXII is 1,9%, the total yield on the basis of the compound of chromene-4-one-carboxylic acid of the formula XXXI is 1,9%.

The compound of (-)-[R(S)]-benzylamine of the formula XXXVII (R) is obtained with 38,1% yield by reaction of the compound of (-)-[R(S)]-6-fluoro-2-oxiranyl-chroman with benzylamine, then the product was reacted with (+)-[S(S)]-epoxide compound of the formula XXXVI (S). Then the benzyl group is eliminated by hydrogenation from the previously obtained ([2R[2S*[S[S*]]]]-benzyl compound, thus obtained the l-nebivolol of the formula I (R,S,S,S) with 42 % yield.

(The yield on the basis of the compound of (-)-[R(S)]-6-fluoro-2-oxiranyl-chromanone of the formula XXXVI (R) is 16%, the yield on the basis of the 6-fluoro-chromane-4-carboxylic acid compound of the formula XXXII is 0,30%, the total yield on the basis of the

compound of chromene-4-one-carboxylic acid of the formula XXXI is 0,25 %.)

The compound of d-nebivolol is prepared in the same manner, using intermediates of formulas XXXV, XXXVI, XXXVII, and XXXVIII, although this synthesis is not described fully in the cited description.

Serious disadvantage of this synthesis is that the resolvation of the compound of the formula XXXII can be carried out with poor yield by using (+)-dehydroabiteinamine and (-)-dehydroabiteinamine. It is very difficult to get at these very expensive reagents. Additional disadvantage is that only one of the two enantiomers can be prepared pure which is shown by the values of optical rotation of the compounds. Using the described conditions the two values of optical rotation can be same instead of the described values of +14,88° and -13,39°.

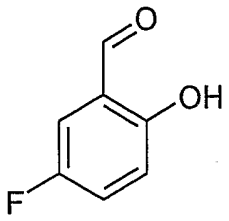
Additional disadvantages of this synthesis are that the several steps of it are carried out at a very low (-70 °C, or -80 °C) temperature which requires special equipments, furthermore the compound of S(S)-epoxide of the formula XXXVI (S) and the compound of R(S)-epoxide of the formula XXXVI (R) are separated by HPLC which is not feasible in industrial scale.

The strategy of the descriptions of the patent US-4,654,362 and EP-334-429 are same, a chroman structure is prepared , which contains a one carbon containing ligand on its second carbon atom, from which either racemic or optically active aldehyde is obtained, then the aldehyde is transferred to an epoxide of the formula XXXVI by chain elongation. The epoxide compounds are separated by chromatograph, then reacted with benzylamine obtained racemate compounds of the

formula XXXVIII. The isomer racemate is supposedly purified by chromatography, then the benzyl group is eliminated, obtained the nebivolol.

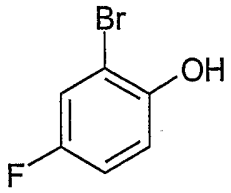
The description of J. Am. Chem. Soc. 1988, 120, 8340-8347 has a different strategy.

Salicylic aldehyde of the formula



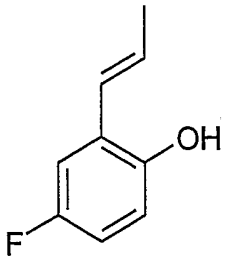
XL

prepared either from the compound of 4-fluoro-phenol of the formula II or from the compound of 2-bromo-4-fluoro-phenol of the formula



XXXIX

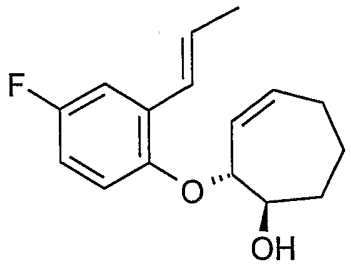
is transferred to the compound of 2-propenyl-4-fluoro-phenol of the formula



XLI

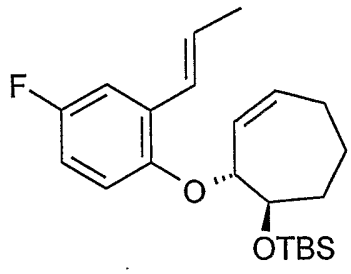
at -78°C. This compound is reacted with 1,2-epoxy-3-cycloheptene, which can be easily produced from cycloheptadiene. The compound of

anti-2-[2-(1'-propenyl)-4-fluoro-phenoxy]-3-cyclohepten-1-ol of the formula



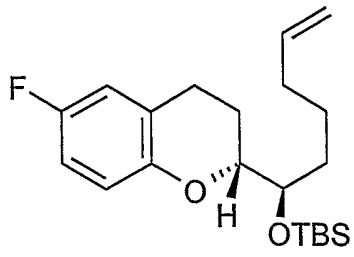
XLIII (rac)

is obtained. The free hydroxyl group of the compound of the formula XLIII is protected by reacting with tert-buthyl-dimethyl-silyloxy-triflate at -78 °C, then the antipodes are separated using (R)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl) zirconium-biphenol ((R)-(EBTHI)Zr-biphenol). The obtained compound of anti-2(R)-[2-(1'-propenyl)-4-fluoro-phenoxy]-1(R)-tert.-buthyl-dimethyl-silyloxy-3-cycloheptene of the formula



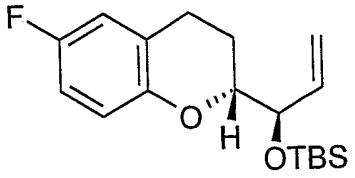
XLIV (R,R)

is transformed to the compound of 2(R)-(1(R)-tert.-buthyl-dimethyl-silyloxy-5-hexenyl)-6-fluoro-chroman of the formula



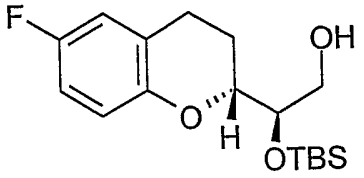
XLV (R,R)

using a complicated molybdenum catalyst, then the given compound reacted with palladium/charcoal produced 2(R)-(1(R)-tert.-buthyl-dimethyl-silyloxy-5-hexyl)-6-fluoro-chroman of the formula XLV (R,R) The product is transferred to 2(R)-(1(R)-tert.-buthyl-dimethyl-silyloxy-2-propenyl)-6-fluoro-chroman of the formula



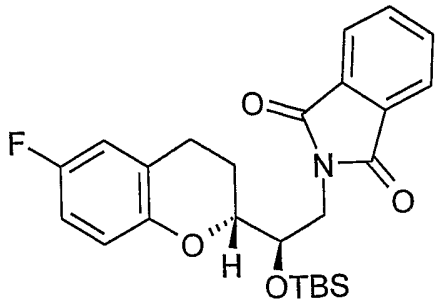
XLVII (R,R)

by irradiation with UV light. It is reacted with ozone, then sodium borohydride, thus the 2(R)-1(R)-2-hydroxyethyl compound of the formula



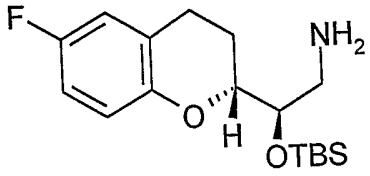
XLVIII (R,R)

is obtained. The product is reacted with tributhylphosphine and phtalimide in subsequently reaction steps. The given product, the 2(R)-1(R)-2-phtalimidyl-ethyl compound of the formula



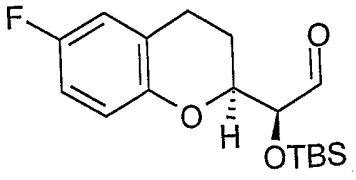
XLIX (R,R)

is reacted with hydrazine to remove the phtalimidyl group, thus obtained the compound of 2(R)-2-(2'(R)-tert.-buthyl-dimethyl-silyloxy-2-aminoethyl)-6-fluoro-chroman of the formula



L (R,R)

Racemic compound of anti-2-[2-(1'-propenyl)-4-fluoro-phenoxy]-3-cyclohepten-1-ol of the formula XLIII is reacted with tertier-buthyl-dimethyl-silyloxy-triflate (TBSOTf), the given racemic tert.-buthyl-dimethyl-silyloxy-ether of the formula XLIV is transferred to syn-2(S)-[2-(1'-propenyl)-4-fluoro-phenoxy]-1(R)-tert.-buthyl-dimethyl-silyloxy-3-cycloheptene of the formula XLIV (S,R) by using (S)-ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium biphenol ((S)-(EBTHI)Zr-biphenol). The obtained product is converted to (S)-(1'-tert.-buthyl-dimethyl-silyloxy-5-hexenyl)-6-fluoro-chroman of the formula XLV (S,R) in presence of difficult molybdenum catalyst as described above, then it is transferred via the compound of the formula XLVI (S,R) into 2(S)-(1(R)-tert.-buthyl-dimethyl-silyloxy-5-propenyl)-6-fluoro-chroman of the formula XLVII according to the description above. The product is converted to the compound of 2(S)-(1(R)-tert.-buthyl-dimethyl-silyloxy-2-oxo-ethyl)-6-fluoro-chroman of the formula

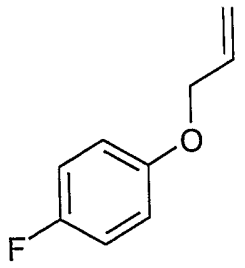


LI (S,R)

The last step of the synthesis is the reductive condensation of the compound of aldehyde of the formula LI (S,R) and the compound of amine of the formula L (R,R), in which the d-nebivolol is produced by acidic hydrolysis of the compound of (-)-[S,R,R,R]-∝,∝'-imino-[bis(methylene)-bis-(6-fluoro-chroman-2-tert.-buthyl-dimethyl-silyloxy-methyl].

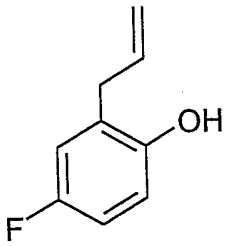
The strategy is based on the synthesis of chroman ring and stereo selective formulation of its side chain ∝ carbon atom. This aim can be solved only with a formation of a difficult, long side chain. Resolvation requires usage of an unusual (R)-(EBTHI)Zr-biphenol reagent, which is not marketed, the side chain is eliminated by photochemical reaction, then it is reacted with ozone at -78°C. After these synthesis steps several additional steps are required to obtain the key compounds of the synthesis, the amine of the formula L (R,R) and the aldehyde of the formula LI (S,R). This synthesis is not feasible in industrial scale too, because the use of very special catalysts and the unusual dilution of the reaction mixture in the photochemical step of the synthesis. Ozonolysis makes the method uneconomical with its dangerous and extreme circumstances and requires special equipments. Yields of synthesis steps are low. The last steps are described only in mg scale.

Another synthesis is of d-nebivolol of the formula I (S,R,R,R) is described in the Tetrahedron 56, 6339 (2000). The starting compound is 4-fluoro-phenol of the formula II, which is reacted with allylbromide to give an O-allyl-ester of the formula



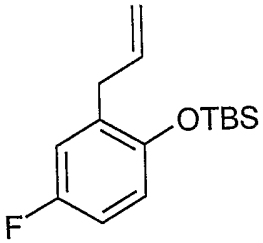
LIII

This product is isomerised to 2-allyl-fuoro-phenol of the formula



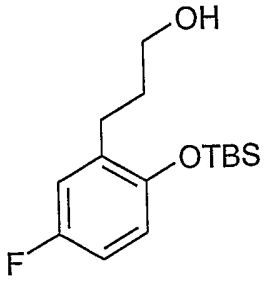
LIV

in circumstances of Claisen reaction, then the phenolic hydroxyl group is protected with 2-tert.-buthyl-dimethyl-silyl chloride given the compound of the formula



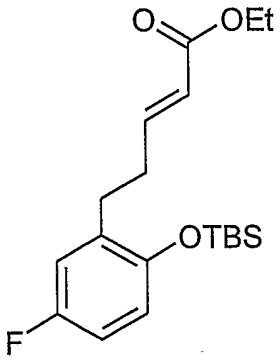
LV

subsequently water addition is performed onto the allyl-group in basic media with a complex of borane/dimethyl sulfide/hydrogen peroxide, thus obtained a propanol compound of the formula



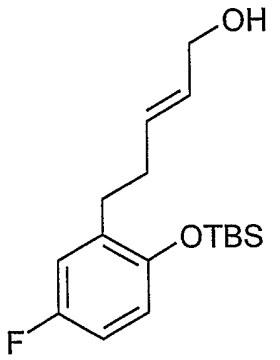
LVI

The product is converted to a 2-pentanoate of the formula



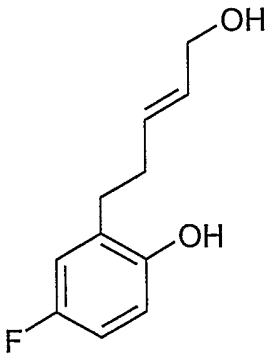
LVII

by the reaction with Dess-Martin reagent, then a Wittig olefin synthesis, using ethyltriphenylphosphorane as reactant. The pentanoate compound is reduced with DIBAL-H reagent to (E)-pentenol of the formula



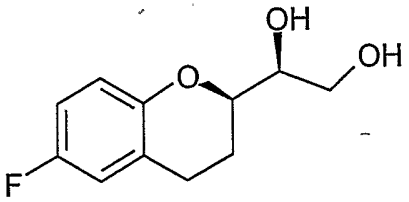
LVIII

at -10°C. The pentenol compound containing free phenolic hydroxyl group of the formula



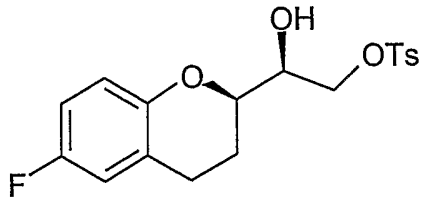
LIX

is obtained by elimination of silyl group. Subsequently the product is subjected to the Sharpless asymmetrical epoxidation reaction and cyclisation in the same time in presence of (+) diethyl L-tartrate, the given product of 2-chromenyl-(2S)('R)-1,2-ethanediol compound of the formula



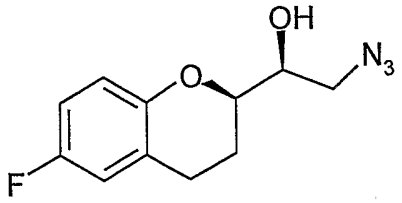
LX

is tosylated with tosyl-chloride, the tosyl-ester of the formula



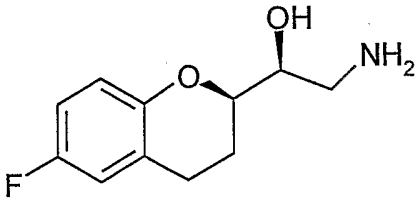
LXI

is reacted with sodium azide. The key intermediate of the synthesis is obtained by transformation of azide compound of the formula



LXII

to the amine compound of the formula

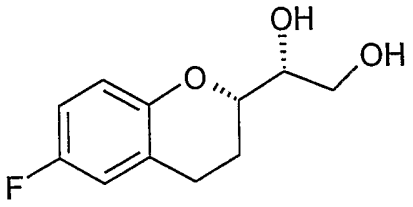


LXIII

which is isolated as hydrochloride salt followed by catalytic hydrogenation of the compound of the azide compound.

