TITLE:

Asymmetric Synthesis of Furo[3,4-c] pyridine derivatives

DESCRIPTION:

The invention relates to a method for the preparation of non-racemic furo [3, 4-c] pyridine derivatives.

In this Specification the term "non-racemic" is used to indicate a single enantiomer or an enantiomer mixture in which one enantiomer predominates.

It is now generally recognized that two enantiomers of a drug molecule, when introduced into a biological environment, behave as if they were different chemical entities. These variations can be demonstrated as differences in:

1. protein binding,
2. metabolism,
3. pharmacokinetics,
4. tissue distribution,
5. receptor binding, and
6. enzyme inhibition;

and are caused by a difference in stereoconfiguration. The two enantiomers are generally labelled as R or S or (-) or (+) to distinguish them.

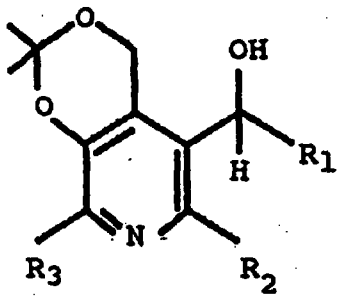
Thus, in vivo, any racemic mixture is constantly subjected to stereodifferentiation by encountering chiral surroundings either in solution or when bound to solid phase structures (cell receptors, etc). As a result of this stereodifferentiation, enantiomers may not only differ in therapeutic activity, but may behave antagonistically.

Consequently, it is becoming increasingly necessary for regulatory approval to provide toxicity, pharmacology, disposition and activity data for each individual isomer as well as the drug racemate (i.e., a 1:1 mixture of stereoisomers). This necessitates that methods be available for the generation of the optically pure drug enantiomers. Generally, three strategies can be employed to prepare pure isomeric products:

1. preparation of a racemate of the desired compound and separation of the racemate into its enantiomers;
2. preparation of a racemate of the desired compound, conversion of the racemate into a racemic derivative, separation of the racemic derivative into its enantiomers, and reconversion of each enantiomer separately into an enantiomer of the desired compound; and
3. asymmetric synthesis of individual enantiomers of the desired compound.

In typical organic synthesis, enantiomeric products are obtained without control over the ratio of one type of stereoisomer to the other and statistically these different enantiomers are obtained in a proportion of 1:1 to form a racemic mixture.

The invention is most particularly concerned with the conversion of a non-racemic compound of the general formula II



II

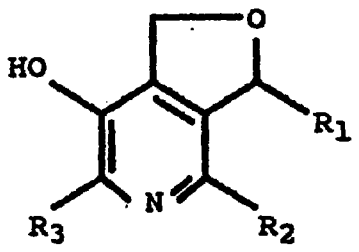
wherein

R_1 represents a straight chain saturated or unsaturated hydrocarbon group having from 1 to 5 carbon atoms, a heterocyclic group having up to 6 ring atoms, a carbomonocyclic group, a phenyl group, a phenylalkyl group or a phenylalkenyl group, each of said groups being optionally substituted by one or more halogen atoms, trifluoromethyl groups, alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms, alkylthio groups having from 1 to 5 carbon atoms, dialkylamine groups in which each of the two alkyl groups has from 1 to 5 carbon atoms, dialkylaminoalkoxy groups in which each of the two alkyl groups and the alkoxy group has from 1 to 5 carbon atoms or an α or-β-alkoxy-N-pyrrolidinyl group in which the alkoxy group has from 1 to 5 carbon atoms;

R_2 represents a hydrogen or halogen atom; and

R_3 represents a straight chain or branched chain alkyl or alkenyl group having up to 6 carbon atoms, optionally substituted by a hydroxy, cyano, amino or substituted amino group or by an alkyl or alkenyl group having up to 4 carbon atoms

