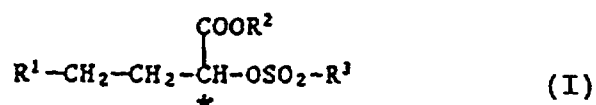


The invention relates to novel sulfonic acid esters, to processes for the preparation thereof, and to the use of these compounds as intermediates for the preparation of ACE inhibitors or their precursors.

The novel sulfonic acid esters have the formula I



wherein R^1 is C_5 - C_6 cycloalkyl which is unsubstituted or substituted by C_1 - C_7 alkyl, or is unsubstituted or substituted phenyl, R^2 is C_1 - C_7 alkyl, R^3 is phenyl which is substituted by halogen or by nitro, and the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration.

A phenyl radical R^1 may carry e.g. substituents selected from the group consisting of C_1 - C_7 alkyl e.g. methyl, hydroxy, C_1 - C_7 alkoxy, e.g. methoxy, C_1 - C_7 alkanoyloxy, e.g. acetoxy, fluorine, C_1 - C_7 alkylenedioxy, e.g. ethylenedioxy, amino, C_1 - C_7 alkylamino, e.g. methylamino, di(C_1 - C_7)alkylamino, e.g. dimethylamino, C_1 - C_7 alkanoylamino, e.g. acetylamino, carbamoyl, C_1 - C_7 alkylcarbamoyl, e.g. methylcarbamoyl, di(C_1 - C_7)alkylcarbamoyl, e.g. dimethylcarbamoyl, C_1 - C_7 alkanesulfonylamino, e.g. methane- or ethanesulfonylamino, sulfamoyl, C_1 - C_7 alkylsulfamoyl, e.g. methylsulfamoyl, di(C_1 - C_7)alkylsulfamoyl, e.g. dimethylsulfamoyl, C_1 - C_7 haloalkyl, e.g. trifluoromethyl, C_1 - C_7 hydroxyalkyl, e.g. hydroxymethyl, and C_1 - C_7 aminoalkyl, e.g. aminomethyl or 2-aminoethyl.

Hereinbefore and hereinafter, the general terms employed

have the following meanings: the prefix "C₁-C₇" denotes organic radicals containing 1 to 7, and especially 1 to 4, carbon atoms.

C₁-C₇Alkyl is e.g. methyl, ethyl, propyl, isopropyl, butyl or tert-butyl, but may also be pentyl, hexyl or heptyl.

C₁-C₇Alkoxy is e.g. methoxy, ethoxy, propoxy, isopropoxy or one of the four butoxy isomers.

C₁-C₇Alkanoyl is e.g. formyl, acetyl, propionyl or butyryl, and also isobutyryl or pivaloyl.

C₁-C₇Alkanoyloxy is e.g. acetoxy, propionyloxy, butyryloxy, and also formyloxy or pivaloyloxy.

C₅-C₆Cycloalkyl is cyclopentyl or cyclohexyl. C₁-C₇Alkyl-substituted C₅-C₆cycloalkyl is e.g. ethylcyclohexyl or methylcyclohexyl such as 4-methylcyclohexyl.

Aryl is e.g. naphthyl or especially phenyl.

1-Aryl-C₁-C₇alkyl is e.g. 1-naphthylethyl, benzyl or, especially, 1-phenylethyl.

Halogen is e.g. fluorine or iodine, but is especially chlorine or bromine.

C₁-C₇Alkylenedioxy is e.g. ethylenedioxy, 1,3-propylenedioxy, 2,3-butylenedioxy or 1,3-(2,2-dimethyl)propylenedioxy.

C₁-C₇Alkylamino or di(C₁-C₇)alkylamino is e.g. methylamino, dimethylamino, ethylamino, diethylamino, propylamino, isopropylamino or butylamino.

C₁-C₇Alkanoylamino is e.g. acetylamino or propionylamino and also formylamino.

C₁-C₇Alkylcarbamoyl or di(C₁-C₇)alkylcarbamoyl is e.g. methylcarbamoyl, dimethylcarbamoyl, ethylcarbamoyl, diethylcarbamoyl, propylcarbamoyl or butylcarbamoyl.

C₁-C₇Alkanesulfonylamino is e.g. methanesulfonylamino, ethanesulfonylamino or propanesulfonylamino.