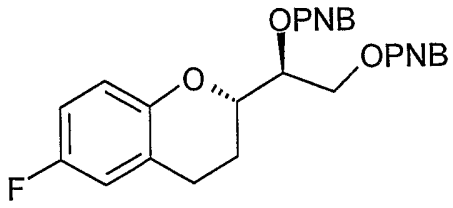
In an other line of the synthesis, the phenolic pentenole compound of the formula LIX is subjected to Sharpless asymmetrical

epoxidation reaction and cyclisation in the same step in presence of (-) diethyl D-tartrate, the given product of 2-chromenyl-(1S)-1,2-ethanediol compound of the formula



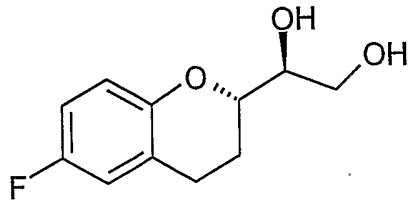
LXIV

reacted with diaza-dicarboxilate, triphenylphosphine and p-nitro-benzoic acid in Mitsunobu reaction conditions. Beside the inversion of the C_2 carbon atom di-(4-nitro-phenyl-carbonyl-oxy) compound of the formula



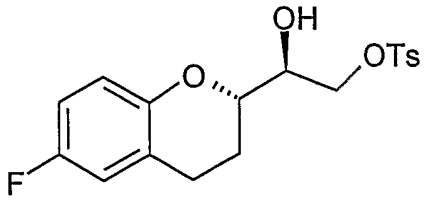
LXV

is obtained. Followed the removing of the alcohol-protecting groups with sodium methylate, the given product, the diol compound of the formula



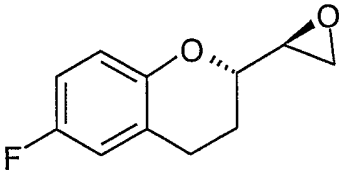
LXVI

is transferred to a mono-methyl compound in basic media. The obtained product is transferred to the tosylate compound of the formula



LXVII

which is subjected to a reaction with sodium-methylate to obtain the epoxide compound of the formula



LXVIII

D-nebivolol of the formula I (S,R,R,R) is obtained by condensation of the amine of the formula LXIII and the epoxide of the formula LXVIII in presence of borontrifluoride etherate.

Although it is impressive that the synthesis uses same intermediates to the Sharpless-reaction it has some serious disadvantages. It is known from the literature (Org. React. 48, 1-300, 1996), that the Sharpless asymmetrical epoxidation reaction has 90 % stereo selectivity in the best case, but it is not rare case that the stereo selectivity is of this reaction only 65%. Most of the compounds of this synthesis are oily products except tosylate compounds of the formula LXI and LXVII and the amine-hydrochloride compound of the formula LXIII. The oily compounds are purified by chromatography. The chromatography process does not increase the stereo selectivity, all intermediates have low stereo selectivity. The given optical purity data of the d-nebivolol of the formula I (S,R,R,R) (c= 0,02g/100ml optical rotation is +0,038°) is similar to the data given in the article J. Am. Chem. Soc. 1988, 120, 8340-8347, in which c= 0,0027g/100ml optical rotation is +0,04°) but using this low concentration with this low rotation value it can not be used to confirm the optical purity.

According to our experiments, the optical purity can be defined correctly by using the chirally HPLC method. Accuracy of this process +- 2%, therefore we gave the optical purity of our products in our examples 98 %, although all are found as 100% optically pure compounds.

Additional disadvantage of this process, that the Sharpless reaction requires not only the cheap (-)-diethyl-D-tartrate, but the expensive (+)-diethyl-L-tartrate is necessary, which is difficult to get at.

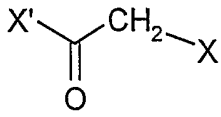
SUMMARY OF THE INVENTION

We found surprisedly that all disadvantages described can be eliminated by using a new synthesis strategy for producing nebivolol, in which a two carbon atoms long ligand is formed containing two hydroxyl group in protected form on the chroman ring and containing an oxo group on its 4th position. Even, the two protected hydroxyl groups or one of them can be protected with cheap d-, or l-glycerinealdehyde in the desired stereochemically form. In this case, after the elimination of protection of hydroxyl group, crystalline diastereomer products are given, which "resolve" themselves. Beside the shorter synthesis, it is not needed to use expensive agents to resolve the enantiomers.

DETAILED DESCRIPTION OF THE INVENTION

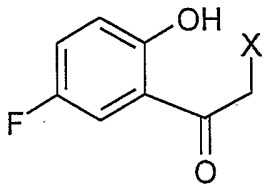
According to our invention the product can be prepared as follows:

The 4-fluoro-phenol of the formula II or the 4-fluoro-anisole is reacted in the Friedel-Crafts reaction with a compound of haloacetyl halogenide of the general formula



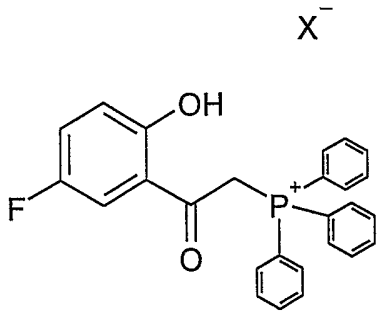
IV

wherein X and X' stand for same or different halogen atom, preferably with bromoacetyl bromide or chloroacetyl chloride, most preferably with chloroacetyl chloride to a haloacetyl compound of the general formula



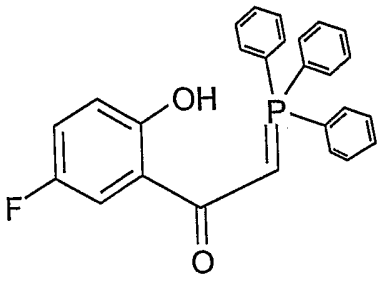
V

wherein X is defined above, which is reacted with triphenylphosphine to give the stabile and solid phosphonium salt of the general formula



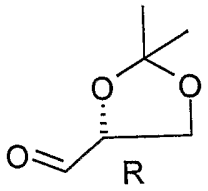
VI

wherein X is defined above. The salt described above reacted with weak base to yield a stabile, solid storagable phosphanylidene-etanone compound of the general formula



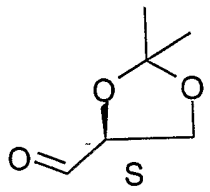
VII

The phosphanylidene-etanone compound of the general formula VII is reacted separately with a protected glycerinealdehyde compound of the formula



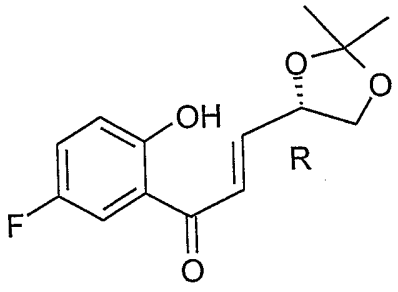
VIII (R)

or



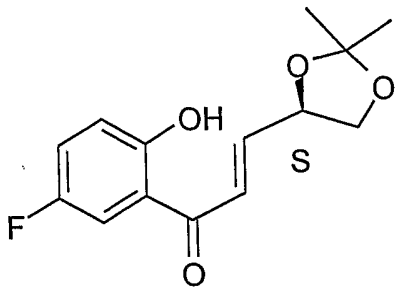
VIII (S)

the obtained product is the ethylene compound of the general formula of



IX (R)

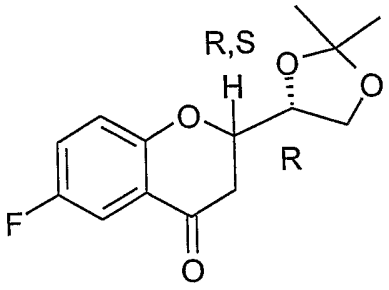
or



IX (S)

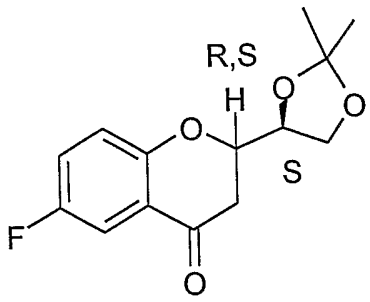
Compounds of the general formula of VIII (R) or VIII (S) can be easily prepared from D-mannit or C-vitamin according to the literature (VIII (R): Org. Synth. Coll. Vol. IX, 1998, 450, VIII (S): Org. Synth. Coll. Vol. IX, 1998, 455).

The chroman-4-one diastereomer mixtures of the general formula



X (R,R+S,R)

or



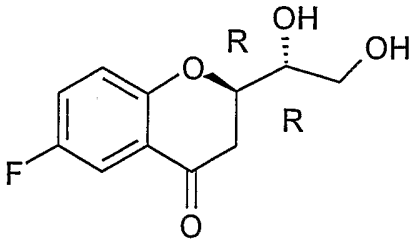
X (R,S+S,S)

are obtained by subjecting the compounds of the general formula of IX (R) or IX (S) to ring closure in a basic media.

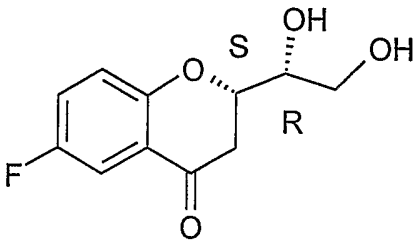
In desired case, the chroman-4-one diastereomer mixtures of the general formula X (R,R and S,R) or X (S,S and R,S) are separated with chromatograph, obtained pure crystalline chroman-4-one

diastereomers of the general formula X(R,R), X(S,R), X(R,S) and X(S,S).

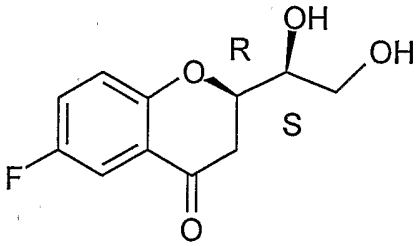
The pure crystalline chroman-4-one diastereomers of the general formula X(R,R), X(S,R), X(R,S) and X(S,S) are subjected to acidic hydrolysis, the pure crystalline chroman-4-one diols are obtained of the general formula



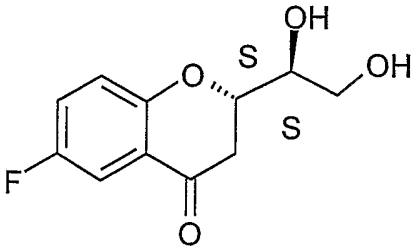
XII (R,R)



XII (S,R)

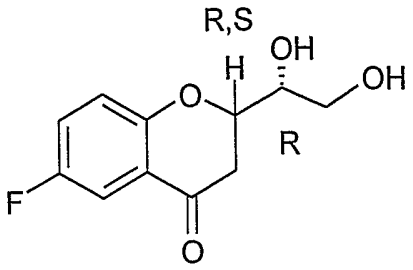


XIII (R,S)



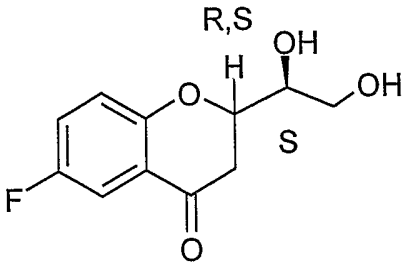
XIII (S,S)

According to our invention the diastereomer mixture of the compound of the general formula



XI (R,R +S,R)

or

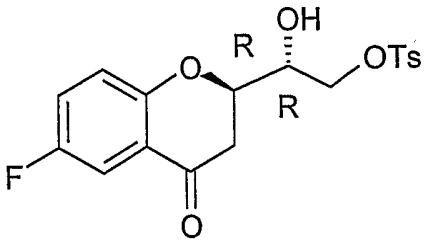


XI (R,S +S,S)

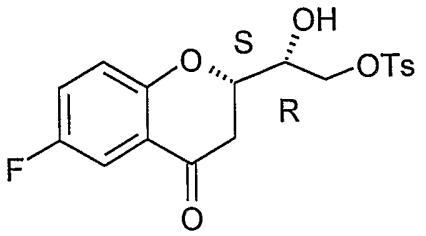
can be prepared by removing the protecting group with acidic hydrolysis of the diastereomer mixtures of the general formula X (R,R and S,R) or X (S,S and R,S). The desired pure enantiomers of the general formula XII (S,R) or XIII (R,S)
can be produced by recrystallisation of the compound of general formula XI (R,R and S,R).

The pure enantiomers of the general formula XII (R,R) or XIII(S,S) can be prepared if it is necessary.

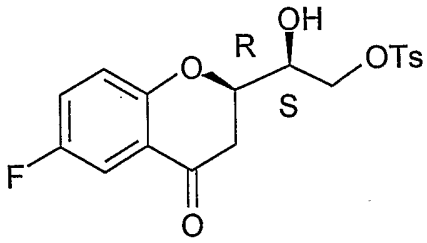
Subsequently all enantiomers of the general formula XII(R,R), XII(S,R), XIII(R,S), XIII(S,S) are separately tosylated to the corresponding tosylates of the general formula



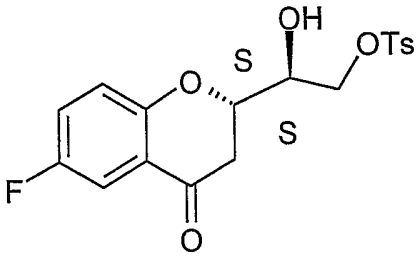
XIV (R,R)



XIV (S,R)



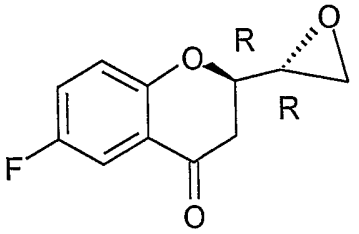
XV (R,S)



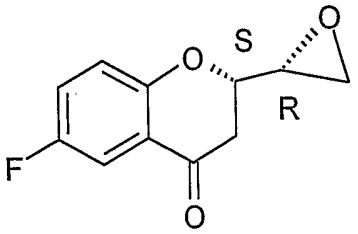
XV (S,S)

According to one of the more advantageous variations of our invention, pure tosylate compounds of the general formula XIV(R,R) XV(S,S) can be prepared easily by the crystallisation of the reaction mixture obtained from the tosylation of the residue of the filtrate remained from the recrystallisation of the compound of general formula XII (S,R) or XIII (R,S), which were crystallised from the mixture of chroman-diol compounds of the general formula XI (R,R and S,R) or XI (S,S and R,S).