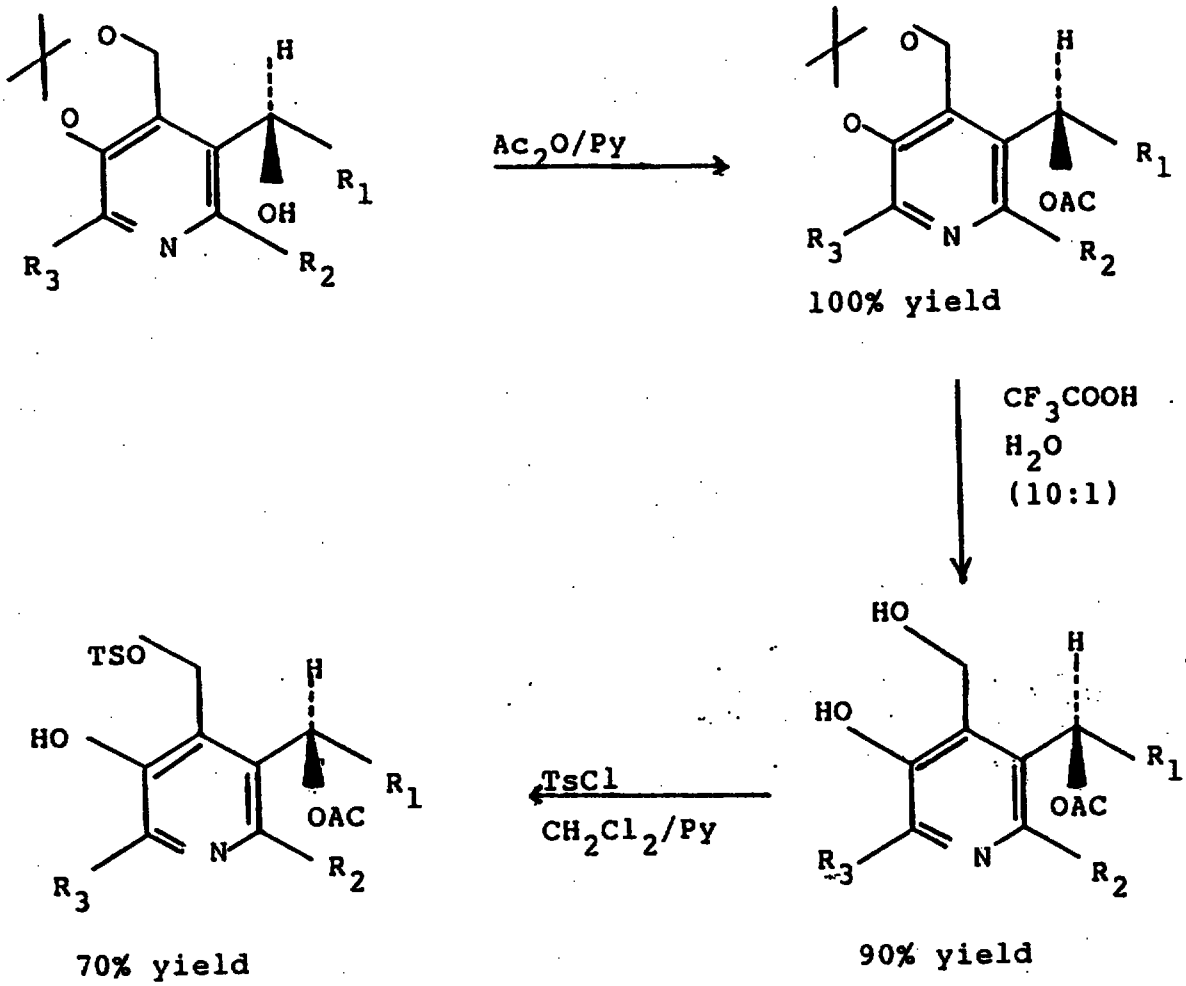
to the corresponding non-racemic furo [3,4-c] pyridine derivative of the general formula I



I

wherein R_1, R_2 and R_3 are as above defined.

A route is known for such a conversion, but is laborious, involving five steps as shown in the following reaction scheme:


Ac2O/Py
100% yield
CF3COOH
H2O
(10:1)
TsCl
CH2Cl2/Py
70% yield
90% yield
MeOH
NH3
HMPT
2 eq NaH
1 hr.
100% yield
70% yield

The hydroxy group must first be protected. The acetonide blocking group can then be removed, and the resulting 4-hydroxymethyl group is then tosylated to provide for easier SN2 displacement subsequently. The acetoxy protecting group is then removed, and a base catalysed cyclisation provides the desired compound.