C₁-C₇Alkylsulfamoyl or di(C₁-C₇)alkylsulfamoyl is e.g. methylsulfamoyl, dimethylsulfamoyl, ethylsulfamoyl, diethylsulfamoyl, propylsulfamoyl or butylsulfamoyl.

C₁-C₇Haloalkyl is e.g. halomethyl such as trifluoromethyl, or 2-chloroethyl.

C₁-C₇Hydroxyalkyl is e.g. hydroxymethyl or 1-hydroxyethyl or, especially, 2-hydroxyethyl.

C₁-C₇Aminoalkyl is e.g. aminomethyl or 1- or 2-aminoethyl.

R³ as nitro-substituted phenyl is e.g. mono- or dinitrophenyl such as 2-, 3- or 4-nitrophenyl or 2,4-dinitrophenyl.

R³ as halogen-substituted phenyl is phenyl which is substituted by 1 to 5 halogen atoms such as fluorine, chlorine or bromine and is for example bromophenyl, trichlorophenyl or pentafluorophenyl.

The asterisk denoting a carbon atom that is present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in

the R configuration signifies that the compounds of formula I, with respect to said carbon atom, are obtained as substantially pure enantiomers and not as racemates. The expression "substantially pure" means, with respect to formula I, a ratio of enantiomers that differs from the equimolar ratio of a racemate in that said ratio is at least 90:10, preferably at least 95:5 and, especially, 98:2 to 100:0, with the R or S form predominating. In preferred compounds of formula I, the R-configuration in a ratio as defined above will predominate.

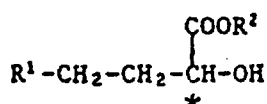
Preferred compounds of formula I are also those wherein R^1 is C_5 - C_6 cycloalkyl, phenyl or phenyl which is substituted by C_1 - C_7 alkyl, hydroxy, C_1 - C_7 alkoxy, C_1 - C_7 -alkanoyloxy, fluorine, trifluoromethyl or C_1 - C_7 alkyl-enedioxy, and R^2 , R^3 and the asterisk have the meanings assigned to them above.

Further preferred compounds of formula I are those wherein R^1 is C_5 - C_6 cycloalkyl, phenyl or phenyl which is substituted by one of the radicals selected from C_1 - C_4 -alkyl, hydroxy, C_1 - C_4 alkoxy or fluorine, R^2 is C_1 - C_4 -alkyl, R^3 is 2-, 3- or 4-nitrophenyl, 2,4-dinitrophenyl or pentafluorophenyl, and the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration, but especially in the R configuration.

Particularly preferred compounds of formula I are those wherein R^1 is cyclohexyl, phenyl, C_1 - C_4 alkylphenyl or C_1 - C_4 alkoxyphenyl, R^2 is C_1 - C_4 alkyl, R^3 is 4-nitrophenyl or 2,4-dinitrophenyl, and the asterisk denotes a carbon atom that is present in the preponderant number of molecules in the R configuration.

Especially preferred compounds of formula I are those wherein R^1 is phenyl, R^2 is C_1 - C_4 alkyl, R^3 is 4-nitrophenyl or 2,4-dinitrophenyl and the asterisk denotes a carbon atom that is present in the preponderant number of molecules in the R configuration; and, among these compounds, first and foremost those wherein R^2 is ethyl.

The compounds of formula I can be prepared in a manner known per se by reacting an α -hydroxy ester of formula II



(II)

wherein R^1 and R^2 are as defined for formula I and the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration, with a compound that converts the -OH substituent into the radical of formula $-\text{OSO}_2\text{-R}^3$, wherein R^3 is as defined for formula I.

Compounds that convert the -OH substituent into the radical of formula $-\text{OSO}_2\text{-R}^3$ are e.g. R^3 -sulfonic acid anhydrides such as mixed anhydrides, for example with hydrohalic acids, i.e. R^3 -sulfonyl halides, such as R^3 -sulfonyl chlorides or bromides, as well as anhydrides of the respective R^3 sulfonic acids themselves, i.e. compounds of the type $R^3\text{-SO}_2\text{-O-SO}_2\text{-R}^3$. The reaction is advantageously carried out in an inert solvent as well as in the presence of a base. Examples of suitable solvents are halogenated hydrocarbons such as dichloromethane, chloroform or carbon tetrachloride, and also hydrocarbons such as toluene, benzene or hexane. Suitable bases are inorganic or organic bases, e.g. basic

alkali metal salts or alkaline earth metal salts such as alkali metal carbonates, e.g. potassium carbonate, sodium carbonate, sodium bicarbonate, and also e.g. tertiary amines, such as pyridine, or trialkylamines, such as triethylamine.