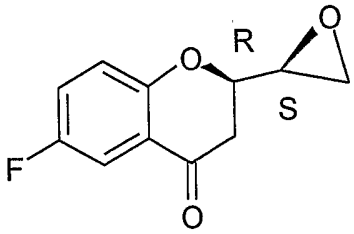
Subsequently the tosylates of the general formula XIV(R,R), XIV(S,R), XV(R,S), XV(S,S) are separately transferred, to corresponding crystalline oxyranes of the formula



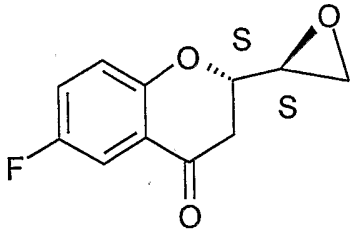
XVI (R,R)



XVI (S,R)

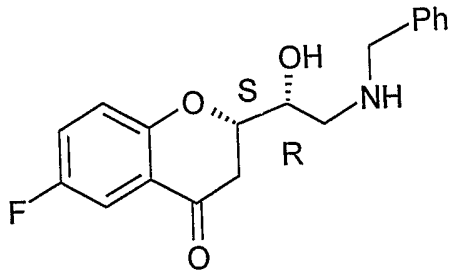


XVII (R,S)



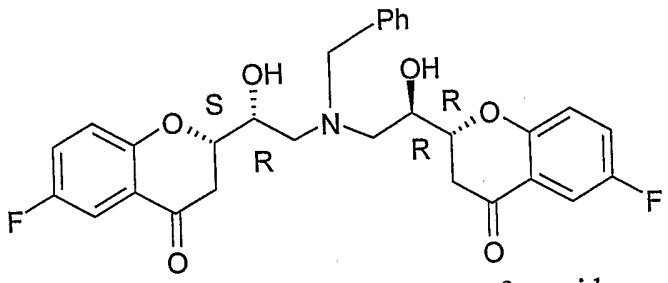
XVII (S,S)

The oxirane compound of the genera formula XVI (S,R) is reacted with benzylamine, the benzyl-amino compound of the formula



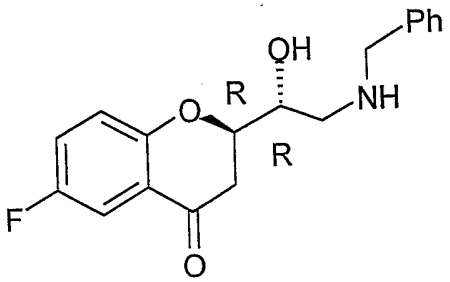
XVIII (S,R)

is produced, which is reacted with an oxirane compound of the formula XVI (R,R). Thus, the compound of the formula



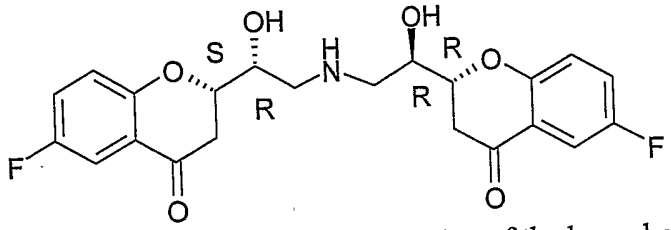
XIX (S,R,R,R)

is obtained. The order of the reactions of epoxide compounds can be changed, thus the intermediate can be the compound of the formula



XX (R,R)

The diketo compound of the formula

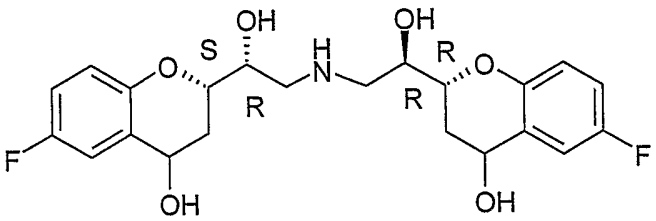


XXI (S,R,R,R)

is prepared by catalytic hydrogenation of the benzyl compound of the formula XIX (S,R,R,R) in a solution containing lower alkanol or a mixture of lower alkanol and water in presence of heavy metal,

preferably palladium /charcoal catalyst, using 1,5-3 bar, preferably 2 bar pressure and room temperature.

The diol compound of the formula

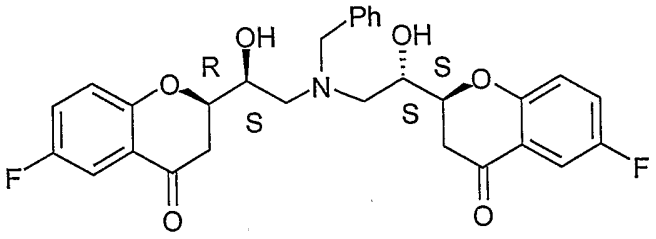


XXII (S,R,R,R)

is prepared by catalytic hydrogenation of the benzyl compound of the formula XIX (S,R,R,R) in a solution containing lower alkanol, a mixture of lower alkanol and water or in a solution containing acetic acid in presence of heavy metal, preferably palladium/charcoal catalyst, under 1,5-3 bar, preferably 2 bar pressure at 40-50°C temperature, or the compound of the formula XXI (S,R,R,R) is reduced onward according to the circumstances described above.

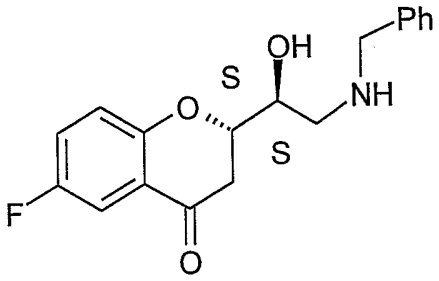
The pure d nebivolol of the formula I (S,R,R,R) is prepared by catalytic hydrogenation of the benzyl compound of the formula XIX (S,R,R,R) in a solution containing lower alkanol, a mixture of lower alkanol and water or in a solution containing inorganic acid, preferably hydrochloric acid in presence of heavy metal, preferably palladium/charcoal catalyst under 2-5 bar, preferably 3 bar pressure at 50-55°C temperature, or the compound of the formula XXI (S,R,R,R) or XXII (S,R,R,R) are reduced in a solution containing lower alkanol, a mixture of lower alkanol and water or in a solution containing inorganic acid, preferably hydrochloric acid in presence of heavy metal, preferably palladium on charcoal catalyst, under 2-5 bar, preferably 3 bar pressure at 50-55°C temperature onward according to the circumstances above.

The reactions mentioned above are repeated with the epoxide compound of the formula XVII (R,S). The obtained benzylamino compound of the formula XXIII(R,S) is reacted with the epoxide compound of the formula XVII (S,S). The given product is the N-benzyl-diketone compound of the formula



XXIV (R,S,S,S)

The sequence of the reactions of epoxide compounds of the formula XVII (R,S) and XII (S,S) can be changed, thus the intermediate can be the benzyl-amino compound of the formula



XXV (S,S)

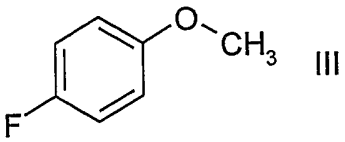
too. The pure l-nebivolol of the formula I (R,S,S,S) is prepared in similar manner as described above by hydrogenation of N-benzyl-diketone compound of the formula XXIV (R,S,S,S) via the intermediates of the formula XXIV (R,S,S,S) and XXV (R,S,S,S).

The marketed racemic nevibolol is a mixture of l-nebivolol and d-nebivolol in a ratio 1:1. The compound of racemic nebivolol of the formula I can be produced directly in a very favourable manner by hydrogenation of a mixture of the N-benzyl-diketone compound of the formula XIX (S,R,R,R) with the N-benzyl-diketone compound of the formula XXIV (R,S,S,S) in a solution containing lower alkanol, a mixture of lower alkanol and water or in a solution containing

inorganic acid, preferably hydrochloric acid in presence of heavy metal, preferably palladium on charcoal catalyst under 2-5 bar, preferably 3 bar pressure at 50-55°C temperature.

The Friedel-Crafts reaction of the 4-fluoro-phenol of the formula II with haloacetyl halogenide, wherein X and X' stand for same or different halogen atom is carried out as it is known in the literature, for example Pharm. Chem. J. (Eng.Transl.), 23, 12 (1989), and J.Indian Chem. Soc. 37, 687 (1960).

Friedel-Crafts reaction of the 4-fluoro-anisole of the formula



III

with chloroacetyl chloride is carried out in a halogenated solvent, preferably in dichloromethane or 1,2-dichloroethane more preferably in dichloromethane, at the temperature between room temperature and temperature of the boiling point of the used solvent. The processing of the reaction mixture is carried out in the known manner, the reaction mixture is poured onto ice, the organic layer is dried and evaporated. Thus, the obtained crude oily product of the formula V, wherein X stands for a chloro atom is ready to use to the next synthesis step, but it can be crystallised by adding cyclohexane.

The reaction of the compounds of the formula V wherein X defined above with triphenylphosphine obtains the compound of the general formula VI, wherein X defined above. The reaction is carried out in a polar protic, or aprotic solvent preferably in methanol, ethanol, propanol, isopropanol, acetonitrile, dichloromethane or 1,2-dichloroethane, between 0-120°C preferably between 10-100°C more preferably between 20-80°C temperature. The product is separated

from solvent and easy to filtrate. The given phosphonium salts are stable, they have good storage properties and they can be used directly in the next step.

The phosphonium salts can be transferred into phosphanylidene-etanon compounds with weak base, like solid hydrogen-carbonates, preferably sodium or potassium hydrogen carbonate more preferable sodium hydrogen carbonate preferably in a mixture of water and a chloroinated solvent, more preferably in a mixture of water and dichloromethane. The product is obtained followed the separation and drying of the dichloromethane layer and evaporated to dryness in vacuum. This stable product has good storage stability and can be used directly in the next reaction step.

The reaction of the phosphanylidene-etanon compound with the glycerinealdehyde compound of the formula VIIII(R) or VIIII(S) is performed in a solvent which is immiscible in water, preferably chloroinated solvent, more preferably dichloromethane, at temperature between 0-60°C preferably between 10-40°C more preferably at room temperature. After completion of the reaction, the mixture is washed with water, dried and the solvent is evaporated. Some ether, preferably diethyl ether is added to the residual oil, then the side product of the reaction of the compound of triphenylphosphine-oxide separated as crystalline, then the mixture is filtrated, and the solvent is evaporated. Lower alkyl alcohol, preferably isopropanol is added to the residual oil, then the product of the reaction of the desired compound of the formula IX (R), or IX(S) is separated as crystalline, thus the product is filtered.

The ring closure of the ethylene compounds of the formula IX (R) or IX(S) to the mixture of the protected chroman-4-one

diastereomers of the formula X (R,R and S,R) or the mixture of diastereomers of the formula X (R,S and S,S) performed by reacting with a strong basis, preferably reacting with an alkali hydroxide, for example lithium, sodium or potassium hydroxide, more preferably with lithium hydroxide or with an organic quaterner ammonium hydroxide, preferably tetramethyl ammonium hydroxide in a solution of water or in a mixture of water and lower alkyl alcohol, or in a mixture of water and tetrahydrofurane at the temperature between 10-100°C preferably between 20-80°C more preferably at 60°C. The product is extracted from reaction mixture with a polar solvent which is immiscible in water, preferably with diethyl ether, the organic layer is separated, dried and the solvent is evaporated. Thus the obtained residue, the oily products of the diastereomers of protected chroman-4-ones are suitable for use to the next step. In desired case the diastereomers of protected chroman-4-ones of the formula X(R,R), X(S,R), X(R,S) and X(S,S) can be obtained as pure crystalline followed by chromatographic separation.

The protecting group can be removed from the protected chroman-4-ones of the general formula X in a mixture of water and of acid preferably in a mixture of water and an organic acid, more preferably in mixture of water and acetic acid, at the temperature between 20-100°C preferably between 40-80°C more preferably at 65°C under stirring. The obtained products, the compounds of chroman-4-ones of the formula XII (R,R), XII(S,R), XIII(R,S) and XIII(S,S) are evaporated in vacuum to eliminate the solvent, then the oily residue is crystallized. For the crystallisation of the pure enantiomer compounds of the formula XII (R,R), XIII (S,S) lower alkyl ether preferably diethyl ether, in the case of the enantiomer

compounds of the formula XII(S,R) and XIII(R,S) a mixture of an organic ester preferably ethylacetate and aliphatic hydrocarbon preferably n-hexane can be used. The ratio of the organic ester and aliphatic hydrocarbon is 1:2 preferably.

For the preparation of pure compounds of chroman-4-ones of the formula XII(R,R), XII(S,R), XIII(R,S) and XIII(S,S) it is not necessary to separate the mixture of the protected chroman-4-one diastereomers of the formula X (R,R and S,R) and the mixture of diastereomers of the formula X (R,S and S,S) in advance, because after removing the protecting group in an acidic-aqueous media and removing the solvent as described above, the obtained diastereomers of the formula XI (R,R and S,R) or from the mixture of diastereomers of the formula X I (R,S and S,S) obtained as an oily residue which can be crystallised from a mixture of ethylacetate and n-hexane in ratio 2:1. The obtained crystalline product is the compound of the formula XII (S,R) or XIII(R,S). After the evaporation of the solvent of filtrate the oily residue is recrystallised from diethyl ether, thus pure crystalline product of the formula XII(R,R) or XIII(S,S) is obtained.

Tosylation of enantiomer compounds of the formula XII(R,R), XII(S,R), XIII(R,S) and XIII(S,S) to their corresponding chromanon-diol-tosylates can be carried out in a chloroinated solvent preferably in dichloromethane, in presence of an organic base as an acid binding agent, preferably pyridine, or pyridine is used as solvent at the temperature -10- +25°C preferably at 0°C. After the completion of reaction the acid binding agent is removed by extraction with water, the organic layer is dried, the solvent evaporated, then the product is crystallised from lower alkyl ether preferably from diethyl ether and filtered, thus pure crystalline tosylates are obtained.

In case of use of pyridine as solvent, the reaction mixture is diluted with water, then, the precipitated product is solved in a solvent immiscible in water and processed as described above.

A favourable variation of the process of our invention is that after removing the protecting group from the diastereomers of the formula XI (R,R and S,R) or from the mixture of diastereomers of the formula XI (R,S and S,S) in an acidic-watery media only the enantiomers of the formula XII (S,R) or XIII (R,S) are crystallised, the filtrate enriched in the compounds of formula XII(R,R) or XIII(S,S). They are s transferred into corresponding tosylates of the formula XIV (R,R) or XV (S,S) which have good crystallisation properties and they are more insoluble than the compounds of the formula XIV (S,R) or XV (S,R) and they can be easily obtained by simple crystallisation and filtration.

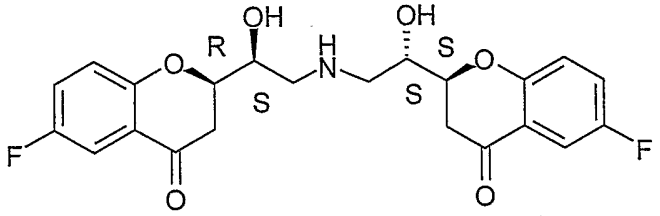
The transformation of tosylates of the general formula XIV (R,R), XIV (S,R), XV (R,S) and XV (S,S) to corresponding crystalline oxyranes of the general formula XVI (R,R), XVI (S,R), XVII (R,S) and XVII (S,S) is performed in an organic aprotic solvent preferably in acetonitrile using basic media preferably an organic base more preferably triethylamine, at the temperature 10- 50°C preferably at room temperature. After completion of reaction, the reaction mixture is evaporated to dryness in vacuum, water is added to the crystalline residue, filtered, then purified by recrystallisation from lower alkyl ether, preferably from diethyl ether.

The reaction of oxyranes of the general formula XVI(R,R), XVI(S,R), XVII(R,S) or XVII(S,S) with benzylamine to the benzyl-amino compounds of the formula XVIII (S,R), XX (R,R), XXIII (R,S) or XXV (S,S) is carried out in an organic aprotic solvent preferably in

acetonitrile in presence of an alkali perchloroate preferably lithium perchloroate at the temperature -10 - +10°C preferably at 0°C. The reaction mixture is poured onto ice and the precipitated crystalline product is filtered, then purified by recrystallisation from a lower alkyl alkanol preferably from isopropanol.

The reaction of benzyl-amino compounds of the formula XVIII (S,R), XX (R,R), XXIII (R,S) or XXV (S,S) and the oxyranes of the general formula XVI(R,R), XVI(S,R), XVII(R,S) or XVII(S,S) is performed by melting after pulverizing and mixing of components. The used temperature is 100- 160°C preferably 145°C. During the cooling of the reaction mixture the compound of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) is crystallised in a high purity (HPLC purity is >98%).

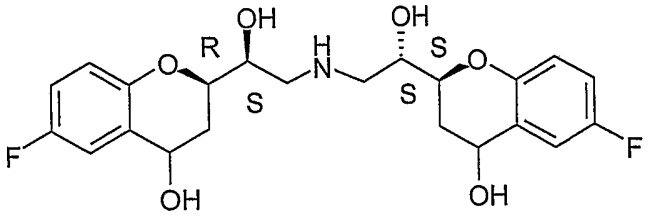
The compounds of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) can be hydrogenated to the corresponding diketo compounds of the formula XXI (S,R,R,R) or



XXVI (R,S,S,S)

in presence of heavy metal preferably, 10 % palladium/charcoal catalyst in a mixture of water and a lower alkyl alkanol preferably in a solution of water and ethanol or water and methanol or in a solution of anhydrous lower alkyl alkanol, preferably in ethanol or methanol at room temperature.

