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Lenfers et al.

(10) **Patent No.: US 6,774,236 B1**
(45) **Date of Patent: Aug. 10, 2004**

(54) **PROCESS FOR THE PREPARATION OF ENANTIOMERICALLY PURE CYCLOALKANO-INDOL -AND AZAINDOL -AND PYRIMIDO [1,2A] INDOLCARBOCYCLIC ACIDS AND THEIR ACTIVATED DERIVATIVES**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/307,980**

(22) Filed: **May 10, 1999**

Related U.S. Application Data

(62) Division of application No. 08/829,566, filed on Mar. 31, 1997, now Pat. No. 5,952,498.

(30) **Foreign Application Priority Data**

Apr. 4, 1996 (DE) 196 13 549

(51) **Int. Cl.**[7] **C07D 471/04**; C07C 487/04; C07C 69/616; C07C 60/612

(52) **U.S. Cl.** **544/252**; 560/8; 544/248; 544/252; 54/84; 54/85; 54/86; 54/87; 548/427

(58) **Field of Search** 560/8; 544/252

(56) **References Cited**

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(57) **ABSTRACT**

The invention relates to a process and intermediates for the preparation of enantiomerically pure cycloalkanoindolecarboxylic acids and azaindolecarboxylic acids and pyrimido [1,2a]indolecarboxylic acids and their activated derivatives, characterized in that the tolyl acetic acid is first esterified with a chiral alcohol, then diastereoselective substitution at α-carbon atoms is carried out and this product is halogenated in the tolyl group and then reacted with appropriate cycloalkanoindoles, cycloalkanoazaindoles or pyrimido[1,2a]indoles. It is possible by this method to prepare specifically, in high purity, the enantiomerically pure carboxylic acids which are intermediates for valuable medicaments.

2 Claims, No Drawings

PROCESS FOR THE PREPARATION OF ENANTIOMERICALLY PURE CYCLOALKANO-INDOL -AND AZAINDOL -AND PYRIMIDO [1,2A] INDOLCARBOCYCLIC ACIDS AND THEIR ACTIVATED DERIVATIVES

This application is a division of Ser. No. 08/829,566 filed on Mar. 31, 1997, now Pat. No. 5,952,498, which claims priority to German Application 196 13 549.4 filed on Apr. 4, 1996.

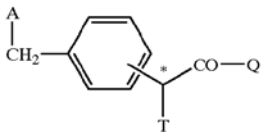
The invention relates to a process for the preparation of enantiomerically pure cycloalkano-indolecarboxylic acids and azaindolecarboxylic acids and pyrimido[1,2a] indolecarboxylic acids and their activated derivatives, which represent important intermediates for the synthesis of antiatherosclerotically active cycloalkanoindole derivatives and azaindole derivatives and pyrimido[1,2a]indole derivatives.

It is known that enantiomerically pure cycloalkano-indolecarboxylic acids and azaindole-carboxylic acids and their activated derivatives can be separated into the corresponding enantiomers by diastereomeric separation by conventional methods, for example by chromatography or fractional crystallization.

This process has a number of disadvantages: both the chromatographic diastereomeric separation and the fractional crystallization of the diastereomers are associated with high equipment requirements. In addition, in this case, generally 50% of the "wrong" diastereomer arises, which can no longer be recycled to the original preparation process.

This 50% loss of yield considerably impairs the economic efficiency of a (large) industrial-scale process, quite apart from the fact that 50% of "by-product" must be disposed of. Furthermore, the customary chiral auxiliary reagents are generally very expensive even in small amounts and can then usually only be prepared via a complex synthetic pathway.