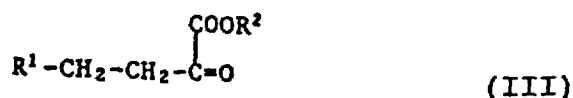
The reaction is advantageously carried out in the temperature range from -50° to $+110^{\circ}\text{C}$, if desired under a protective gas, for example under nitrogen or argon.

The reaction proceeds in a stereochemically uniform manner in such a way that the configuration at the carbon atom indicated by an asterisk is retained. Accordingly, the asterisk in formula II denotes a ratio of enantiomers in the range as defined for formula I, but a ratio of enantiomers of at least 80:20, preferably of at least 85:15.

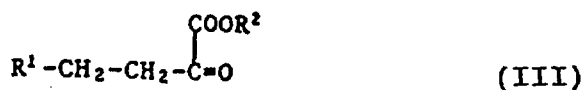
Starting compounds of formula II are known or can be prepared in known manner. Numerous known preparatory methods (see for example European patent application 126 986) such as the reduction of corresponding α -keto esters with Raney nickel and hydrogen or the acid hydrolysis of corresponding α -hydroxy nitriles and subsequent esterification lead to racemic α -hydroxy esters which have to be separated in a subsequent step, e.g. via diastereoisomers, by chromatography or fractional crystallisation. This separation step always entails the loss of at least 50% of the substance being separated. There is consequently a need for a process that avoids such a wasteful separation of isomers.

Within the scope of the present invention it has been found that a known process for the asymmetrical reduction of certain α -keto esters (see for example US patent specification 4 329 487 or Japanese published patent

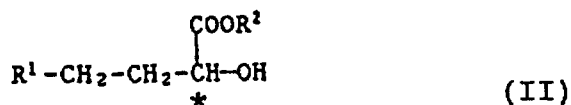
application 80 35 060) can be applied with good success to compounds of formula III



wherein R^1 and R^2 are as defined for formula I. A further subject of the invention therefore resides in preparing a compound of formula I as defined above by enantio-selective reduction of a compound of formula III



wherein R^1 and R^2 are as defined for formula I, in the presence of a platinum catalyst on a carrier as well as of a cinchona alkaloid, to a compound of formula II as defined above



and reacting the resulting compound of formula II with a compound that converts the -OH substituent into the radical of formula $\text{-OSO}_2\text{-R}^3$, wherein R^3 is as defined for formula I.

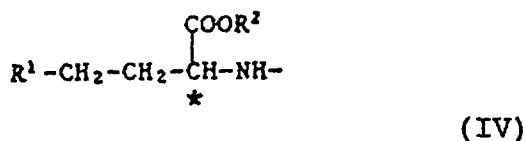
The reduction of a compound of formula III is said to be enantio-selective if the optical yield is 60% or more, preferably 70% or more, especially 80% or more. The predominance of a configuration at the carbon atom indicated by an asterisk therefore refers in connection with formula II to enantiomer ratios of at least 80:20, preferably of at least 85:15 and, most preferably, of at least 90:10, with the R or S form predominating.

The enantio-selective reduction is carried out in a manner known per se. The platinum catalysts employed are applied to inert carriers, e.g. to carbon, alumina, calcium carbonate or barium sulfate, preferably to alumina. The catalysts are activated in known manner with hydrogen at 200°-400°C and then modified (impregnated) with a solution of a cinchona alkaloid and/or a cinchona alkaloid is added direct during the reduction. Cinchona alkaloids will be understood as meaning the group of quinoline plant bases, also known as china alkaloids, that can be isolated principally from the bark of trees of the genera Cinchona and Remijia. They comprise in particular the alkaloids (-)-quinine, (+)-quinidine, (+)-cinchonine and (-)-cinchonidine. The use of (-)-quinine and (-)-cinchonidine leads to compounds of formula II in the R form, whereas compounds of formula II in the S form are obtained when (+)-quinidine and (+)-cinchonine are used. It is preferred to use (-)-cinchonidine. Advantageously, the hydrogenation takes place in a pressure reactor such as an autoclave under a hydrogen pressure of 10 to 170 bar, especially of 50 to 150 bar, and at room temperature $\pm 30^{\circ}\text{C}$, especially in the range from 0° to 30°C. Preferred solvents for the impregnation are those that dissolve the china alkaloid employed, in particular C₁-C₇alkanols such as ethanol, or ethers such as tetrahydrofuran. Examples of suitable solvents for the hydrogenation are aromatic hydrocarbons such as benzene or toluene, and also halogenated hydrocarbons such as dichloromethane, ethers such as tert-butyl methyl ether, or low-boiling carboxylates such as ethyl acetate.