Diol compounds of the formula XXII(S,R,R,R), or



XXVII (R,S,S,S)

are obtained in case of the hydrogenation of the compounds of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) under 1,5-3 preferably 2 bar, in a mixture of water and a lower alkyl alkanol preferably in a solution of water and ethanol or water and methanol or in a solution of anhydrous lower alkyl alkanol, preferably in ethanol or methanol or acetic-acid at temperature 45- 50°C, or in case of the hydrogenation of the diketo compounds of the formula XXI (S,R,R,R) or XXVI (R,S,S,S) onward.

The pure d-nebivolol of the formula I (S,R,R,R) or l-nebivolol of the formula (R,S,S,S,) is the product in case of the hydrogenation of the compounds of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) under 1,5-3 preferably 3 bar, in a mixture of water and a lower alkyl alkanol preferably in a solution of water and ethanol or water and methanol or in a solution of anhydrous lower alkyl alkanol, preferably in ethanol or methanol in presence of an inorganic acid preferably hydrochloric acid at temperature 50- 55°C, or the in case of the hydrogenation of diketo compounds of the formula XXI (S,R,R,R) or XXVI (R,S,S,S) or diol compounds of the formula XXII(S,R,R,R), or XXVII (R,S,S,S) onward.

The hydrogenation is performed as described above in case of hydrogenation of the mixture of the compound of formula XIX (S,R,R,R) and the compound of formula XXIV (R,S,S,S) in a ratio 1:1.

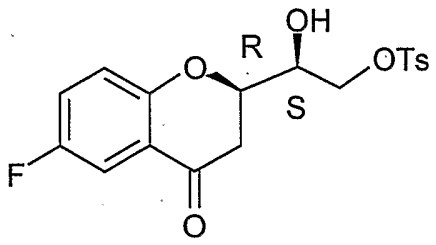
The diketo compound of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) and the diol compound of the formula XXII(S,R,R,R) or XXVII (R,S,S,S) can be isolated from the reaction mixture after hydrogenation by diluting the reaction mixture, then the reaction mixture is filtered, the solvent evaporated, and the residue is recrystallized.

The compound of the formula I (S,R,R,R) or I (R,S,S,S) can be obtained by the filtration of the reaction mixture of hydrogenation reaction, then the filtrate is partly evaporated and then the precipitated product as its hydrochloride is filtered.

In case the desired compound is the base of the formula I (S,R,R,R) or I (R,S,S,S), it can be obtained by the filtration of the reaction mixture of hydrogenation reaction, then the filtrate is partly evaporated, diluted with water then the given suspension is neutralized with an alkalimetal hydrogen carbonate preferably sodium hydrogen carbonate, then the hydrochloride salts turned to free basic form and precipitated, thus the product can be filtered.

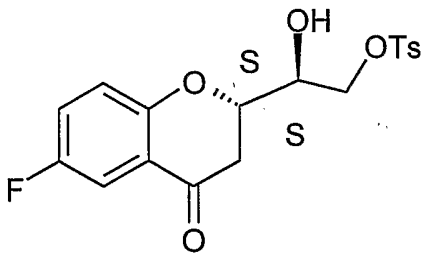
This invention relates to a new process for the preparation of the racemic ([2S[2R*[R[R*]]]]- and ([2R[2S*[S[S*]]]]-(±)-α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the compound of the formula I and its ([2S[2R*[R[R*]]]]- and ([2R[2S*[S[S*]]]]- enantiomers characterized in that 4-fluorophenol of the formula II or 4-fluoro-anizole of the formula III are objected to a Friedel-Crafts reaction with a haloacetyl halogenide of the general formula IV, wherein X and X' are same or different halo atoms, the obtained haloacetyl compound of the formula V, wherein X defined above reacted with triphenylphosphine, the given phosphonium salt of the general formula VI, wherein X defined above is treated with a

weak acid, the obtained phosphanylidene compound of the formula VII is reacted separately with a glycerinealdehyde compound of the formula VIII (R) or VIII(S), the given ethylene-compound of the formula IX (R) or IX(S) is subjected to a ring closure reaction in basic condition, the given protected chroman-4-ones of the formula X(R,R and S,R) or X (R,S and S,S) are subjected to acidic hydrolysis to eliminate the protecting group. The obtained chroman-4-one diol of the formula XI (R,R and S,R) or XI (R,S and S,S) is transformed to the enantiomer compound of formula XII (R,S) or XIII (R,S) and the pure diastereomer compounds of the XII (R,R) or XIII (S,S) are prepared with the work up of the filtrate of the crystallisation, then the chroman-4-one diol compounds are separately tosylated to pure enanatiomer tosylate compounds of the formula XIV (S,R), XIV (R,R),



XV (R,S)

or



XV (S,S)

or the filtrate of the crystallisation of the enantiomer compounds of formula XII (R,S) or XIII (R,S) prepared from chroman-4-one diol of the formula XI (R,R and S,R) or XI (R,S and S,S) are evaporated then

the residue is subjected to tosylation, tosylates of the formula XIV (R,R) and XV (S,S) are obtained.

Tosylates of the formula XIV (S,R), XIV (R,R), XV (R,S) or XV (S,S) are separately reacted with base to the corresponding oxirane compounds of the formula XVI (S,R), XVI (R,R), XVII (R,S) or XVII (S,S) which are reacted with benzylamine. The corresponding benzyl-amino compounds of the formula XVIII (S,R), XX (R,R), XXIII (R,S) or XXV (S,S) are prepared, the obtained benzyl-amino compounds are reacted with the proper oxirane compound of the formula XVI (S,R), XVI (R,R), XVII (R,S) or XVII (S,S), the given N-benzyl-diketo compounds of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) are hydrogenated under 1,5-3 bar pressure, in a solution of a lower alkanol or a lower alkanol-watery or in a solution containing acetic acid in presence of heavy metal catalyst at 40-50°C, or the diketo compound is hydrogenated onward in the circumstance described above, the diol compound of the formula XXII (S,R,R,R) or XXVII (R,S,S,S) is obtained,

or the N-benzyl-diketo compounds of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) are hydrogenated in presence of heavy metal catalyst, at 50-55°C, under 2-5 bar pressure in a solution of a lower alkanol and water preferably in a solution of water and methanol in presence of an inorganic acid, or diol compound of the formula XXII (S,R,R,R) or XXVII (R,S,S,S) the diketo compound of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) is hydrogenated onward in the circumstance described above, obtained the pure ([2R[2S*[S[S*]]]]-(±) -α,α' - [imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the compound of the formula I I (S,R,R,R) or,

([2S[2R*[R[R*]]]]-(±)-α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the compound of the formula I (R,S,S,S),

or the mixture of N-benzyl-diketone compounds of the formula XIX (S,R,R,R) and XXIV (R,S,S,S) in a ratio 1:1 is hydrogenated in presence of a heavy metal catalyst at 50-55°C under 2-5 bar pressure in a mixture of water and a lower alkyl alcohol preferably water and ethanol or water and methanol in presence inorganic acid to obtain the racemate , ([2S[2R*[R[R*]]]] and ([2R[2S*[S[S*]]]]-(±)-α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the compound of the formula I (R,S,S,S+S,R,R,R).

Optical purity of D-nebivolol prepared according to our invention can be characterised that values of optical rotation in different concentrations are as follows: $[\alpha]_D^{20}$(c=0,2 methanol) = 20,8°, $[\alpha]_D^{20}$(c=0,02 methanol) = 18±2° (±2° is the accuracy in this concentration range).

The value of the optical rotation of d-nebivolol can be compared with the values described in literature $[\alpha]_D^{20}$(c=0,02 methanol) = 0,04 ° (J. Am Chem. Soc.b 1998, **120,** 8340-8347) and $[\alpha]_D^{20}$(c=0,02 methanol) = 0,038 ° (Tetrahedron **56**, 6339 (2000)).

The main advantages of the process according to present invention are as follows:

1. The use of protected optically active glycerinealdehyde compounds of the formula VIII(R) or VIII(S) causes that the α-hydroxyl group of the diol side chain at the 2nd place of the chroman-4-on structure is formed as an optically active group and it "resolves" the compound without other resolving agent.

2. The oxo- group at the 4th position of the chroman structure causes that the intermediates are crystalline compounds, which makes the purification of diastereomer intermediates easy without chromatography.

3. Serious advantage is that the pure tosylates of the formula XIV (R,R) and XV (S,S) are obtained with good yield by simple recrystallisation, without chromatographic separation from the reaction mixture, which is given by tosylation of the filtrate, which is produced from the crystallisation of the compound of the formula XII (S,R) or XIII (R,S) from of diastereomer mixtures of the formula XI (R,R and S,R) or XI (R,S and S,S).

4. Additional advantage is that the phosphanylidene compound of the formula VII used in Wittig reaction is a stable compound and it has good storage properties without time limit and special conditions.

5. All steps of the synthesis according to present invention undergo between 0-145°C therefore the process does not require special equipments.

Further details of our inventions are described in the examples below without limiting our invention to these examples:

Example 1

2-chloro-1-(5-fluoro-2-hydroxy-phenyl)-ethanone

146,7 g (1,1 moles) of anhydrous aluminium chloride is added during 30 min. into a solution of 124,2g (87,5 ml, 1,1 moles) of chloroacetyl chloride and 126,1 g (114,6 ml, 1,0 moles) of 4-fluoro-anisole in 750 ml dichloromethane. Aluminium chloride is dissolved and the temperature of the reaction mixture is increased from 24°C to 38°C (during the developing of gas, the solvent is gently refluxed). The yellowish-brown solution is stirred at room temperature for 72 hours, then it is poured onto a mixture 1500g of cracked ice and 250ml of water during 40 minutes under vigorous stirring. The icy solution is stirred until all of ice is melted, then layers are separated. The layer containing water is washed with 2x100 ml of dichloromethane, the collected organic layer is washed with 2x100 ml of water. The dichloromethane layer is dried over sodium sulphate, filtered, and the solvent is evaporated. 130 g of cyclohexane is added to the 188 g yellowish oily product. The product is crystallised, filtered and washed with cyclohexane. Thus 152 g (80,5%) yellow powder is obtained. Additional 8,4g (4,5%) product is prepared by partial evaporation of the filtrate. Thus the total yield is 85%. The crude product is ready to use in the subsequent reaction.

The crude product can be purified by under reduced pressure (at 0,1 torr), thus 131 g of pure product can be crystallised from cyclohexane after distillation of 150 g of the crude product described above. The melting point of pure product is: 55,6-58°C. (This product is characterised only in the J. Indian Chem. Soc. 37, 687 (1960) as an oil with 177°C/10 torr boiling point.)

Example 2

[2-(5-fluoro-2-hydroxy-phenyl)-2-oxo-ethyl]-triphenyl-phosphponium chloride

183,4 g (0,7 moles) of triphenylphosphine is added to a solution of 132,0 g (0,7 moles) of 2-chloro-1-(5-fluoro-2-hydroxy-phenyl)-ethanone in 1100 ml acetonitrile at room temperature and the obtained suspension is stirred for 37 hours. The precipitated product is filtered and washed with acetonitrile. Thus the obtained product is 270,2 g (85,5%) white crystalline. Additional 24,0 g (7,5%) of [2-(5-fluoro-2-hydroxy-phenyl)-2-oxo-ethyl]-triphenyl-phosphponium chloride can be prepared by evaporation of filtrate to its fifths part. Thus the total yield is 93%. The crude product is ready to use in the subsequent reaction.

Example 3

[2-(5-fluoro-2-hydroxy-phenyl)-2-oxo-ethyl]-triphenyl-phosphonium chloride

The process is same as in Example 2 except 143,3 g (0,76 moles) of crude 2-chloro-1-(5-fluoro-2-hydroxy-phenyl)-ethanone is used instead of pure one. The yield is 279,2+26,0 g (81,5+7,5%). The quality of the product is similar as described in the Example 2.

Example 4

[2-(5-fluoro-2-hydroxy-phenyl)-2-oxo-ethyl]-triphenyl-phosphonium chloride

The process is same as in Example 2 except the amount of reagents, and the used temperature and reaction time. Thus 0,15 moles of 2-chloro-1-(5-fluoro-2-hydroxy-phenyl)-ethanone is used, the

reaction mixture is kept at the boiling point of acetonitrile for 7 hours. The yield is 61,8g (91 %). The quality of the product is similar as described in the Example 2.

Example 5

[2-(5-fluoro-2-hydroxy-phenyl)-2-oxo-ethyl]-triphenyl-phosphonium chloride

The process is same as in Example 2 except the amount of reagents, and the used temperature solvent and reaction time. Thus 0,01 moles of 2-chloro-1-(5-fluoro-2-hydroxy-phenyl)-ethanone is used, 15 ml of isopropanol is used as solvent the reaction mixture is kept on the boiling point of isopropanol for 4 hours. The yield is 3,92g (87 %). The quality of the product is similar as described in the Example 2.

Example 6

[2-(5-fluoro-2-hydroxy-phenyl)-2-oxo-ethyl]-triphenyl-phosphonium chloride

The process is same as in Example 2 except the amount of reagents, and the used temperature solvent and reaction time. Thus 0,01 moles of 2-chloro-1-(5-fluoro-2-hydroxy-phenyl)-ethanone, 15 ml of 1,2-dichloroethane is used as solvent, the reaction mixture is kept on the boiling point of 1,2-dichloroethane for 4 hours. The yield is 3,85g (85,5 %). The quality of the product is similar as described in the Example 2.

Example 7

1-(5-fluoro-2-hydroxy-phenyl)-2-(triphenyl-λ^5-phosphanilydene)-ethanone

67,2 g (0,8 moles) of sodium hydrogen carbonate is added to a suspension containing 324,65 g (0,72 moles) of [2-(5-fluoro-2-hydroxy-phenyl)-2-oxo-ethyl]-triphenyl-phosphonium chloride and 1200 ml of dichloromethane and 400 ml of water in a rate permitted by effervescence. The reaction mixture is stirred for an additional 30 minutes, the layers are separated, the aqueous layer is washed with 150 ml of dichloromethane, the collected organic layer is extracted with 200 ml of water, dried over sodium sulphate, the solvent is evaporated in vacuum, the solid residue is washed with a small amount of diethyl ether. Thus 292,8g (98%) product is obtained. Uniformity of the product is observed by thin layer chromatography, its melting point is 196-200°C. The product is ready to use in the subsequent reaction.

The crude product can be recrystallised from 100-fold amount of ethanol. The melting point of the obtained product is: 199-200°C.

Example 8

(E)-(4R)-4,5-isopropylydene-dioxy-1-(2-hydroxy-5-fluoro-phenyl)-prop-2E-ene-1-one (IX-R compound)

60 ml of saturated sodium hydrogen carbonate solution is added to a solution of 159 g (0,61moles) 1,2:5,6-di-O-isopropylydene-D-mannitole in 1 l of dichloromethane, then 148 g (0,7moles) of solid sodium periodate is added to the obtained dispersion under stirring in a rate which permits the temperature of reaction mixture is kept under 30°C. The reaction mixture is stirred for additional 30 minutes, 100 g of anhydrous magnesium sulphate is added, the mixture is stirred

additional 10 minutes, filtered. The given 1200 ml solution of D(+)R-O,O-isopropylydene-glycerinealdehyde (VIII-R) is stirred and 251 g (0,61 moles) of 1-(5-fluoro-2-hydroxy-phenyl)-2-(triphenyl-λ ^{5}-phosphanilydene)-ethanone is added, then the reaction mixture is left to stay overnight. The given solution is extracted with 2x100 ml of water, dried over magnesium sulphate, filtrated and the solvent is removed by vacuum distillation. 400 ml of diethyl ether is added to the obtained 380 g oily product and the mixture is stirred for 10 minutes. The precipitated crystalline triphenylphosphin oxide is filtered, and washed with 3x100 ml diethyl ether. The filtrate is evaporated in vacuum. The residue is 300 g. Then 100 g of isopropanol is added to the residue at room temperature. The reaction mixture is stirred for 10 minutes, filtered, the crystalline is washed with 2x 20 ml isopropanol. Thus 87,9g (54,1%) titled product is obtained. Mp.: 80,5-82°C. The filtrate is evaporated to 200 ml, is left to stay overnight in fridge, then the precipitated crystalline is filtered, washed with 2x20 ml cold (5°C) isopropanol. Thus 50,1 g (30,8%) second product is obtained. Mp.: 80-82°C. Both products are ready to use in the subsequent reaction.