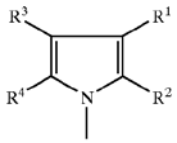
It has now been found that enantiomerically pure cycloalkano-indolecarboxylic acids and azaindolecarboxylic acids and pyrimido[1,2a]indole-carboxylic acids and their activated derivates of the general formula (I)



(I)

in which

A represents a radical of the formula



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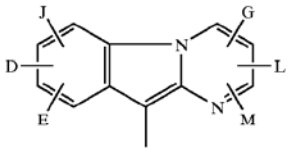
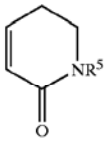


J, D, E, G, L and M are identical or different and denote hydrogen, halogen, trifluoromethyl, carboxyl, hydroxyl, linear or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, or linear or branched alkyl having up to 6 carbon atoms, which itself can be substituted by hydroxyl or by linear or branched alkoxy having up to 4 carbon atoms,

in which

R^1 and R^2, including the double bond linking them, together form a phenyl ring or pyridyl ring or a ring of the formula



where

R^5 denotes hydrogen or linear or branched alkyl having up to 4 carbon atoms,

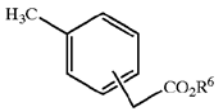
R^3 and R^4, including the double bond linking them, together form a phenyl ring or a 4- to 8-membered cycloalkene or oxocycloalkene radical, where all the ring systems listed under R^1/R^2 and R^3/R^4 are optionally up to trisubstituted identically or differently by halogen, trifluoromethyl, carboxyl, hydroxyl, by linear or branched alkoxy or alkoxycarbonyl each having up to 6 carbon atoms, or by linear or branched alkyl having up to 6 carbon atoms, which itself can be substituted by hydroxyl or by linear or branched alkoxy having up to 4 carbon atoms,

T represents cycloalkyl having 4 to 12 carbon atoms, or represents linear or branched alkyl having up to 12 carbon atoms,

Q represents hydroxyl or an activating radical,

and their salts are obtained

by firstly converting compounds of the general formula (II),



(II)

in which

R^6 together with the oxygen atom represents a chiral alcohol radical, by means of compounds of the general formula (III)

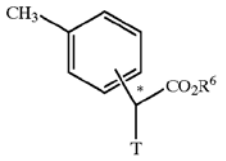
T—Z (III)

in which

T has the meaning specified and

Z represents a typical leaving group, such as bromine, chlorine, iodine, mesyl, tosyl, or trifluoromethylsulphonyl, preferably iodine or bromine,

n inert solvents in the presence of a base by diastereoselective alkylation into the enantiomerically pure compounds of the general formula (IV)

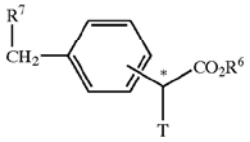


(IV)

in which

T and R^6 have the meaning specified,

then converting these, by halogenation, into the enantiomerically pure compounds of the general formula (V)



(V)

in which

T and R^6 have the meaning specified

and

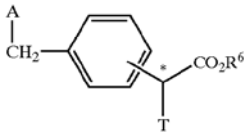
R^7 represents halogen, such as chlorine, bromine, iodine, preferably bromine, reacting these in a further step with compounds of the general formula (VI)

(VI)

in which

R^1, R^2, R^3 and R^4 have the meaning specified,

to give the enantiomerically pure compounds of the general formula (VII)



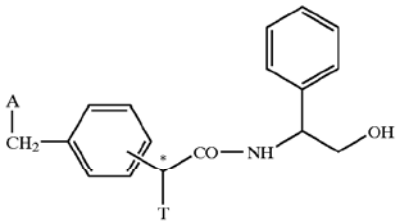
(VII)

in which

A, T and R^6 have the meaning specified,

and, in the case of compounds of the general formula (I) where Q═OH, carrying out a hydrolysis, and in the case where Q=activating radical, starting from the enantiomerically pure acids reacting with activating reagents.