As may be inferred from the definition of the asterisk in formula II, the compounds of formula II can be obtained in the above described manner in optical yields of at least 60%, preferably 70% and, especially, 80%. In the

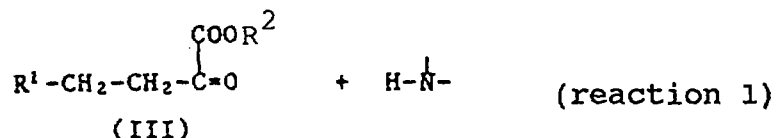
course of the further reaction to sulfonic acid esters of formula I as described above, the optical yield can be increased in such a manner that compounds of formula I are obtained in substantially pure form, i.e. in optical yields of at least 95%, preferably of at least 97.5% and, especially, 99 to 100%.

The compounds of formula I are valuable intermediates for the preparation of ACE inhibitors or precursors thereof. This class of active ingredient has met with increasing interest in recent years. It extends the potential of available antihypertensives and thus the therapeutic possibilities of combating hypertension. In numerous effective ACE inhibitors (see, for example, European patent applications 50 850 and 72 352), importance is attached to the structural unit of partial formula IV

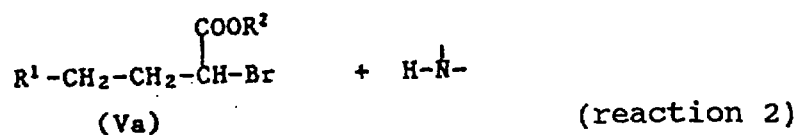


wherein R^1 and R^2 are as defined for formula I and the asterisk denotes a carbon atom in the S configuration.

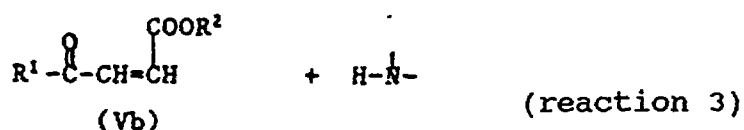
The bond between the nitrogen atom of partial formula IV and the adjacent carbon atom of partial formula IV has been formed by the processes that have become known hitherto, for example by reacting a compound of formula III, under conditions of reductive alkylation, with a primary or secondary amine (reaction 1)



or by using an α -bromo ester of formula Va (reaction 2)



or by using an unsaturated compound of formula Vb
(reaction 3)



wherein R¹ and R² are as defined above.

In the processes according to reactions 1 and 2, the desired compounds having the S configured structure of partial formula IV cannot be obtained direct. Instead, the racemic material obtained must be separated, resulting in the loss of at least 50% of the material used. As the nitrogen atom of partial formula IV is usually itself already the constituent of a complex chiral molecule at the time when reaction 1 or 2 takes place, a product loss of at least 50% in this late stage of the total synthesis of an ACE inhibitor must be regarded as unacceptable.

Although in the process according to reaction 3 it is possible to obtain a somewhat better ratio of isomers than that of a racemate, viz. up to 2:1, it is then, however, necessary to carry out an additional reaction step, i.e. a reduction.

The use according to the invention of compounds of formula I avoids the shortcomings described above since, starting from compounds of formula III, it is possible to obtain compounds containing the partial

formula IV in chemical yields of more than 50%.

Specifically, the advantage of using compounds of formula I derives, inter alia, from the fact that the compounds of formula I can be reacted with primary or secondary amines without any appreciable racemisation or formation of elimination products. Thus compounds having the partial formula IV are obtained in high chemical and optical yield, with inversion, by using compounds of formula I in which the asterisk denotes a carbon atom that is present in the preponderant number of molecules in the R configuration. In the same way, starting from compounds of formula I in which the asterisk denotes a carbon atom that is present in the preponderant number of molecules in the S configuration, it is possible to obtain compounds having a structure corresponding to the partial formula IV, wherein the asterisk denotes a carbon atom that is in the R configuration.