The total yield is 84,9% the optical rotation of product is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = + 28,1°.

Example 9

(E)-(4S)-4,5-isopropylydene-dioxy-1-(2-hydroxy-5-fluoro-phenyl)-prop-2E-ene-1-one (IX-S compound)

The pH to 5,5 of the suspension 85,5 g (0,4 moles) of sodium periodate in 200 ml of water is adjusted with dropping a solution about 16 g (0,4moles) of sodium hydroxide in 130 ml of water into the

reaction mixture between 0-7°C. 43,6 g (0,2 moles) of 5,6-isopropylydene –L-gylono-1,4-lactone is added to the given oxidizer mixture under 30°C, the pH is kept at 5,5 with adding a 15% aqueous solution of sodium hydrogen carbonate until reaction is finished. The reaction mixture is stirred for additional 30 minutes. Then the pH is adjusted to 6,7 with adding a 15% aqueous solution of sodium hydrogen carbonate. 100 g of sodium chloride is added to the given suspension, filtered, the compound on the filter is washed 3x100 ml dichloromethane. Filtrates are collected, dried over sodium sulphate, then filtered.

The obtained solution containing L(-)S-O,O-isopropylydene-glycerinealdehyde (VIII-S) is stirred and 66g (0,16 moles) of 1-(5-fluoro-2-hydroxy-phenyl)-2-(triphenyl-λ^5-phosphanilydene)-ethanone is added, and stirred overnight at room temperature. Then the solution is extracted with 2x50 ml of water, dried over magnesium sulphate, the solvent is evaporated in vacuum. 200 ml of diethyl ether is added to the given oily product then stirred for 10 minutes at room temperature.

The precipitated crystalline triphenylphosphin oxide is filtered, and washed with 3x50 ml of diethyl ether. The filtrate is evaporated in vacuum, the residue is about 100 g. Then 50 ml of isopropanol is added to the residue at room temperature under stirring. The reaction mixture is stirred for additional 10 minutes, then filtered, the crystalline is washed with 2x 10 ml of isopropanol. Thus 22,4g (42,1%) titled product is obtained. Mp.: 79-81°C. The filtrate is evaporated to 100 ml, is left to stay overnight in fridge, then the precipitated crystalline is filtered, washed with 2x10 ml cold (5°C) isopropanol. Thus 10,4 g (19,5%) second product is obtained. Mp.: 80-82°C. Both products are ready to use in the subsequent reaction.

The total yield is 61,6% the optical rotation of product is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = - 28,1°.

Example 10

(R,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one and (S,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one[X (R,R) and X (S,R)]

51.6 g (0,19 moles) of (E)-(4R)-4,5-isopropylydene-dioxy-1-(2-hydroxy-5-fluoro-phenyl)-prop-2E-ene-1-one is suspended in water at 60°C, then 120 mg (0,005 moles) of lithium hydroxide is added to the reaction mixture and stirred at 60°C for an hour. The reaction mixture is allowed to cool to 35°C, then 200 ml of diethyl ether and 5 ml of ethanol is added to the reaction mixture. The layers are separated, the organic layer is dried, and the solvent is evaporated in vacuum. The obtained oily product is separated by vacuum chromatography. Eluents are increasing polarity mixtures of diethyl ether and petrolether (40-70°C). Acceptable fractions are collected, evaporated. The obtained 21 g (40%) of (R,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is recrystallised from n-hexane. Mp.: 61,5-63,5°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = - 58,1°.

Continued the chromatographic process, the acceptable fractions are collected, evaporated. The obtained 12 g (24%) of (S,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is recrystallised from n-hexane. Mp.: 44-45°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +57,1°.

Example 11

(S,S)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one and (R,S)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one[X (S,S) and X (R,S)]

51.6 g (0,19 moles) of (E)-(SR)-4,5-isopropylydene-dioxy-1-(2-hydroxy-5-fluoro-phenyl)-prop-2E-ene-1-one is suspended in 65 ml of water at 60°C, then 48 mg (0,0052 moles) of lithium hydroxide is added to the reaction mixture and stirred at 60°C for an hour. The reaction mixture is allowed to cool to 35°, 100 ml of diethyl ether and 2,5 ml of ethanol is added to the reaction mixture. The layers are separated, the organic layer is dried, and the solvent is evaporated in vacuum. The obtained oily 26 g oily product is separated by vacuum chromatography. Eluents are increasing polarity mixtures of diethyl ether and petrolether (40-70°C). Acceptable fractions are collected, evaporated. The obtained 10,2 g (28,2%) of (S,S)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is recrystallised from n-hexane. Mp.: 62-63°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +58,0°.

Continued the chromatographic process, the acceptable fractions are collected, evaporated. The obtained 5,6 g (21%) of (R,S)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is recrystallised from n-hexane. Mp.: 42,5-45°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -57,2°.

Example 12

(R,R)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one (XII-R,R)

21 g (0,079 moles) of (R,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is suspended in 50 ml of water, then 120 ml of acetic acid is added, the reaction mixture is stirred at 60-65°C for 3 hours. The solvent of the reaction mixture is evaporated in vacuum. The oily residue is mixed with 20 ml of diethyl ether and the mixture is left to be crystallised. The precipitated crystalline is filtered, washed with small amount of cold diethyl ether. The given 11,6 g (65%) of titled compound is recrystallized from acetonitrile. Mp.: 122-124°C. Optical rotation is $[\alpha]_D^{20}$(c=1, MeOH) = -80,3°.

Example 13

(S,R)-2-(1',2'-dihydroxy-ethyl)-6-fluoro-chroman-4-one (XII-S,R)

12 g (0,05 moles) of (S,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is suspended in 25 ml of water, then 60 ml of acetic acid is added, the reaction mixture is stirred at 60-65°C for 3 hours. The solvent of the reaction mixture is evaporated in vacuum. The oily residue is mixed with 25 ml of the mixture of ethylacetate and n-hexane in a ratio 2:1 and left to crystallise. The precipitated crystalline is filtered, washed with small amount of cold solvent mixture described above. Thus 7,2 g (70,6%) of titled compound is obtained. Mp.: 91-92°C. Optical rotation: $[\alpha]_D^{20}$(c=1, $CHCL_3$) = +66,2° $[\alpha]_D^{20}$(c=1, $CHCL_3$) = +67,5°.

Example 14

(S,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one and (R,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one[XII (S,R) and X (R,R)]

51.6 g (0,19 moles) of (E)-(4R)-4,5-isopropylydene-dioxy-1-(2-hydroxy-5-fluoro-phenyl)-prop-2E-ene-1-one is suspended in 100 ml of water at 60°C, then 120 mg (0,005 moles) of lithium hydroxide is added to the reaction mixture and stirred at 60°C for an hour. 230 ml of acetic acid is added to the given suspension and the mixture is stirred for additional 3 hours at 60°C. The solvent of the given reaction mixture is evaporated in vacuum, the oily product (about 40 g) is solved in a mixture of ethylacetate and of n-hexane in a ratio 2:1 and the mixture is left to be crystallised.

Thus 7,2 g (18,2%) (S,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is obtained. Mp.: 90-92°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCL_3$) = +67,4°.

The filtrate is evaporated in vacuum and the residue is solved in diethyl ether and left to crystallise. The precipitated crystalline is filtered, washed with small amount of cold diethyl ether. Thus 20,2 g (51,3%) of (R,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is obtained. Mp.: 118-123°C. The product is recrystallised from acetonitrile, thus the yield is 12,3 g (30,6%) of pure (R,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one. Mp.: 121,5-124°C, optical rotation is $[\alpha]_D^{20}$(c=1, MeOH) = -80,4°.

Example 15

(S,S)-2-(1',2'-dihydroxy-ethyl)-6-fluoro-chroman-4-one (XIII-S,S)

10,5 g (0,04 moles) of (S,S)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is suspended in 25 ml of water, then 60 ml acetic acid is added to the reaction mixture and stirred at 60-65°C for 3 hours. The solvent of the given reaction mixture is evaporated in vacuum, the oily product is dissolved in diethyl ether and the mixture is left to be crystallised.

Thus 5,5 g (62,5%) titled product is obtained. Melting point of the product after recrystallisation from acetonitrile is 121-123°C. Optical rotation is $[\alpha]_D^{20}$(c=1, MeOH) = +79,9°.

Example 16

(R,S)-2-(1',2'-dihydroxy-ethyl)-6-fluoro-chroman-4-one (XIII-R,S)

4 g (0,017 moles) of (R,S)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one is suspended in 10 ml of water, then 20 ml acetic acid is added to the reaction mixture and stirred at 60-65°C for 3 hours. The solvent of the given reaction mixture is evaporated in vacuum, the oily product is dissolved in 9 ml of the mixture of ethylacetate and n-hexane in a ratio 2:1 and the mixture is left to be crystallised.

The product is filtered, washed with the mixture described above. Thus 2,2 g (65%) titled compound is obtained. Mp.: 91-92°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -67,8°.

Example 17

(R,S)- and (S,S)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one (XIII-R,S and XIII-S,S)

26.6 g (0,1 moles) of (E)-(4S)-4,5-isopropylydene-dioxy-1-(2-hydroxy-5-fluoro-phenyl)-prop-2E-ene-1-one is suspended in 65 ml of water at 60°C, then 50 mg (0,002 moles) of lithium hydroxide is added to the reaction mixture and stirred at 60-65°C for 3 hours. 150 ml of acetic acid is added to the suspension and stirred at 60-65°C for additional 3 hours. The solvent is evaporated in vacuum, the oily residue (about 22 g) is dissolved in the mixture of ethyl acetate and of n-hexane in a ratio 2:1 and the mixture is left to be crystallised. Thus 4,0g (17,6%) of (R,S)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one is obtained. Mp.: 91-92°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +67,6°.

The filtrate is evaporated, the residue is solved in 12 ml of diethyl ether left to crystallise. The product is filtered, washed with a small amount of cold diethyl ether. Thus 10,9g (48,2%) of (S,S)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one is obtained. Mp.: 118-122°C. The product is recrystallised from acetonitrile. The yield is 6,8 g (30,1%) of pure (S,S)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one with a melting point 121-123 °C. The optical rotation is $[\alpha]_D^{20}$(c=1, MeOH) = +80,4°.

Example 18

(R,R)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one (XIV-R,R)

15,3 g (0,07moles) of (R,R)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one is dissolved in the mixture of 200 ml of dichloromethane and 30 ml of pyridine, the solution is cooled to $0^{o}C$, then keeping this temperature 13,0 g (0,07moles) of p-toluenesulphonyl chloride is added, and the reaction mixture is stirred for two days. The reaction mixture is extracted with 2x20 ml of water, dried over sodium sulphate, then evaporated. The given oily product is dissolved in 160 ml of diethyl ether left to crystallise. The product is filtered, washed with a small amount of diethyl ether. Thus 10,2g (39,6%) of titled product is obtained. Mp.: 100-103^{o}C. The filtrate is evaporated to dryness. The obtained product is separated on a layer of 60H by vacuum chromatography. Eluents are increasing polarity mixtures of ethylacetate-cyclohexane. Acceptable fractions are collected, evaporated, recrystallised from diethyl ether. The obtained additional product is 7,3 g (28,4%) Mp.: 100-103^{o}C. The total yield of the reaction is increased to 68%. The product is recrystallised from a mixture of ethyl acetate-cyclohexane 2:8. The melting point of the given product is 102-104^{o}C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = - 40,3^{o}.

Example 19

(S,R)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one (XIV-S,R)

The process is same as described in the Example 18 except instead of 15,3 g (0,07 moles) of (R,R)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one 15,3 g (0,07 moles) of (S,R)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one is used. 6,9 g (26,7%) of crystalline product with 111-115 ^{o}C melting point is obtained after working up of the reaction mixture and crystallisation of the oily raw product (about 30 g). The filtrate is evaporated to dryness. The obtained product is separated on a layer of 60H by vacuum chromatography. Eluent is a mixture of petrolether dichloromethane and acetonitrile in a ratio 70:1:1. The obtained additional product is 7,6 g (29,5%) Mp.: 117-120^{o}C. The total yield of the reaction is increased to 56,2 %. The product is recrystallised from a diisopropyl ether. The melting point of the given product is 118-120^{o}C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +50,7^{o}.

Example 20

(S,S)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one (XV-S,S)

4,5 g (0,02moles) of (S,S)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one is dissolved in the mixture of 60 ml of dichloromethane and 19 ml of pyridine, the solution is cooled to 0^{o}C, then keeping this temperature 3,8 g (0,02 moles) of p-toluenesulphonyl chloride is added, and the reaction mixture is stirred for two days. The reaction mixture is extracted with 2x6 ml water, dried over sodium

sulphate, then evaporated. The given oily product is dissolved in 50 ml of diethyl ether and is left to crystallise. The product is filtered, washed with a small amount of diethyl ether. Thus 3,1 g (41%) of titled product is obtained. Mp.: 99-101°C. The filtrate is evaporated to dryness. The obtained product is separated on a layer of 60H by vacuum chromatography. Eluents are increasing polarity mixtures of ethylacetate-cyclohexane. Acceptable fractions are collected, evaporated, recrystallised from diethyl ether. The obtained additional product is 2,2 g (28,7%). Mp.: 97-100°C. The total yield of the reaction is increased to 69,7%. The product is recrystallised from a mixture of ethylacetate-cyclohexane 2:8. The melting point of the given product is 102-104°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = + 40,4°.

Example 21

(R,S)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one (XV-R,S)

The process is same as described in the Example 19 except instead of 15,3 g (0,07 moles) of (S,R)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one 15,3 g (0,07 moles) of (R,S)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one is used. 1,8 g (24 %) of crystalline product with 116-119 °C melting point is obtained after working up the reaction mixture and crystallisation of the oily raw product (about 9 g) from diethyl ether. The filtrate is evaporated to dryness. The obtained product is separated on a layer of 60H by vacuum chromatography. Eluent is a mixtures of petrolether, dichloromethane and acetonitrile in a ratio 70:1:1. The obtained

additional product is 2,2 g (28,7%) Mp.: 117-120°C. The total yield of the reaction is increased to 52,7 %. The product is recrystallised from a diisopropyl ether. The melting point of the given product is 118-120°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -50,7°.