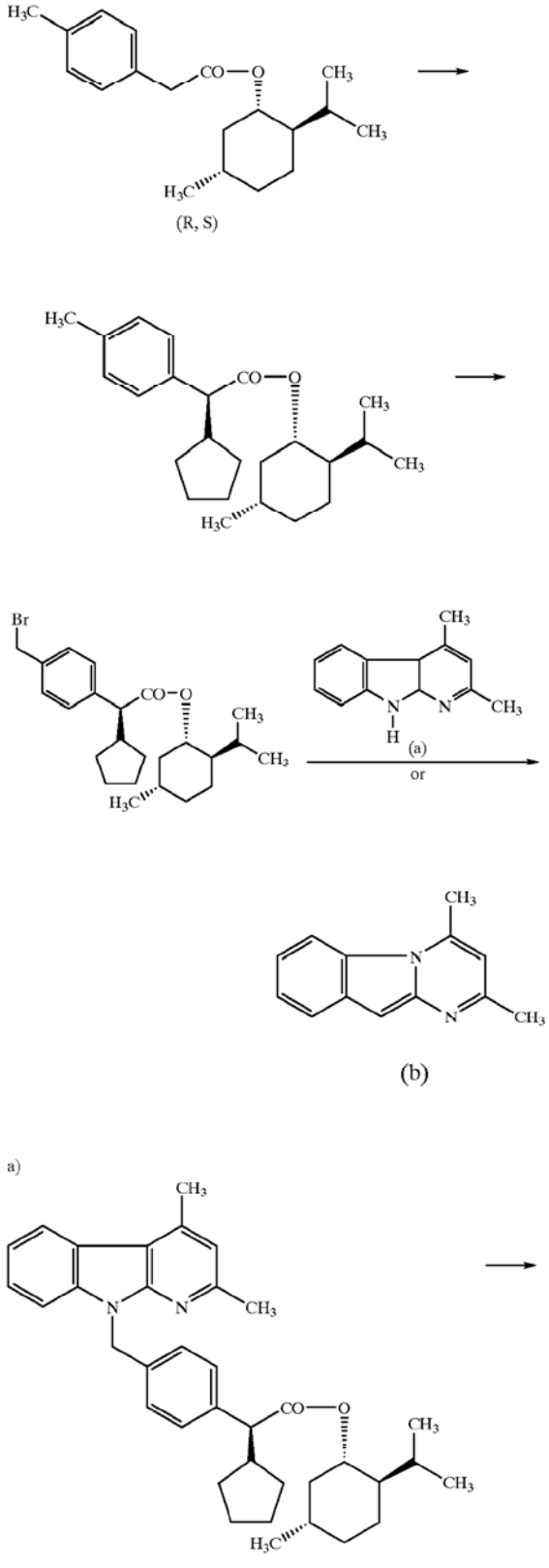
These can be reacted in a further step with D- or L-phenylglycinol to give compounds of the general formula (VIII)



(VIII)

where these are in this case active compounds for medicaments.

The process according to the invention can be described by way of example by the following formula diagram:



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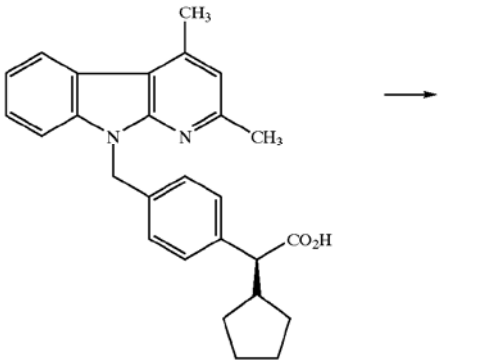
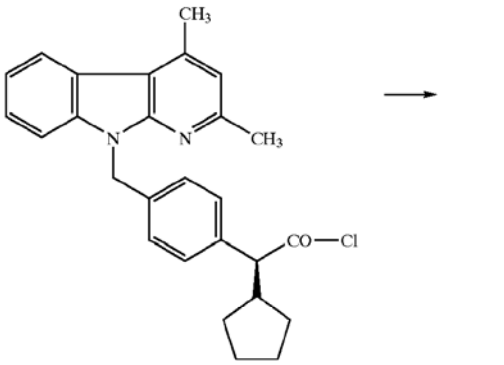
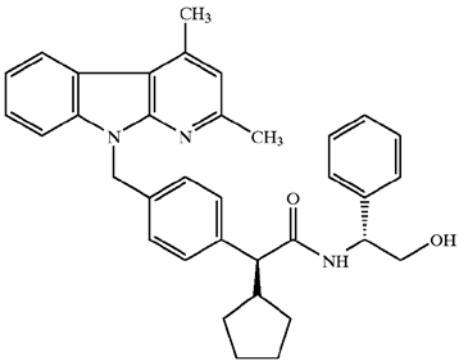
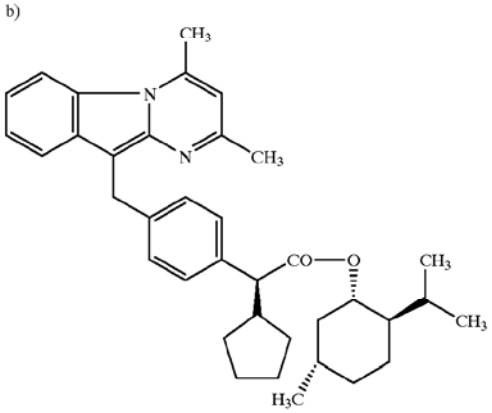