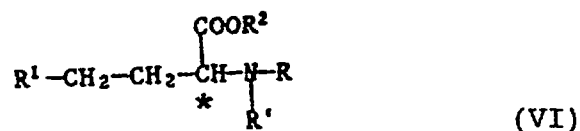
This result is unexpected and surprising, as the prior art would lead one to expect secondary reactions and racemisation, both of which would cause the chemical yields to fall appreciably below 50%.

F. Effenberger et al., *Angew. Chem.* 95, 50, (1983), describe a leaving group that is suitable for synthesising N-substituted α -amino acids without racemisation, starting from α -hydroxycarboxylates. This leaving group is the α -trifluoromethanesulfonyloxy group. However, in the same publication, the authors advise against using other leaving groups, as the use of α -methanesulfonyloxy-carboxylic acid derivatives and α -toluenesulfonyloxycarboxylic acid derivatives results in the formation, inter alia, of racemisation and elimination products owing to drastic reaction conditions. Further, the use of ethyl esters of α -bromo-, α -methanesulfonyloxy-, α -toluenesul-

fonyloxy- and α -chloropropionic acid gives yields of 40, 10, 5 and 1%, respectively, after 22 hours, whereas the reaction with the proposed α -trifluoromethanesulfonyloxy compound is 100% after 20 minutes.

Aside from the essentially unexpected result that aromatic sulfonyloxy compounds are excellently suitable for synthesising α -amino acids without racemisation, the compounds used according to the invention containing the radical R^3 have lasting advantages compared with the known prior art compounds containing the CF_3SO_2-O -leaving group: they are appreciably cheaper, ecologically safer and very much less toxic.

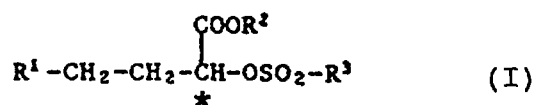
A further aspect of the present invention therefore consists in the use of compounds of formula I for the preparation of compounds of formula VI



which comprises alkylating a compound of formula VII

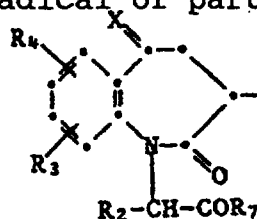


with inversion, with a compound of formula I



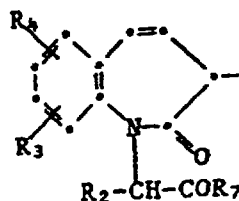
wherein R^1 , R^2 and R^3 are as defined above, the asterisk denotes a carbon atom that is either present in the

preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration, and R' is hydrogen or C₁-C₇alkyl and R is the radical of partial formula VIII



(VIII)

wherein, in this partial formula VIII, the radicals R₂, R₃, R₄, R₇ (with dropped indices) and X are as defined in European patent application 72 352, or wherein R' is hydrogen or C₁-C₇alkyl and R is the radical of partial formula IX



(IX)

wherein, in this partial formula IX, the radicals R₂, R₃, R₄ and R₇ are as defined in European patent application 72 352, or wherein R' is hydrogen and R is 1-aryl-C₁-C₇alkyl, or wherein R' and R are hydrogen.

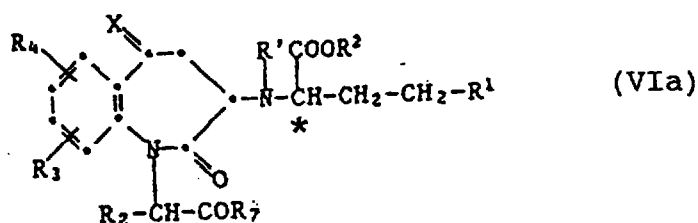
The meanings of the substituents of partial formula VIII or IX in European patent application 72 352 are hydrogen or lower alkyl for R₂, and for R₃ and R₄, independently of each other, are hydrogen, lower alkyl, lower alkoxy, lower alkanoyloxy, hydroxy, halogen or trifluoromethyl, or R₃ and R₄ together are lower alkylendioxy, R₇ together with the carbonyl group to which it is attached is carboxy or a functionally modified carboxy group COR₇, and X is oxo, two hydrogen atoms or a hydrogen atom together with a hydroxy group. The term "lower" denotes organic radicals or compounds that contain up to 7, preferably up to 4 and, advantageously, 1 or 2, carbon atoms. More specific definitions will be found by referring to the mentioned Offenlegungsschrift.