Example 22

(R,S)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one (XV-R,S)

The process is same as described in the Example 14 with a difference that after the filtration of (S,R)-2-(1',2"-dihydroxy-ethyl)-6-fluoro-chroman-4-one the filtrate containing of (R,R)-2-(1',2"-dihydroxy-ethyl)-6-fluoro-chroman-4-one as main component is evaporated. The residue is dissolved in a mixture of 400 ml of dichloromethane and 60 ml of pyridine, then cooled to 0 °C. Keeping this temperature 28,6 g (0,15 moles) of p-toluenesulphonyl chloride is added into the mixture, and stirred for two days. The reaction mixture is extracted with 2x40 ml water, dried over sodium sulphate, then evaporated in vacuum. About 60 g oily product is obtained, then it is dissolved in 160 ml of diethyl ether then the mixture is left to be crystallised. The product is filtered, washed with a small amount of diethyl ether. Thus 17,0g (23,5%) of titled product is obtained. Mp.: 98-100°C. The filtrate is evaporated to dryness. The obtained product is separated on a layer of 60 H by vacuum chromatography. Eluents are increasing polarity mixtures of ethylacetate-cyclohexane. Acceptable fractions are collected, evaporated, recrystallised from diethyl ether. The obtained additional product is 15,4 g (21,3%) Mp.: 99-101°C. The total yield of the reaction is increased to 44,6%. The

product is recrystallised from a mixture of ethylacetate-cyclohexane 2:8. The melting point of the given product is 101-103°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = - 40,4°

Example 23

(S,S)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one (XV-S,S)

The process is same as described in the Example 17 with a difference that after the filtration of (R,S)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one the filtrate is evaporated. The residue containing about 17 g (0,08 moles) of (S,S)-2-(1',2''-dihydroxy-ethyl)-6-fluoro-chroman-4-one as main component is dissolved in a mixture of 200 ml of dichloromethane and 30 ml of pyridine, then cooled to 0 °C. Keeping this temperature 14,3 g (0,08 moles) of p-toluenesulphonyl chloride is added into the mixture, and stirred for two days. The reaction mixture is extracted with 2x20 ml of water, dried over sodium sulphate, then evaporated in vacuum. About 30 g oily product is obtained, then it is dissolved in 150 ml of diethyl ether and left to be crystallised. The product is filtered, washed with a small amount of diethyl ether. Thus 8,0g (22,1%) of titled product is obtained. Mp.: 99-101°C. The filtrate is evaporated to dryness. The obtained product is separated on a layer of 60H by vacuum chromatography. Eluents are increasing polarity mixtures of ethylacetate-cyclohexane. Acceptable fractions are collected, evaporated, recrystallised from diethyl ether. The obtained additional product is 8,1 g (24,0 %). Mp.: 100-102°C. The total yield of the reaction is increased to 46,1 %. The product is recrystallised from a mixture of ethylacetate-cyclohexane

2:8. The melting point of the given product is 102-104°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = + 40,2°

Example 24

(R,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one (XVI-R,R)

9,9 g (0,026 moles) of (R,R)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one is dissolved in 140 ml of acetonitrile then 20 ml (0,143 moles) of triethylamine is added under stirring. The reaction mixture is stirred additional 24 hours at room temperature. The reaction mixture is evaporated to dryness in vacuum under 35°C, then the residue is filtered from water, dried (4.1 g), recrystallised from diethyl ether. Thus 3,3 g (61%) of pure titled compound is obtained. Mp.: 98-101°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -66,0°

Example 25

(S,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one (XVI-S,R)

6,54 g (0,017 moles) of (S,R)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one is dissolved in 90 ml of acetonitrile then 14 ml (0,143 moles) of triethylamine is added under stirring. The reaction mixture is stirred additional 24 hours at room temperature. The reaction mixture is evaporated to dryness in vacuum under 35°C, then the residue is filtered from 15 ml of water, dried (3,0 g), recrystallised from 30 ml of diethyl ether. Thus 2,08 g (58,1%) of pure titled compound is obtained. Mp.: 93-97°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +78,3°

Example 26

(S,S)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one (XVII-S,S)

5,0 g (0,013 moles) of (S,S)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one is dissolved in 70 ml of acetonitrile then 10 ml (0,07 moles) of triethylamine is added under stirring. The reaction mixture is stirred additional 24 hours at room temperature. The reaction mixture is evaporated to dryness in vacuum under 35°C, then the residue is filtered from 11 ml of water, dried (2,0 g), recrystallised from 20 ml of diethyl ether. Thus 1,6 g (59,%) of pure titled compound is obtained. Mp.: 98-101°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +66,2°

Example 27

(R,S)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one (XVIII-R,S)

3,8 g (0,01 moles) of (R,S)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one is dissolved in 50 ml of acetonitrile then 7 ml (0,05 moles) of triethylamine is added under stirring. The reaction mixture is stirred additional 24 hours at room temperature. The reaction mixture is evaporated to dryness in vacuum under 35°C, then the residue is filtered from 9 ml of water, dried (1,7 g), recrystallised from 22 ml of diethyl ether. Thus 1,27 g (61 %) of pure titled compound is obtained. Mp.: 93-96°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -78,0°

Example 28

(R,R)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one (XX-R,R)

2,8g (0,01 moles) of (R,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one is dissolved in 25 ml of acetonitrile, cooled to 0°C, then keeping this temperature 4,28 g (0,04 moles) of benzylamine and 1,06 g (0,01 moles) of lithium perchloroate are added under stirring. The stirring of the reaction mixture is continued for 3 days, then the mixture is poured onto a mixture of 100 g of ice and water, the crystalline precipitate is filtered. Thus 1,84 g (58,3 %) of pure titled compound is obtained. Mp.: 118-120°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -35,8°

Example 29

(S,S)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one (XXV-S,S)

The process is same as described in the Example 18 except instead of (R,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one (S,S)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one is used.

The yield is 2,35 g (74,9 %) of titled compound. Mp.: 105-117°C. The crude product is recrystallised from 13 ml of isopropanol. Thus, the melting point of the given 1,63 g (51,6%) of pure product is 117,5-120°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +35,2°

Example 30

(S,R)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one (XXV-S,R)

The process is same as described in the Example 18 except instead of

(R,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one (S,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one is used.

The yield is 2,27 g (72,1 %) of titled compound. Mp.: 98-100°C. The crude product is recrystallised from 25ml of isopropanol. Thus, the melting point of the given 1,63 g (51,6%) of pure product is 101-104°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +46,8°

Example 31

(S,R)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one (XXV-S,R)

The process is same as described in the Example 18 except instead of

(R,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one (R,S)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one is used.

The yield is 2,33 g (74,1 %) of titled compound. Mp.: 99-101°C. The crude product is recrystallised from 25ml of isopropanol. Thus, the melting point of the given 1,8 g (56,6%) of pure product is 101,5-104°C. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -46,6°

Example 32

N-benzyl-N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine (XIX (S,R,R,R))

A mixture of 1,26 g (0,004 moles) of powdered (R,R)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one and 0,84 g (0,004 moles) of powdered (S,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one is stirred for 15 minutes at 145°C. The reaction mixture is recrystallised after cooling. Thus 2,1 g (100%) of titled compound is

obtained. Mp.: 55-62°C. HPLC purity is 98,4%. Optical purity monitored by chiral HPLC method is >98%. Product is suitable to use in the next synthesis step. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +56,8°

Example 33

N-benzyl-N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine (XIX (S,R,R,R))

A mixture of 1,26 g (0,004 moles) of powdered (S,R)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one and 0,84 g (0,004 moles) of powdered (R,R)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one is stirred for 15 minutes at 145°C. The reaction mixture is recrystallised after cooling. Thus 2,1 g (100%) of titled compound is obtained. Mp.: 56-63°C. HPLC purity is 98,4%. Optical purity monitored by chiral HPLC method is >98%. Product is suitable to use in the next synthesis step. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = +56,9°

Example 34

N-benzyl-N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine (XIX (R,S,S,S))

A mixture of 1,26 g (0,004 moles) of powdered (S,S)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one and 0,84 g (0,004 moles) of powdered (R,S)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one is stirred for 15 minutes at 145°C. The reaction mixture is recrystallised after cooling. Thus 2,1 g (100%) of titled compound is

obtained. Mp.: 53-62°C. HPLC purity is 98,1%. Optical purity monitored by chiral HPLC method is >98%. Product is suitable to use in the next synthesis step. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -56,5°.

Example 35

N-benzyl-N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine (XIX (R,S,S,S))

A mixture of 1,26 g (0,004 moles) of powdered (R,S)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one and 0,84 g (0,004 moles) of powdered (S,S)-6-fluoro-2-(oxiran-2-yl)-chromane-4-one is stirred for 15 minutes at 145°C. The reaction mixture is recrystallised after cooling. Thus 2,1 g (100%) of titled compound is obtained. Mp.: 54-62°C. HPLC purity is 98,2%. Optical purity monitored by chiral HPLC method is >98%. Product is suitable to use in the next synthesis step. Optical rotation is $[\alpha]_D^{20}$(c=1, $CHCl_3$) = -56,8°.

Example 36

N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4 one-2-yl)]-amine (XXI (S,R,R,R)

2,62 g (0,005 moles) of N-benzyl-N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine is dissolved in 70 ml of ethanol, then 0,3 g of 10% palladium/charcoal catalyst is added. The reaction mixture is hydrogenated for two hours under 2 bar pressure. 250 ml of methanol is added and the reaction mixture is heated to 50°C to dissolve the

precipitated product. The catalyst is filtered, and washed with 50 ml of methanol. Organic solutions are collected and evaporated in vacuum. The residue (1,9 g) is filtered from small amount of diethyl ether. Thus 1,59g (73,4%) of titled compound is obtained. Mp 182,5-183,5°C (recrystallised from acetonitrile). HPLC purity is > 98%. Optical purity monitored by chiral HPLC method is >98%. Optical rotation is $[\alpha]_D^{20}$(c=0,2, dimethyl-formamide) = +2,35°, is $[\alpha]_{365}^{20}$(c=0,2, dimethyl-formamide) = +127,2°.

Example 37

N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4 one-2-yl)]-amine (XXVI (R,S,S,S)

2,62 g (0,005 moles) of N-benzyl-N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine is dissolved in 70 ml of ethanol, then 0,3g of 10% palladium/charcoal catalyst is added. The reaction mixture is hydrogenated for two hours under 2 bar pressure. 250 ml of methanol is added and the reaction mixture is heated to 50°C to dissolve the precipitated product. The catalyst is filtered, and washed with 50 ml of methanol. Organic solutions are collected and evaporated in vacuum. The residue (1,9 g) is filtered from small amount of diethyl ether. Thus 1,63g (75,2%) of titled compound is obtained. Mp: 182-183,5°C (recrystallised from acetonitrile). HPLC purity is > 99%. Optical purity monitored by chiral HPLC method is >98%. Optical rotation is $[\alpha]_D^{20}$(c=0,2, dimethyl-formamide) = -2,33°.

Example 38

N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4 one-2-yl)]-amine (XXII (S,R,R,R)

2,62 g (0,005 moles) of N-benzyl-N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine is dissolved in 25 ml of acetic acid, then 0,4g of 10% palladium/charcoal catalyst is added. The reaction mixture is hydrogenated for 20 hours under 3 bar pressure at 30°C. The catalyst is filtered, 200 ml of water is added to the filtrate and the pH of mixture is adjusted to 7 with sodium hydrogen carbonate. The precipitated product is filtered, washed with water. Thus 1,55g (71%) of titled compound is obtained. Mp: 180-190°C (degradation). HPLC purity is > 96%.

Example 39

N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4 one-2-yl)]-amine (XXII (S,R,R,R))

2,62 g (0,005 moles) of N-benzyl-N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine is dissolved in 50 ml of ethanol, then 0,4g of 10% palladium/charcoal catalyst is added. The reaction mixture is hydrogenated for 24 hours under 3 bar pressure at 50°C. The catalyst is filtered and washed with 20 ml of ethanol. The filtrate is evaporated in vacuum, the residue is recrystallised from acetonitrile, filtrated and dried. Thus 1,2g (54,6%) of titled compound is obtained. Mp: 180-190°C (degradation). HPLC purity is > 96%.

Example 40

N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4 one-2-yl)]-amine (XXVII (S,R,R,R)

2,62 g (0,005 moles) of N-benzyl-N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine is dissolved in 25 ml of acetic acid, then 0,4g of 10% palladium/charcoal catalyst is added. The reaction mixture is hydrogenated for 20 hours under 2,5 bar pressure at 30°C. The catalyst is filtered, 200 ml of water is added to the filtrate and the pH of mixture is adjusted to 7 with sodium hydrogen carbonate. The precipitated product is filtered, washed with water. Thus 1,51g (69%) of titled compound is obtained. Mp: 181-190°C (degradation). HPLC purity is > 96%.

Example 41

([2S[2R*[R[R*]]]]-(±)-α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] (I (R,S,S,S), d-nebivolol

2,1 g (0,004 moles) of N-benzyl-N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine is dissolved in 25 ml of ethanol, then 2 ml of cc. hydrochloric acid and 0,4g of 10% palladium/charcoal catalyst is added. The reaction mixture is hydrogenated for 20 hours under 3 bar pressure at 50-55°C. After cooling the catalyst is filtered and washed with small amount of ethanol, then the solvent is evaporated. The residual suspension is diluted with 30 ml of water and the pH of mixture is adjusted to 8 with sodium hydrogen carbonate. The precipitated product is filtered, washed with water then small

amount of diethyl ether. Thus 1,15g (70%) of titled compound is obtained. Mp 144-147°C (degradation). HPLC purity is 99,7%. Optical purity monitored by chiral HPLC method is >98%.

Optical rotation is $[\alpha]_D^{20}$(c=0,2 methanol) = 20,8°, $[\alpha]_D^{20}$(c=0,02 methanol) = 18±2°

Example 42

([2S[2R*[R[R*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol]-hydrochloride (I (R,S,S,S). HCl, d-nebivolol-hydrochloride)

The process is same as described in the Example 41 except with a difference that only ethanol is evaporated from the reaction mixture containing water and ethanol which obtained after the hydrogenating reaction of the d-nebivolol of the formula I (S,R,R,R). The precipitated d-nebivolol hydrochloride of the formula I (S,R,R,R). HCl is filtered. Thus 1,84 g (83,5%) of titled compound is obtained. Mp: 180-190°C (degradation). HPLC purity is >98,6%. Optical purity monitored by chiral HPLC method is >98%.

Example 43

([2R[2S*[S[S*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] I (R,S,S,S,), l-nebivolol

2,1 g (0,004 moles) of N-benzyl-N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine is dissolved in 25 ml of ethanol, then 2 ml of cc. hydrochloric acid and 0,8g of 10% palladium/charcoal catalyst is added. The reaction mixture is hydrogenated for 16 hours under 3 bar pressure at 50-55°C. After cooling the catalyst is filtered

and washed with small amount of ethanol, then evaporated to dryness. The residue is diluted with 30 ml of water and the pH of obtained suspension is adjusted to 8 with sodium hydrogen carbonate. The precipitated product is filtered, washed with water then small amount of diethyl ether. Thus 0,97g (62%) of titled compound is obtained. Mp: 145-147°C (degradation). HPLC purity is 99,8%. Optical purity monitored by chiral HPLC method is >98%.

Example 44

([2R[2S*[S[S*]]]] and ([2S[2R*[R[R*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] (I (R,S,S,S+S,R,R,R) nebivolol)

1,05 g (0,002 moles) of N-benzyl-N-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine and 1,05 g (0,002 moles) of N-benzyl-N-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine are dissolved in 25 ml of ethanol, then 2 ml of cc. hydrochloric acid and 0,8g of 10% palladium/charcoal catalyst is added. The reaction mixture is hydrogenated for 20 hours under 3,5 bar pressure at 50-55°C. After cooling the catalyst is filtered and washed with small amount of ethanol, then evaporated to dryness. Crystalline residue is diluted with 30 ml of water and the pH of obtained suspension is adjusted to 8 with solid sodium hydrogen carbonate. The precipitated product is filtered, washed with water, then small amount of diethyl ether. Thus 0,85g (52%) of titled compound is obtained. Mp 140,5-142°C. HPLC purity is 99,7%.

Example 45

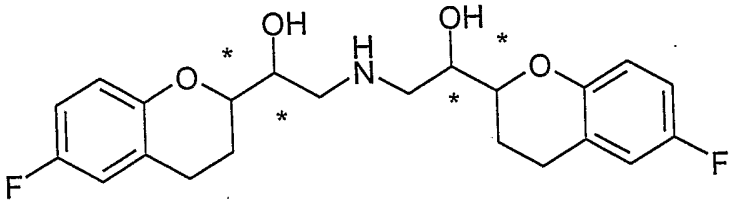
Experiment for the hydrogenation of the mixture of racemates of N-benzyl-N-[1-hydroxy-2-(6-fluoro-chroman-2-yl)]-amine of the formula XXXVIII-"A" and "B" in a ratio 1:1, which is prepared from racemates of 6-fluoro-2-(oxiran-2-yl)-chroman (XXXVI-A racemate) and of racemate 2-(2-benzylamino-1-hydroxy-ethyl)-6-fluor-chroman (XXXVII-B racemate) according to the description of US 4,654,362, then the separation of two isomeric racemate (A= nebivolol, B= undesired isomer) mixture by crystallisation.