b)



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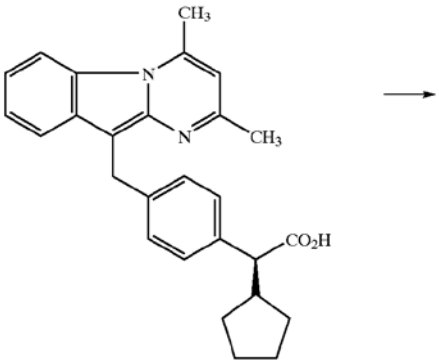
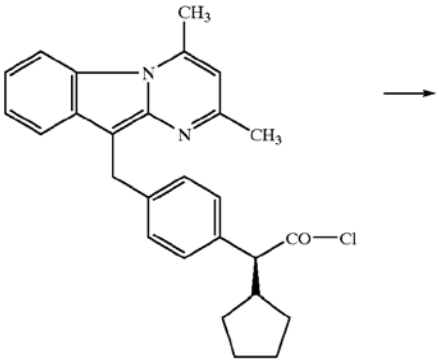
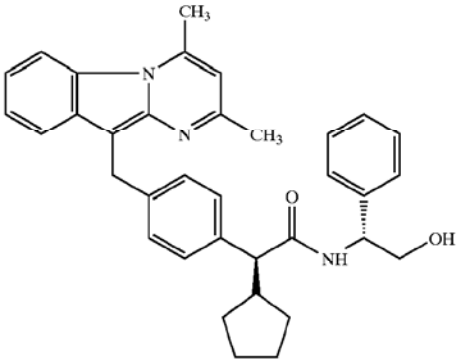






Surprisingly, the process according to the invention gives the wanted enantiomerically pure cycloalkano-indolecarboxylic acids and azaindole-carboxylic acids and pyrimido-indolecarboxylic acids and their activated derivatives without great equipment requirements in very good yields and high purity.

Depending on the configuration of the radical R^6 and stearic effects of the alkyl halide (II) used, the alkylation of the compound (II) proceeds in high yields and in a simple manner diastereoselectively for the first time. The compounds (IV) arise with high diastereomeric excess and crystallize out of the reaction mixture directly, as a result of which even the simple crystallization of crude products gives the compounds of the formula (IV) in diastereomerically pure form.

A further advantage of the process according to the invention is that, by suitable choice of the solvent and a base, the unwanted diastereomer can be epimerized to the desired diastereomer, which in turn crystallizes out directly. Thus, further (wanted) diastereomerically pure product can be produced from the mother liquors by repeated epimerization and crystallization. Direct addition of the mother liquors to the alkylation step can optimize the entire process in the form of a cyclic process.

A further advantage of the process according to the invention is that the halogenated compounds of the general formula (V) surprisingly react with the compounds of the general formula (VI) without racemization at the carbon atom in the 2 position to the carboxylic acid function, to give the compounds of the general formula (VII).

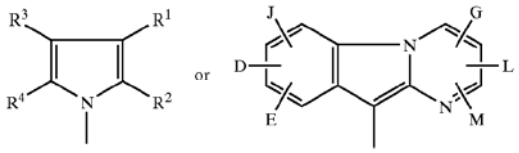
A further advantage of the process according to the invention is the racemization-free reaction at the carbon atom at the 2 position to the carboxylic acid function of the compounds of the general formula (I) where Q=activated radical, preferably chlorine, to give the compounds of the general formula (VIII).