The invention provides a method for conversion of a non-racemic compound of the general formula II as herein defined to the corresponding non-racemic furo [3,4-c] pyridine derivative of the general formula I as herein defined, the method comprising adding concentrated sulphuric or perchloric acid to a solution of the compound II in an amount sufficient to catalyse a deprotection/cyclodehydration reaction. There is thus achieved in a single step that which hitherto necessitated five steps.

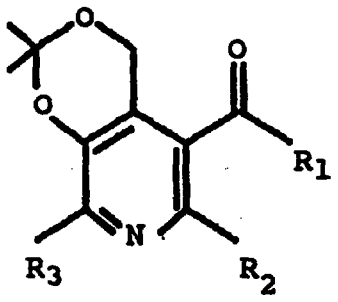
Preferably the non-racemic compound II is dissolved in a solvent which forms an azeotrope with water. From a variety of such solvents, there may be mentioned benzene, toluene, ethyl acetate and chloroform.

In a preferred embodiment, the starting material II is initially purified by alcohol or ethyl acetate crystallization before being dissolved in the solvent. When the starting material of the general formula II is optically enriched, i.e. 80/20, ethyl acetate crystallization may provide a product that is typically greater than 95% optically pure.

The non-racemic furo [3,4-c] pyridine derivative may be recovered by decanting the excess solution, including the unreacted compound of the general formula II, from a

residue produced by the cyclodehydration reaction, dissolving the residue in alcohol to produce a mixture, determining what part of the alcohol mixture is a compound of the general formula I, and isolating the same from the alcohol mixture.

The non-racemic compound II which is the starting material for the method of the invention may be obtained from the corresponding racemic compound by oxidation to a ketone of the general formula III



III

wherein R_1, R_2 and R_3 are as defined hereinabove, followed by stereospecific reduction of the ketone. In detail, this method may comprise:

(a) dissolving the racemic form of the compound of the general formula II in an organic solvent to form a solution;

(b) adding dropwise an oxidizing agent to said solution in a sufficient amount to completely react with all the compound racemates of the general formula II;

(c) quenching the excess oxidizing agent with an alcohol;

(d) cooling the liquid to produce a solid compound precipitate;

(e) dissolving said solid crystals in tetrahydrofuran to form a mixture;

(f) adding to said mixture a chiral reducing agent to

reduce said solid compound to the desired non-racemic compound of the general formula II and

(g) isolating the non-racemic compound of the general formula II and dissolving it in a solvent.

The organic solvent may be acetone. A suitable oxidizing agent is Jones Reagent (CrO_3 /H_2SO_4/H_2O). The alcohol used in quenching is suitably isopropanol.

The initial stereocontrolled step of adding a hydride from a chiral metal hydride or borohydride reagents to acyclic ketones has been widely used for the preparation of optically active secondary alcohols, see for example, Brown, H.C., et al., J.Org.Chem, 52: 5406 - 12 (1987).

The chiral reducing agent may be N,B-Enantride^{TM}(Aldrich Chemical Co.) or $MDBH_2$ (Expansia, European patent N° 0 061 408) in tetrahydrofuran (THF). Such reducing agents are produced by chiral modifications of complex metal hydrides as well as borohydrides (Brown, H.C., et al., J.Org.Chem., 52: 5406-12 (1987).

N,B-Enantride^{R} is lithium hydrido (9-BBN-nopolbenzyl ether adduct), in a 0.5 m solution in THF. The following reagents are all suitable for use in the present invention: B-Ipc-9-BBN (Alpine - borane, Aldrich), N,B - Entrane (Aldrich), Ipc_2BCl (Aldrich), BM_3-ANDPB (2:1) (see S.Itsuno, J. Chem.Soc., Chem.Comm.1981, 315), (R,R)-2,5--dimethylborolane (see S.Masamune, J.Am Chem.Soc.1986, 108, 7402), N,B - Enantride (Aldrich), $LIBH_4$-DBC-t- BuOH (see K.Soal, J.Chem.Soc., Chem.Com. 1984, 413), $NaBH_4$-IBA-DIPGF (see S.Itsuno, J.Chem.Soc., Perkin Trans.1, 1981, 900), K-Glucoride (see H.C. Brown, J.Org.Chem. 1986, 51, 1934), $LiAlH_4$-Darvon Alc (see H.Mosher, J.Am.Chem.Soc.,1972, 94, 9254) $LiAlH_4$-MEP-ArOH (see J.P. Vigneron, Tetrahedron 1976,