0,495 g (0,001 moles) of the mixture of racemates of N-benzyl-N-[1-hydroxy-2-(6-fluoro-chroman-2-yl)]-amine of the formula XXXVIII-"A" and "B" in a ratio 1:1, is dissolved in 50 ml of ethanol, 0,2g of 10% palladium/charcoal catalyst is added. The hydrogenation is carried out at room temperature under atmospheric pressure and intensive stirring until the half of theoretically amount of hydrogen is reacted. Then the reaction mixture is filtered, the solvent is evaporated, residue is purified by vacuum chromatographic method using Kieselgel 60H layer. Fractions are solved in a mixture of chloroform and of methanol in a ratio 50:1 then collected and evaporated. The residue is rubbed with small amount of diethyl ether, then filtered. The given crystalline product is 0,025 g (51%). Mp.: 141-143°C. The product is a mixture of the racemates in a ratio 1:1 of the racemate "A"= (R,S,S,S)+(S,R,R,R) (nebivolol) and the racemates of "B"=(R,S,R,R) +(S,R,S,S) (undesired isomer) according to CMR analysis.

40 mg of the product is recrystallised from 1 ml of acetonitrile. The melting point of obtained product is 138-140°C. The product is a mixture of the racemates in a ratio 1:1 according to CMR analysis.

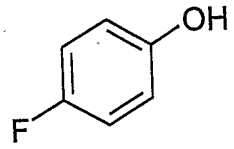
Claims:

1. Process for the preparation of racemic ([2S[2R*[R[R*]]]]- and ([2R[2S*[S[S*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the compound of the formula



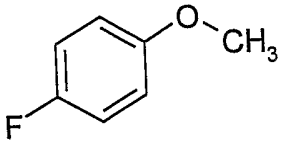
I

and its pure ([2S[2R*[R[R*]]]]- and ([2R[2S*[S[S*]]]]- enantiomer compounds **characterized in that** 4-fluoro-phenol of the formula



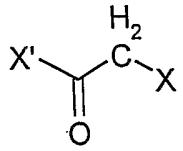
II

or 4-fluoro-anizole of the formula



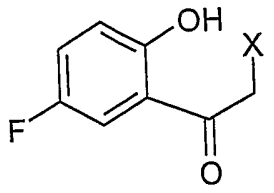
III

subjected to a Friedel-Crafts reaction with a haloacetyl halogenide of the general formula



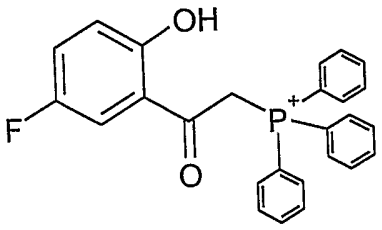
IV

wherein X and X' are same or different halo atoms, the obtained haloacetyl compound of the formula



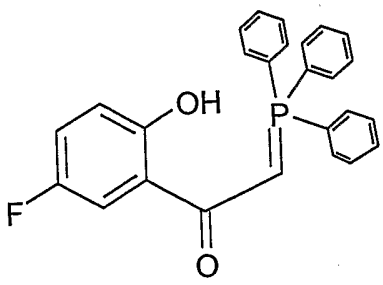
V

wherein X defined above, reacted with triphenylphosphine, the given phosphonium salt of the general formula



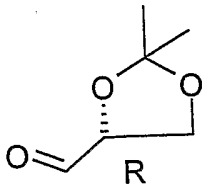
VI

wherein X defined above is treated with a weak base compound, the obtained phosphanylidene-ethanone compound of the formula



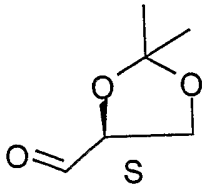
VII

is reacted separately a glycerinealdehyde compound of the formula



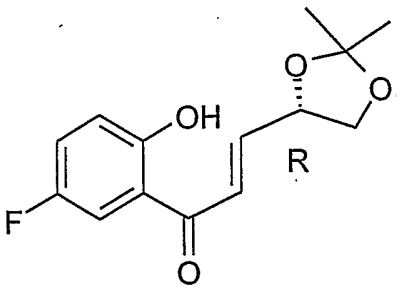
VIII (R)

or



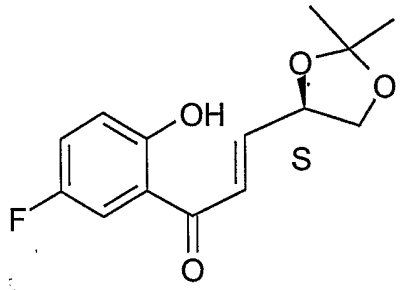
VIII (S)

the given ethylene-compound of the formula



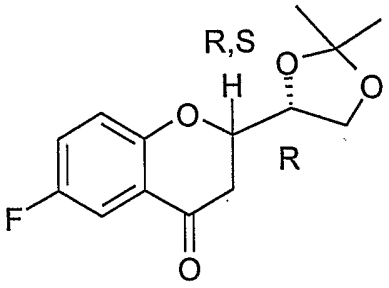
IX (R)

or



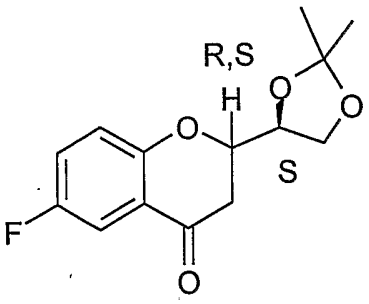
IX (S)

is subjected to a ring closure reaction in alkaline condition, the protecting group of the given protected chroman-4-one of the formula



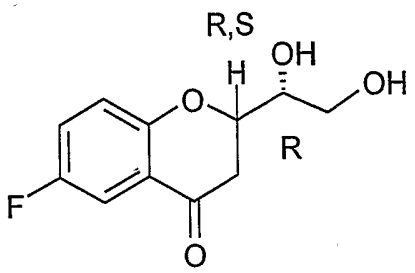
X (R,R+S,R)

or



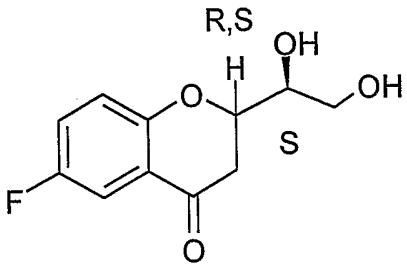
X (R,S+S,S)

is removed by acidic hydrolysis, the obtained diastereomer mixtures of chroman-4-one diol of the formula



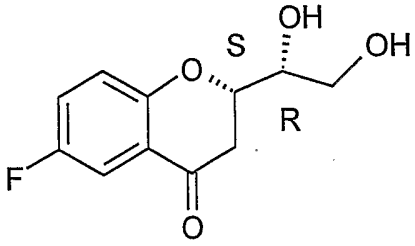
XI (R,R +S,R)

or



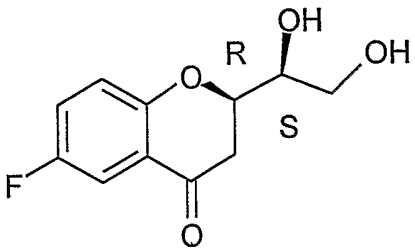
XI (R,S +S,S)

are separated to the pure enantiomers of the formula



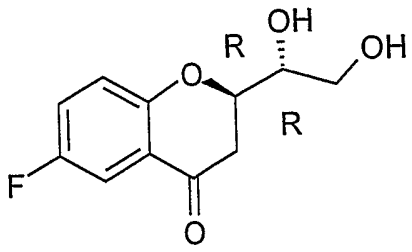
XII (S,R)

or



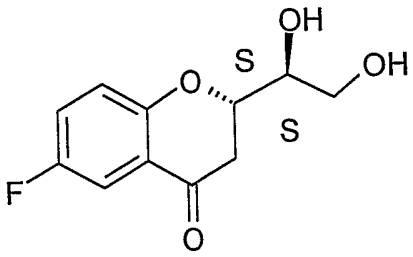
XIII (R,S)

by crystallisation of diastereomer mixtures, the pure diastereomer compounds of the



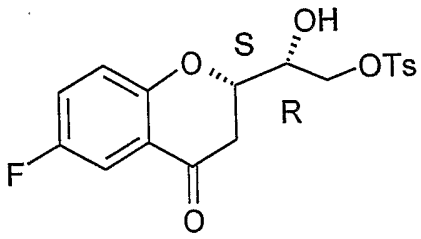
XII (R,R)

or

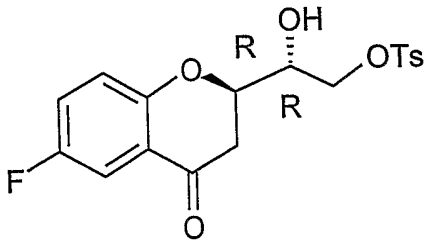


XIII (S,S)

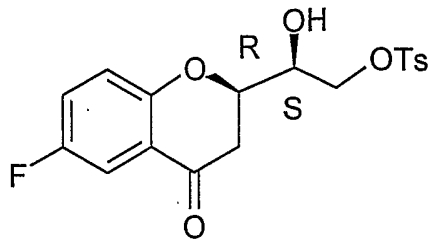
are obtained by treatment of filtrate, then the chroman-4-one diol compounds are tosylated separately , pure enantiomer tosylate compounds of the formula



XIV (S,R)

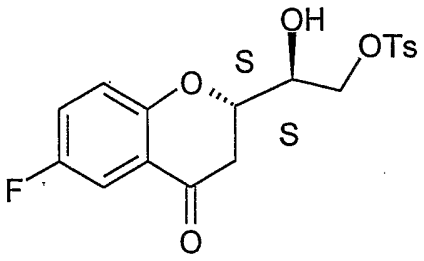


XIV (R,R)



XV (R,S)

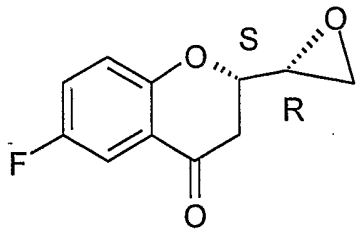
or



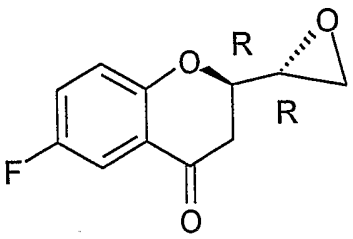
XV (S,S)

are obtained,

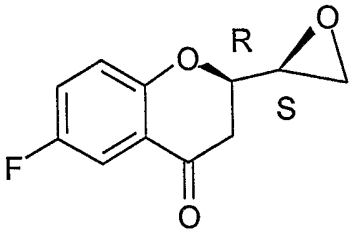
or the filtrate of the crystallisation of the enantiomer compounds of formula XII (S,R) or XIII (R,S) prepared from chroman-4-one diol of the formula XI (R,R and S,R) or XI (R,S and S,S) is evaporated, then the residue is subjected to tosylation, the tosylate compounds of the formula XIV (R,R) and XV (S,S) are obtained, the tosylate compounds of the formula XIV (S,R), XIV (R,R), XV (R,S)or XV (S,S) are separately reacted with base to the corresponding oxirane compounds of the formula



XVI (S,R)

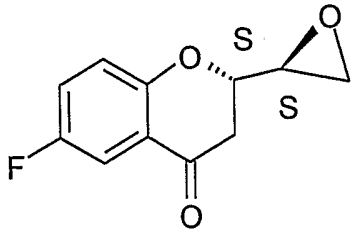


XVI (R,R)



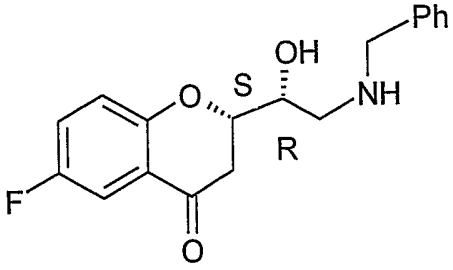
XVII (R,S)

or

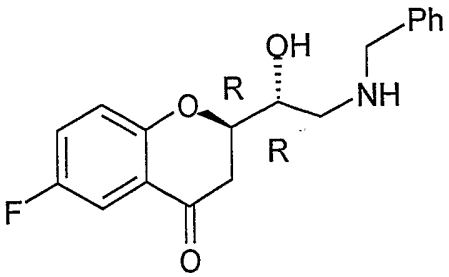


XVII (S,S)

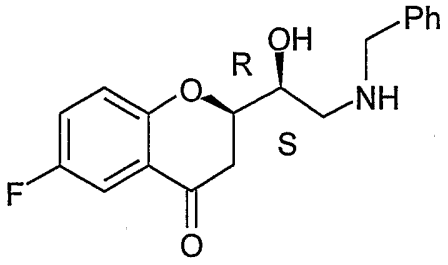
which are reacted with benzylamine the corresponding benzyl-amino compounds of the formula



XVIII (S,R)

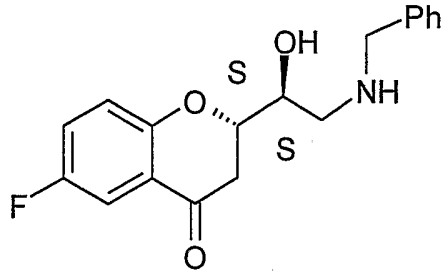


XX (R,R)



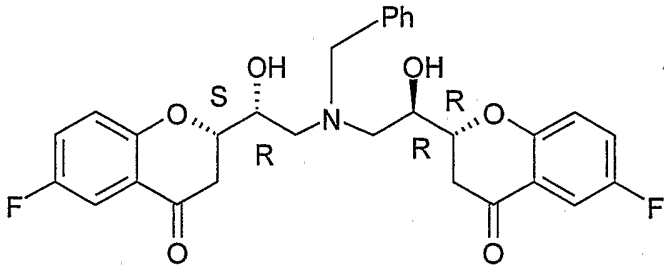
XXIII (R,S)

or



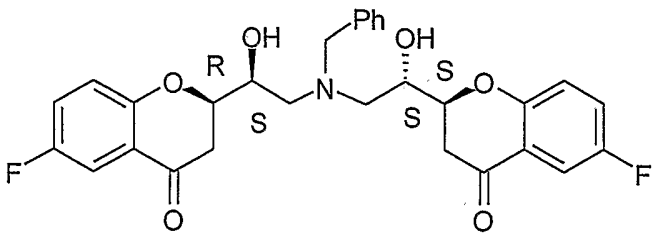
XXV (S,S)

are prepared, the obtained benzyl-amino compounds are reacted with the proper oxirane compound of the formula XVI (S,R), XVI (R,R), XVII (R,S) or XVII (S,S), the given N-benzyl-diketo compounds of the formula



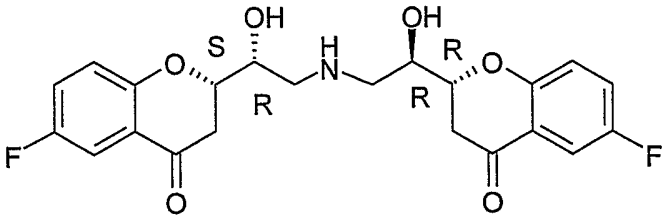
XIX (S,R,R,R)

or



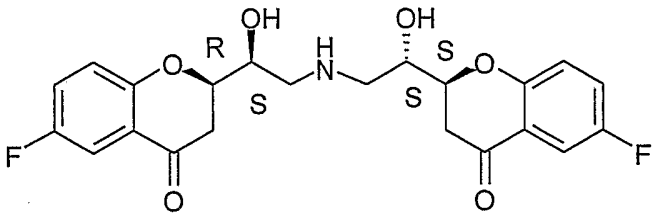
XXIV (R,S,S,S)

are hydrogenated under 1,5-3 bar pressure, in a solution of lower-alkanol or in a mixture of lower-alkanol and water in presence of heavy metal catalyst, obtained compounds of the formula