Furthermore, it is a great advantage of the process according to the invention that the starting compounds are very readily accessible. They may be prepared in good yields from relatively simple building blocks with low equipment requirements. Furthermore, the process according to the invention enables amounts of known racemates of the compounds of the general formula (I) present to be converted into the corresponding enantiomers. The process according to the invention enables the preparation of the compounds according to the invention of the general formula (I) using few synthetic stages and in a considerably higher overall yield than by processes known from the prior art.

R^6, in the context of the above specified definition, represents a chiral alcohol radical, such as (+)- or (−)-menthyl, (+)- or (−)-bornyl, (+)- or (−)-isobornyl or (−)-8-phenylmenthyl. Preferably, R^9 represents (+)- or (−)-menthyl.

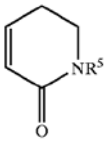
Activating radicals (Q), in the context of the invention, generally represent chloride, bromide, mesylate, tosylate or trifluoride. Preference is given to chloride. Preferably, by the process according to the invention, compounds of the general formula (I) are prepared, in which

A represents a radical of the formula



in which

J, D, E, G, L and M are identical or different and denote hydrogen, fluorine, chlorine, bromine trifluoromethyl, carboxyl, hydroxyl, linear or branched alkoxy or alkoxycarbonyl each having up to 4 carbon atoms, or linear or branched alkyl having up to 4 carbon atoms which itself can be substituted by hydroxyl or by linear or branched alkoxy having up to 3 carbon atoms, R^1 and R^2, including the double bond linking them, together form a phenyl ring or pyridyl ring or a ring of the formula



in which

R^5 denotes hydrogen or linear or branched alkyl having up to 3 carbon atoms,

R^3 and R^4, including the double bond linking them, together form a phenyl ring or a cyclopentene, cyclohexene, cycloheptene, cyclooctene, oxocyclopentene, oxocyclohexene, oxocycloheptene or oxocyclooctene radical,

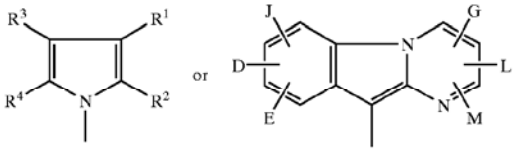
where all ring systems, listed under R^1/R^2 and R^3/R^4 are optionally up to disubstituted identically or differently by fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, by linear or branched alkoxy or alkoxycarbonyl each having up to 4 carbon atoms, or by linear or branched alkyl having up to 4 carbon atoms, which itself can be substituted by hydroxyl or by linear or branched alkoxy having up to 3 carbon atoms,

T represents cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, or represents linear or branched alkyl having up to 10 carbon atoms,

Q represents hydroxyl or represents an activating radical, and their salts.

Particularly preferably, compounds of the general formula (I) are prepared by the process according to the invention in which

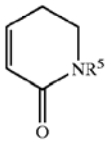
A represents a radical of the formula



in which

J, D, E, G, L and M are identical or different and denote hydrogen, fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, linear or branched alkoxy or alkoxycarbonyl each having up to 3 carbon atoms, or denote linear or branched alkyl having up to 3 carbon atoms,

R^1 and R^2, including the double bond linking them, together form a phenyl ring or pyridyl ring or a ring of the formula



in which

R^5 denotes hydrogen or methyl,

R^3 and R^4, including the double bond linking them, together form a phenyl ring or a cyclopentene, cyclohexene, cycloheptene, cyclooctene, oxocyclopentene, oxocyclohexene, oxocycloheptene or oxocyclooctene radical,

where all ring systems listed under R^1/R^2 and R^3/R^4 are optionally up to disubstituted identically or differently by fluorine, chlorine, bromine, trifluoromethyl, carboxyl, hydroxyl, by linear or branched alkoxy or alkoxycarbonyl each having up to 3 carbon atoms or by linear or branched alkyl having up to 4 carbon atoms which itself can by substituted by hydroxyl, methoxy or ethoxy.

T represents cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl or linear or branched alkyl having up to 6 carbon atoms,

Q represents hydroxyl or an activating radical, and their salts.

Very particularly preferably, the compounds of the general formula (I), in which

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