32, 939), $LIAlh_4$-Diamine (see M.Asami, Heterocycles, 1979, 12, 499), $LiAlH_4$-Aminobutanol (see T.Sato, Tet.Letters 1982, 23, 4111), Binal H (See R.Noyori, J.Am.Chem.Soc. 1979, 101, 3129), $LiAlH_4$-DBP-EtOH (see K.Yamamoto, J.Chem.Soc., Chem.Comm. 1984, 1490), $LiAlH_4$-MEP-NEA (see K.J.Koga, J.Chem.Soc., Chem.Comm.1980,1026), $LiAlH_4$-MEP-EAP (see S.Terashima, Chem.Letters 1984, 239), TBADH (thermoanaerobium brockii alcohol dehydrogenase, Sigma Chem.Co.)

The non-racemic compound II may alternatively be obtained from the ketone III by:

(a) dissolving it in a vigorously stirred fermenting slurry of yeast, water and a carbohydrate;

(b) adding additional carboydrate and yeast to provide continued vigorous fermentation to form the desired chiral compound of the general formula II;

(c) continuing said fermentation until formation of the compound of the general formula II ceases and

(d) isolating the compound of the general formula II.

The following Examples describe the preparation of the ketone III: R_1 = 4-chlorophenyl, R_2 = H, R_3 = CH_3 from the corresponding racemic alcohol II (Example 1), the preparation of the corresponding non-racemic alcohol II from the ketone III (Example 2), and the preparation of the corresponding non-racemic furo [3,4-c] pyridine derivative I : R_1 = 4-chlorophenyl, R_2 = H, R_3 = CH_3 from the non-racemic alcohol II by the method of the invention (Example 3).

EXAMPLE 1

Synthesis of ketone III by oxidation of racemic 2,2,8-trimethyl-5-(4-chloro-α-hydroxybenzyl)-pyrido-[4,3-e]--1,3-Dioxane

2.16 g (6,7 mmoles) of racemic 2,2,8-trimethyl-5-(4-chloro -α-hydroxybenzyl)-pyrido- [4,3-e] -1,3-dioxane were poured into an Erlenmeyer flask and dissolved in 150 ml acetone. Jones reagent ($CrO_3/H_2SO_4/H_2O$) was added dropwise to the stirred solution until the starting material was completely used up as determined by TLC (thin layer chromatography). Excess oxidizing agent was quenched in isopropanol. The reaction mixture was poured into iced water and the solid that formed was removed by filtration. The reaction mixture was washed several times with water. The crude product was dissolved in methanol and set aside to crystallize. Two crops of plate-like crystals were collected (1.7 g) and thoroughly dried under nitrogen. The final product was homogeneous by TLC (dichloromethane: methanol, 10:1 by volume, Rf = 0.8) and HPLC.

EXAMPLE 2

Synthesis of (+) -2, 2, 8-trimethyl-5-(4-chloro-α-hydroxy-benzyl)-pyrido-[4,3-e]-1,3-dioxane

1.1 g (3.5 mmol) of the ketone prepared in Example 1 were poured into a 50 ml round bottomed flask and dissolved in 35 ml of dry THF (tetrahydrofuran). The flask was sealed with a septum, placed under a nitrogen atmosphere and set into a dry ice/acetone bath. [1S]-N,B-Enantride^R (13.3 ml, 6,65 mmoles) was then added in one portion and the rate of reduction was followed by HPLC (high pressure liquid chromatography) at T - 0, T - 1 hr and T - 2 hr. Typically, most of the ketone was reduced to (+)-2,2,8-trimethyl-5(4-chloro-α-hydroxybenzyl)-pyrido-[4,3-e]-1,3-dioxane after two hours. The reaction mixture was evaporated to dryness on a roto-vac, the residue was redissolved in dichloromethane, loaded on the top of a silica gel column (42 g) and eluted with dichloromethane. The separation was assayed by TLC and fractions nos 131-160 were combined. The solvent was removed by rotary evaporation and the residue (1.05 g) was redissolved in

12 ml of ethyl acetate. On cooling, a fluffy white crop of crystals precipitated and was collected (0.25 g). This sample was homogeneous by TLC (dichloromethane: methanol, 10:1 by volume) and HPLC and provided (+)-2,2,8-trimethyl-5-(4-chloro-α-hydroxybenzyl)-pyrido-[4,3-e]-1,3-dioxane of high enantiomeric enrichment (> 86%).