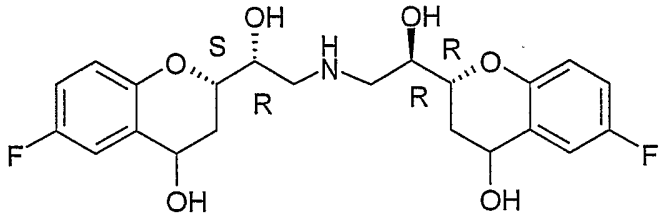
XXI (S,R,R,R)

or



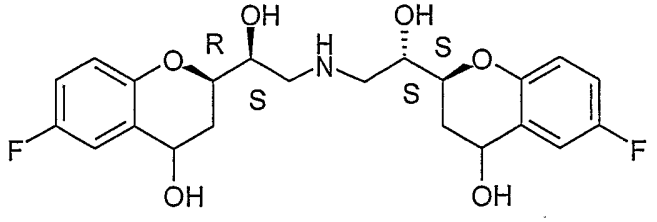
XXVI (R,S,S,S)

or the N-benzyl-diketo compounds of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) are hydrogenated under 1,5-3 bar pressure , in a solution of lower alkanol or in a mixture of lower alkanol and water or in a solution containing acetic acid in presence of heavy metal catalyst at 45-50°C, the diol compound of the formula



XXII (S,R,R,R)

or



XXVII (R,S,S,S)

is given,
or the N-benzyl-diketo compounds of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) are hydrogenated in presence of heavy metal catalyst, at 50-55°C, under 2-5 bar pressure in a solution of lower alkanol and water in presence of inorganic acid, or diketo compounds of the formula XIX (S,R,R,R) or XXIV (R,S,S,S) or diol compounds of the formula XXII (S,R,R,R) or XXVII (R,S,S,S) are hydrogenated onward in the circumstance described above, the pure ([2R[2S*[S[S*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the compound of the formula I (S,R,R,R) or, ([2S[2R*[R[R*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the compound of the formula I (R,S,S,S) is obtained,
or
the mixture of N-benzyl-diketone compounds of the formula XIX (S,R,R,R) and XXIV (R,S,S,S) in a ratio 1:1 is hydrogenated in presence of heavy metal catalyst at 50-55°C under 2-5 bar pressure in a lower alkyl alcoholic solvent or in a mixture of water and a lower alkyl alcohol in presence of inorganic acid to obtain the racemate , ([2S[2R*[R[R*]]]] and ([2R[2S*[S[S*]]]]-(±)- α,α' -[imino-bis(methylene)]bis[6-fluoro-chroman-2-methanol] of the compound of the formula I (R,S,S,S+S,R,R,R).

2. A process according to Claim 1, **characterized in that** the Friedel-Crafts reaction of 4-fluoro-anisole of the formula III with chloroacetyl chloride is carried out in dichloromethane between 20-40°C.

3. A process according to Claim 2, **characterized in that** the 2-chloro-1-(5-fluoro-2-hydroxy-phenyl)-ethanone, wherein X stands for a chloro atom is used in the next reaction step without additional purification after the evaporation of its solution in dichlorometan.

4. A process according to Claim 1, **characterized in that** the reaction of the haloacetyl compounds of the formula V, wherein X stands for a halo atom with triphenylphosphine is carried out in acetonitrile or dichloromethane between 20-80°C.

5. A process according to Claim 1, **characterized in that** the transformation of the phosphonium salts of the formula VI , wherein X stands for a halo atom to a phosphanylidene-etanon compound of the formula VII is carried out with solid sodium hydrogen carbonate in a mixture of dichloromethane and of water.

6. A process according to Claim 1, **characterized in that** the reaction of the phosphanylidene-etanon compound of the formula VII with the protected glycerinealdehyde compounds of the formula VIII (S) or of the formula VIII (R) is carried out in dichloromethane at room temperature.

7. A process according to Claim 6, **characterized in that** the ethylene compounds of the formula IX (R) or IX (S) are separated from triphenylphosphine which is produced as side product, the solvent is evaporated, diethyl ether is added, then crystallised from isopropanol.

8. A process according to Claim 1, **characterized in that** the ring closure of ethylene compounds of the formula IX (R) or IX (S) to diastereomer mixtures of 2-(2',2'-dimethyl-[1,3]-dioxolan-4-yl)-chroman-4-one of the formula X (R,R+S,R) or of the formula X (R,S+S,S) is carried out in aqueous media at 60°C , the product is extracted from reaction mixture with diethyl ether, the organic layer is dried, the solvent is evaporated in vacuum, the residual oily mixture of protected 2-(2',2'-dimethyl-[1,3]-dioxolan-4-yl)-chroman-4-one diastereomers are used directly in the subsequent reaction step.

9. A process according to Claim 8, **characterized in that** the diastereomers of 2-(2',2'-dimethyl-[1,3]-dioxolan-4-yl)-chroman-4-one of the formula X (R,R), X(R,S) , X(S,R) and X (S,S) are obtained as their crystalline form after separation from their mixture.

10. A process according to Claim 1, **characterized in that** the protecting group is removed from diastereomers of 2-(2',2'-dimethyl-[1,3]-dioxolan-4-yl)-chroman-4-one of the formula X (R,R), X(R,S) , X(S,R) and X (S,S) in a mixture of acetic acid and water at 65°C under stirring.

11. A process according to Claim 10, **characterized in that** the enantiomer diols of the formula XII (R,R) and XIII (S,S) are obtained in crystalline form crystallised from a mixture of ethylacetate n-hexane in a ratio 2:1.

12. A process according to Claim 10, **characterized in that** the diastereomer diol mixtures of the formula XI (R,R and S,R) or XI (R,S

and S,S) obtained after the protecting groups are eliminated from the diastereomer mixtures of 2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-chroman-4-one of the formula X (R,R and S,R) or X (R,S and S,S) are subjected to a crystallisation in a mixture of ethylacetate and n-hexane in a ratio 2:1, the obtained pure crystalline enantiomers of formula XII (S,R) or XIII (R,S) are filtered, then the filtrate is evaporated, the residue is crystallised from diethyl ether, the pure crystalline enantiomers of formula XII (R,R) or XIII (S,S) are obtained.

13. A process according to Claim 1, **characterized in that** the enantiomer chromanone-diol compounds of the formula XII (R,R), XII (S,R) , XIII (R,S) or XIII(S,S) are transformed to the corresponding compounds of the formula XIV (R,R), XIV (S,R) , XV(R,S) or XV(S,S) by tosylation in dichloromethane containing pyridine as acid binding agent at 0°C.

14. A process according to Claim 13, **characterized in that** the enantiomer tosylate compounds of the formula XIV (R,R), XIV (S,R) , XV(R,S) or XV(S,S) are obtained in their crystalline forms by crystallisation from diethyl ether.

15. A process according to Claim 1, **characterized in that** the diastereomer diol mixtures of the formula XI (R,R and S,R) or XI (R,S and S,S) obtained after the protecting groups are eliminated from the diastereomer mixtures of 2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-chroman-4-one of the formula X (R,R and S,R) or X (R,S and S,S) subjected to a crystallisation in a mixture of ethylacetate and n-hexane in a ratio 2:1, the obtained pure crystalline enantiomers of formula XII

(S,R) or XIII (R,S) are filtered, then the filtrate is evaporated, then the residue is tosylated without further purification, the obtained enantiomer tosylate compounds of the formula XIV (R,R) or XV(S,S) are obtained in their crystalline forms.

16. A process according to Claim 1, **characterized in that** the enantiomer tosylate compounds of the formula XIV (R,R), XIV (S,R) , XV(R,S) or XV(S,S) are transformed to the corresponding chromanone-oxirane compounds of the formula XVI (R,R), XVI (S,R), XVII(R,S) or XVII(S,S) in acetonitrile in presence of triethylamine at room temperature.

17. A process according to Claim 16, **characterized in that** the enantiomer chromanone-oxirane compounds of the formula XVI (R,R), XVI (S,R) , XVII(R,S) XVII(S,S) are purified by the evaporation of reaction mixture to dryness, the crystalline residue is filtered from water, then recrystallised from diethyl ether.

18. A process according to Claim 1, **characterized in that** the enantiomer benzylamino compounds of the formula XX (R,R), XVIII (S,R) , XXIII(R,S) or XXV (S,S) are obtained from corresponding oxirane compounds of the formula XVI (R,R), XVI (S,R) , XVII(R,S) or XVII(S,S) by reaction with benzylamine in presence of lithium perchloroate catalyst in acetonitrile at 0°C.

19. A process according to Claim 18, **characterized in that** the enantiomer benzylamino compounds of the formula XX (R,R), XVIII

(S,R) , XXIII(R,S) or XXV (S,S) are purified after the working up the reaction mixture by recrystallisation of products from isopropanol.

20. A process according to Claim 1, **characterized in that** the reaction of enantiomer benzyl-amino compounds of the formula XX (R,R), XVIII (S,R) , XXIII(R,S) or XXV (S,S) with the corresponding enantiomer oxirane compounds of the formula XVI (R,R), XVI (S,R) , XVII(R,S) XVII(S,S) obtaining the compounds of N-benzyl-diketones of the formula XIX (S,R,R,R), or XXIV (R,S,S,S) is carried out in a melted mixture of previously powdered compounds at 145°C.

21. A process according to Claim 1, **characterized in that** the hydrogenation of N-benzyl-diketones of the formula XIX (S,R,R,R), or XXIV (R,S,S,S) to the corresponding diketo compounds of XXI (S,R,R,R) or XXVI (R,S,S,S) is carried out in a solution containing ethanol, in presence of 10% Pd/charcoal catalyst under 2 bar pressure at room temperature.

22. A process according to Claim 1, **characterized in that** the hydrogenation of N-benzyl-diketones of the formula XIX (S,R,R,R), or XXIV (R,S,S,S) to the corresponding diol compounds of XXII (S,R,R,R), or XXVII (R,S,S,S) is carried out in a solution containing ethanol or in a solution containing acetic acid in presence of 10% Pd/charcoal catalyst under 2 or 3 bar pressure at the temperature of 40-45°C.

23. A process according to Claim 1, **characterized in that** the hydrogenation of N-benzyl-diketones of the formula XIX (S,R,R,R), or

XXIV (R,S,S,S) to the d-nebivolol of the formula I (S,R,R,R), or l-nebivolol of the formula I (R,S,S,S) is carried out in a mixture containing ethanol and water in presence of hydrochloric acid and in presence of 10% Pd/charcoal catalyst at the temperature of 50-55°C.

24. A process according to Claim 1, **characterized in that** the hydrogenation of N-benzyl-diketones of the formula XIX (S,R,R,R), or XXIV (R,S,S,S) to the d-nebivolol of the formula I (S,R,R,R), or l-nebivolol of the formula I (R,S,S,S) is carried out in a mixture containing ethanol and water in presence hydrochloric acid and in presence of 10% Pd/charcoal catalyst at the temperature 50-55°C

25. A process according to Claim 1, **characterized in that** the hydrogenation of the mixture of N-benzyl-diketones of the formula XIX (S,R,R,R) and XXIV (R,S,S,S) in a ratio 1:1 to racemic nebivolol of the formula I (S,R,R,R+R,S,S,S) is carried out in a solution of ethanol or in a mixture ethanol and water in presence of hydrochloric acid and in presence of 10% Pd/charcoal catalyst at the temperature of 50-55°C.

26. [2-(5-fluoro-2hydroxy-phenyl)-2-oxo-ethyl]-triphenyl-phosphonium chloride

27. 1-(5-fluoro-2hydroxy-phenyl)-2-(triphenyl-λ^5-phosphanilidene)-ethanone

28. (E)-(4R)-4,5-isopropylydene-dioxy-1-(2-hydroxy-5-fluoro-phenyl)-prop-2E-ene-1-one (IX-R compound)

29. (E)-(4S)-4,5-isopropylydene-dioxy-1-(2-hydroxy-5-fluoro-phenyl)-prop-2E-ene-1-one (IX-S compound)

30. (R,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one [X (R,R) compound]

31. (S,R)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one [X (S,R) compound]

32. (S,S)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one [X (S,S) compound]

33. (R,S)-2-(2',2'-dimethyl-[1,3]-dioxolane-4-yl)-6-fluoro-chroman-4-one [X (R,S) compound]

34. (R,R)-2-(1',2'-dihydroxy-ethyl)-6-fluoro-chroman-4-one [(XII-R,R) compound]

35. (S,R)-2-(1',2'-dihydroxy-ethyl)-6-fluoro-chroman-4-one [(XII-S,R) compound]

36. (S,S)-2-(1',2'-dihydroxy-ethyl)-6-fluoro-chroman-4-one [(XIII-S,S) compound]

37. (R,S)-2-(1',2'-dihydroxy-ethyl)-6-fluoro-chroman-4-one [(XIII-R,S) compound]

38. (R,R)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one [(XIV-R,R) compound]

39. (S,R)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one [(XIV-S,R) compound]

40. (S,R)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one [(XV-S,R) compound]

41. (S,S)-6-fluoro-{2-[4-methyl-phenyl)-sulphonyl-oxy]-1-hydroxy-ethyl}-chroman-4-one [(XV-S,S) compound]

42. (R,R)-6-fluoro-2-(oxiran-2-yl)-chroman-4-one [(XVI-R,R) compound]

43. (S,R)-6-fluoro-2-(oxiran-2-yl)-chroman-4-one [(XVI-S,R) compound]

44. (S,S)-6-fluoro-2-(oxiran-2-yl)-chroman-4-one [(XVI-S,S) compound]

45. (R,S)-6-fluoro-2-(oxiran-2-yl)-chroman-4-one [(XVI-R,S) compound]

46. (R,R)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one [(XX-R,R) compound]

47. (S,S)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one [(XXV-S,S) compound]

48. (R,S)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one [(XXIII-R,S) compound]

49. (S,R)-2-(2-benzylamino-1-hydroxy-ethyl)-6-fluoro-chroman-4-one [(XVIII-S,R) compound]

50. N-benzyl-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine [XIX (S,R,R,R) compound]

51. N-benzyl-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine [XXIV (R,S,S,S) compound]

52. N-benzyl-[(R,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine [XXI (S,R,R,R) compound]

53. N-benzyl-[(S,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine [XXVI (R,S,S,S) compound]

54. N-[(R,R)-1-hydroxy-2-(6-fluoro-4-hydroxy-chroman-2-yl)]-N-[(S,R)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine [XXII (S,R,R,R) compound]

55. N-[(S,S)-1-hydroxy-2-(6-fluoro-4-hydroxy-chroman-2-yl)]-N-[(R,S)-1-hydroxy-2-(6-fluoro-chroman-4-one-2-yl)]-amine [XXVII (R,S,S,S) compound]

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 03/00093

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D311/58 C07D317/26 C07D311/22 C07D407/04 C07F9/535 C07F9/54

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)
IPC 7 C07D C07F

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 practical, search terms used)
CHEM ABS Data, EPO-Internal, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 654 362 A (GUY VAN LOMMEN) 31 March 1987 (1987-03-31) cited in the application column 15 -column 28	1
A	J. HENDRICKX ET AL.: "LOCATION OF THE OH FUNCTIONS IN HYDROXYLATED METABOLITES OF NEBIVOLOL" JOURNAL OF CHROMATOGRAPHY A, vol. 729, no. 1+2, 1996, pages 341-354, XP002270638 GB page 353; figure V	1,54,55

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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

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Date of the actual completion of the international search	Date of mailing of the international search report
17 February 2004	02/03/2004

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 03/00093

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