The above reaction, a substitutive alkylation, is carried out under customary general conditions in the temperature range from about 0° to the boiling point of the reaction mixture, preferably in the range from room temperature to about 100°C. The reaction advantageously takes place in the presence of a solvent that is inert to the reactants, e.g. in the presence of a chlorinated lower alkane (e.g. chloroform or methylene chloride), of an acyclic or cyclic ether (e.g. diethyl ether, 1,2-dimethoxyethane, dioxane or tetrahydrofuran), of a lower alkane carbonitrile (e.g. acetonitrile), of a low-boiling lower alkyl ester of a lower alkanoic acid, (e.g. ethyl acetate), or of a tertiary amide of low molecular weight (e.g. N,N-dimethylformamide, N,N-dimethylacetamide, N-methylpyrrolidone, N-ethylpiperidone and hexamethylphosphoramide). It is advantageous to neutralise the strong acid $\text{HOSO}_2\text{-R}^3$ freed during the reaction by adding an acid-acceptor, such as, preferably, an inorganic base, such as a bicarbonate, carbonate or hydroxide of an alkali metal, an organic quaternary ammonium salt (e.g. a tetrabutylammonium salt) or an organic tertiary base, such as triethylamine, N-ethylpiperidine, N-methylmorpholine, pyridine or quinoline.

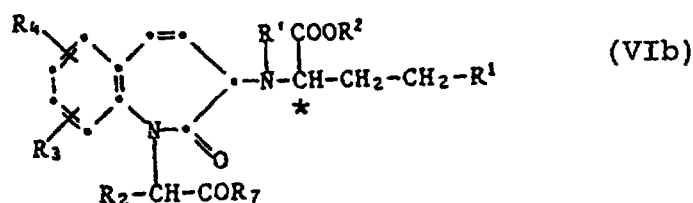
This reaction proceeds with inversion, i.e. in a stereochemically uniform manner in such a way that the configuration at the carbon atom indicated by the asterisk is inverted. If, therefore, in a compound of formula I the asterisk indicates a carbon atom that is present in the preponderant number of molecules in the R configuration, the asterisk will then indicate in the compound of formula VI obtained from this compound of formula I a carbon atom that is present in the preponderant number of molecules in the S configuration, and vice versa. The

expression "in the preponderant number of molecules in one configuration" with respect to formula VI has the same meaning as that given for formula I. If R and R' in formula VII are hydrogen, i.e. if a compound of formula I is reacted with ammonia, the reaction will preferably be carried out under elevated pressure, e.g. at 10 to 20 bar, in an inert solvent such as acetonitrile.

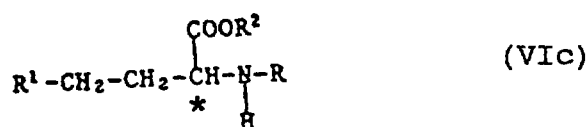
The starting compounds of formula VII are known or can be prepared in a manner known per se (see for example European patent application 72 352). The compounds of formula VI obtained are either ACE inhibitors of formula VIa



wherein R¹, R², R', the asterisk and R₂, R₃, R₄, R₇ and X are as defined above, or they are precursors of ACE inhibitors of formula VIb

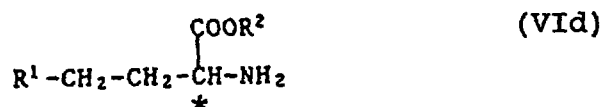


wherein R¹, R², R', the asterisk and R₂, R₃, R₄ and R₇ are as defined above, or they are precursors of ACE inhibitors of formula VIc



wherein R¹, R² and the asterisk are as defined above and R is 1-aryl-C₁-C₇alkyl, e.g. benzyl, 1-phenylethyl or

1-naphthylethyl or, if R is also hydrogen, they are precursors of ACE inhibitors of formula VIId



wherein R¹, R² and the asterisk are as defined above.