EXAMPLE 3

Deprotection/cyclodehydration of (+)-2,2,8-trimethyl-5-(4-chloro-α-hydroxybenzyl)-pyrido-[4,3-e]-1,3-dioxane to (+)-3-(4-chlorophenyl)-1,3-dihydro-7-hydroxy-6-methylfuro[3,4-c]-pyridine

317 mg (1 mmol) of (+)-2,2,8-trimethyl-5-(4-chloro-α-hydroxybenzyl)-pyrido-[4,3-e]-1,3-dioxane, prepared as described in Example 2, were poured into 100 ml round bottomed flask and dissolved in 60 ml of benzene. Two drops of concentrated sulphuric acid were added, a Dean-Stark adaptor was attached and the reaction mixture was refluxed for two hours. The benzene solution (which contained unreacted starting material) was poured off from the yellow green solid which had formed on the bottom of the flask. The insoluble material was dissolved in methanol, spotted onto a 2000 μ silica gel TLC plate and eluted with dichloromethane: methanol, 7:1 by volume.

The major U.V. visible band which co-eluted with a spot of known (+)-3-(4-chlorophenyl)-1,3-dihydro-7-hydroxy-6-methyl-furo-[3,4-c]-pyridine was excised from the plate and the organic material from the silica was washed with methanol. Removal of the methanol by rotary evaporation gave a solid product shown to be (+)-3-(4-chlorophenyl)-1,3-dihydro-7-hydroxy-6-methylfuro-[3,4-c]-pyridine by spectroscopic and chromatographic comparison with an authentic sample.

Chiral phase HPLC of the isolated product showed it to be a mixture of (-) and (+)-3-(4-chlorophenyl)-1,3-dihydro-7--hydroxy-6-methylfuro- [3,4-c] pyridine in a ratio that is identical to that of the starting (+)-2,2,8-trimethyl-5--(4-chloro-α-hydroxybenzyl)-pyrido-[4,3-e]-1,3-dioxane.

The furo [3,4-c] pyridine derivative compounds obtained according to this invention are of use in the variou pharmaceutical fields described in British patents Nos. 2.092.586, 2.137.618, 2.148.292, 2.149.782, 2.153.824 and 2.166.136. Accordingly, this invention also provides a pharmaceutical composition comprising a non-racemic compound of the general formula I prepared according to the method herein defined in admixture with a pharmaceutically acceptable diluent or carrier.

The appropriate administration modes are described in the above mentioned patents, but the dosage required is lower due to the enhanced activity of the selected enantiomer or of the enantiomer mixtures wherein said enantiomer is predominant.

PRESENTATION

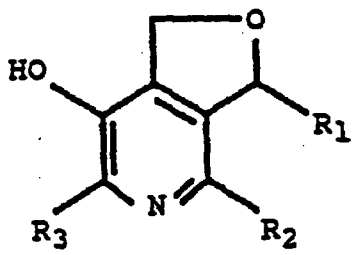
The preferred administration mode is tablets and capsules. For tablets, each dosage unit contains from 5 to 100 mg or, preferably, 10 to 25 mg of the active principle associated with an appropriate inert carrier, such as starch.

POSOLOGY

In human therapy, the doses to be used are from 50 to 150 mg/day for at least one week, and preferably for longer periods of time.

CLAIMS

1. A method for the preparation in non-racemic form (that is as a single enantiomer or as an enantiomeric mixture in which one enantiomer predominates) of a compound of the general formula I:



I

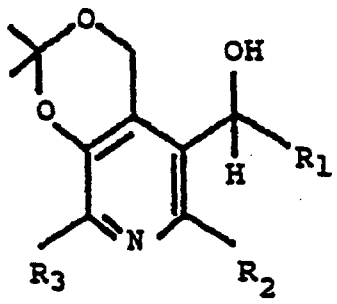
wherein

R_1 represents a straight chain saturated or unsaturated hydrocarbon group having from 1 to 5 carbon atoms, a heterocyclic group having up to 6 ring atoms, a carbomonocyclic group, a phenyl group, a phenylalkyl group or a phenylalkenyl group, each of said groups being optionally substituted by one or more halogen atoms, trifluoromethyl groups, alkyl groups having from 1 to 5 carbon atoms, alkoxy groups having from 1 to 5 carbon atoms, alkylthio groups having from 1 to 5 carbon atoms, dialkylamine groups in which each of the two alkyl groups has from 1 to 5 carbon atoms, dialkylaminoalkoxy groups in which each of the two alkyl groups and the alkoxy group has from 1 to 5 carbon atoms or an α or-β-alkoxy-N-pyrrolidinyl group in which the alkoxy group has from 1 to 5 carbon atoms;

R_2 represents a hydrogen or halogen atom; and

R_3 represents a straight chain or branched chain alkyl or alkenyl group having up to 6 carbon atoms, optionally substituted by a hydroxy, cyano, amino or substituted amino group or by an alkyl or alkenyl group having up to 4 carbon atoms;

...ne method comprising adding concentrated sulphuric or perchloric acid to a solution of a non-racemic compound of the general formula II:



II

wherein R_1, R_2, R_3 are as defined in this claim in an amount sufficient to catalyze a deprotection/cyclodehydration reaction.

2. A method according to claim 1 in which the solution of the compound II is a solution in a solvent which forms an azeotrope with water.

3. A method according to claim 2 in which the solvent is benzene, toluene, ethyl acetate or chloroform.

4. A method according to any preceding claim in which the compound II is purified by crystallization from an alcohol or from ethyl acetate before dissolution.

5. A method according to any preceding claim further comprising recovering the compound I from the reaction mixture.

6. A method according to claim 5 in which the compound I is recovered by decanting excess solution, including any unreacted compound II, from a residue produced by the cyclodehydration reaction, dissolving the residue in an alcohol to produce a mixture, determining what part of the alcohol mixture is the compound I, and isolating the same from the alcohol mixture.

7. A method according to any preceding claim in which the solution of the non-racemic compound II is prepared by

dissolving the racemic form of compound II in an organic solvent to form a solution;

adding dropwise an oxidizing agent to the said solution in an amount sufficient completely to react with the compound II racemate;

quenching the excess oxidizing agent with an alcohol;

cooling the liquid to precipate a solid compound;

dissolving the solid compound in tetrahydrofuran to form a mixture;

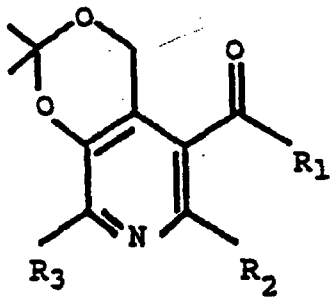
adding to the mixture a chiral reducing agent to reduce the solid compound to the desired non-racemic compound II; and

isolating the non-racemic compound II and dissolving it in a solvent.

8. A method according to claim 7 in which the organic solvent is acetone, the oxidizing agent is Jones Reagent, the alcohol is isopropanol and the chiral reducing agent is lithium hydrido (9-BBN-nopolbenzyl ether adduct).

9. A method according to any of claims 1 to 6 in which the solution of the non-racemic compound II is prepared by

dissolving a compound of the formula III:



III

wherein R_1, R_2 and R_3 are as defined in claim 1 in a vigorously stirred fermenting slurry of yeast, water and a carbohydrate,

adding additional carbohydrate and yeast to provide continued vigorous fermentation to form the desired non-racemic compound II;

continuing said fermentation until formation of the non-racemic compound II ceases; and

isolating the non-racemic compound II and dissolving it in a solvent.

10. A pharmaceutical composition comprising a non-racemic compound of the general formula I prepared according to any preceding claim in admixture with a pharmaceutically acceptable diluent or carrier.