Compounds of formula VIb can be converted in a manner known per se by reduction (hydrogenolysis) into compounds of formula VIa, wherein X denotes 2 hydrogen atoms. This process is especially advantageous, and is therefore preferred, if in a compound of formula VIb R₇ is 1-aryl-C₁-C₇alkoxy, e.g. benzyloxy, as in this event the reduction of the C-C double bond and the conversion of e.g. a benzyloxycarbonyl group COR₇ into the carboxy group COR₇ can be carried out simultaneously.

Aside from the direct route (compound of formula I + ammonia), compounds of formula VIId are also obtainable by a two-step route without adversely affecting the chemical or optical yield. Thus compounds of formula VIc can be converted into compounds of formula VIId in a manner known per se, under mild conditions (hydrogenolysis) and with retention of the configuration at the carbon atom indicated by the asterisk.

The amino acid esters of formula VIId are in turn suitable for use as essential components for synthesising ACE inhibitors, as they contain the structural unit of partial formula IV which is recognised to be important.

To summarise, the novel compounds of formula I prove to be key compounds for synthesising ACE inhibitors whether by the direct route of I to VIa, by the route of I via VIb to VIa, or by the route starting from I via VIId, in

which case compounds of formula VIc may be processed direct without isolation. The synthesis according to the invention is distinguished by high chemical and optical yields.

The following Examples are intended to illustrate the present invention without limiting it, for example to the scope of the examples. The percentages additionally qualified by "ee" denote optical yields. Temperatures are given in degrees Celsius.

Example 1: The preparation of the catalyst and the hydrogenation may be carried out in accordance with the particulars of US patent 4 329 487:

Preparation of the catalyst: 1 g of 5% Pt/C (e.g. Degussa Type F 101 R) is heated to 300°C for 3 hours in a weak stream of hydrogen. After cooling under argon, the catalyst is refluxed in 80 ml of a 1% ethanolic solution of cinchonidine, isolated by filtration, washed with a small quantity of ethanol and subsequently with the solvent employed for the hydrogenation.

Hydrogenation: 20 g of ethyl 4-phenyl-2-oxo-butyrate are dissolved in 100 ml of benzene and flushed in a 300 ml autoclave equipped with an aerating stirrer. Then 0.1 g of cinchonidine and the prepared catalyst are added and the hydrogenation is carried out in conventional manner at 150 bar total pressure and 20°-30°C. When hydrogen absorption is terminated, the catalyst is isolated by filtration and the solvent is removed on a rotary evaporator. The chemical yield of ethyl 2-hydroxy-4-phenyl-butyrate is c. 95% and the optical yield of the R form is 70%.

Example 2: The procedure of Example 1 is repeated,

except that 1 g of 5% Pt/Al₂O₃ (e.g. Engelhard Type 4759 b) is used and the hydrogenation is carried out for 2 hours at 400°C. The chemical yield is c. 95% and the optical yield 72%.

Example 3: The procedure of Example 2 is repeated, except that the catalyst is not treated beforehand with a cinchonidine solution. The chemical yield is c. 95% and the optical yield 68%.

Example 4: The procedure of Example 2 is repeated, but using the following solvents for the hydrogenation:
a) toluene, b) dichloromethane, c) ethyl acetate, d) t-butyl methyl ether. The chemical yields are c. 95% and the optical yields are between 60 and 70%.

Example 5: The reaction is carried out as in Example 3, but at a temperature of 5°C. The chemical yield is c. 95% and the optical yield 80%.

Example 6: 104.16 g of ethyl (-)-R-2-hydroxy-4-phenyl-butyrate with an angle of rotation $[\alpha]_D^{20} = -17.0^\circ$ (82% ee) and 121.89 g of 4-nitrobenzenesulfonyl chloride are dissolved at room temperature in 500 ml of toluene. At an internal temperature of 0°C, 66.8 g of triethylamine are added dropwise over 1 hour. The batch is then stirred for 1 hour at room temperature. After aqueous working up and extraction of the toluene phase with 1N hydrochloric acid, the combined toluene phases are filtered over a small amount of silica gel and concentrated on a rotary evaporator. The residual oil is taken up in 100 ml of a 4:1 mixture of cyclohexane/ethyl acetate and the solution is stirred for 48 hours at room temperature, then for 8 hours at 0°C, and subsequently filtered. The filter residue is dried and gives 41.5 g of racemic ethyl 2-(4-nitrobenzenesulfonyloxy)-4-phenyl-

butyrate of m.p. 68°-70°C. The filtrate is concentrated on a rotary evaporator and degassed in a high vacuum at 45°C, affording 146.5 g of enriched ethyl (+)-R-2-(4-nitrobenzenesulfonyloxy)-4-phenyl-butyrate with an angle of rotation $[\alpha]_D^{20} = + 10.6^\circ$ (3%, abs. ethanol). The product so obtained has a 90% excess of enantiomers and is 95% pure according to HPLC.

Ethyl (+)-R-2-(4-nitrobenzenesulfonyloxy)-4-phenyl-butyrate prepared from pure ethyl (-)-R-2-hydroxy-4-phenyl-butyrate ($[\alpha]_D^{20} = -20.8^\circ$, 1%, chloroform) according to the above particulars has an angle of rotation $[\alpha]_D^{20} = + 13.2^\circ$ (3%, abs. ethanol).

Example 7: Following the procedure of Example 6, the corresponding ethyl (-)-R-2-(2-nitrobenzenesulfonyloxy)-4-phenyl-butyrate is prepared from ethyl (-)-R-2-hydroxy-4-phenyl-butyrate (82% ee) with 2-nitrobenzenesulfonyl chloride. The ester obtained as an oil in 95% yield has an angle of rotation $[\alpha]_D^{20} = -9.6^\circ$ (3%, abs. ethanol).

Example 8: Following the procedure of Example 6, ethyl (+)-R-2-(3-nitrobenzenesulfonyloxy)-4-phenyl-butyrate is prepared from ethyl (-)-R-2-hydroxy-4-phenyl-butyrate (82% ee) with 3-nitrobenzenesulfonyl chloride. The product has an angle of rotation $[\alpha]_D^{20} = + 6.9^\circ$ (3%, abs. ethanol).

Example 9: Following the procedure of Example 6, ethyl (-)-R-2-(pentafluorobenzenesulfonyloxy)-4-phenyl-butyrate of m.p. 64°-65°C (from ether/cyclohexane) is obtained in 98% yield from ethyl (-)-R-2-hydroxy-4-phenyl-butyrate (84% ee) with pentafluorobenzenesulfonyl chloride. The product has an angle of rotation $[\alpha]_D^{20} = -2.5^\circ \pm 0.2^\circ$; $\alpha_{436}^{20} = -12.4^\circ$ (5% chloroform).

Example 10: Following the procedure of Example 6, ethyl (-)-R-2-(2,4-dinitrobenzenesulfonyloxy)-4-phenyl-butyrate is obtained as an oil in 95% yield from ethyl (-)-R-2-hydroxy-4-phenyl-butyrate (100% ee) with 2,4-dinitrobenzenesulfonyl chloride. The oil is crystallised from a 1:4 mixture of ethyl acetate/cyclohexane and gives an almost white crystalline solid in 83.7% yield; m.p. 69°-71°C; $[\alpha]_D^{20} = -10.6^\circ$ (3%, abs. ethanol).

Example 11: 393.4 g of enriched ethyl (+)-R-2-(4-nitrobenzenesulfonyloxy)-4-phenyl-butyrate (90% ee) are dissolved in 600 ml of acetonitrile and there are added to the solution at room temperature 121.4 g of triethylamine. After heating to 70°C, 210 g of (+)-R-1-phenylethylamine are added dropwise over 2 hours. The reaction mixture is then stirred for a further 16 hours at 70°C. When the reaction is complete, the mixture is cooled, precipitated ammonium salt is removed by filtration and the filtrate is concentrated by evaporation. Then the residue is partitioned between water and dichloromethane and the aqueous phase is adjusted to pH 6 with 2N hydrochloric acid. The combined organic phases are concentrated on a rotary evaporator and the oil obtained is subsequently dissolved in a mixture of 1000 ml of diethyl ether and 250 ml of dichloromethane and the resultant solution is saturated, with stirring, with gaseous hydrogen chloride. 700 ml of cyclohexane are added to the precipitated crystalline suspension at 0°C and the batch is filtered at -12°C. The filter product is washed with cyclohexane and dried to constant weight in a high vacuum. The yield is 287.5 g. The ratio of diastereoisomers determined by HPLC is SR:SS = 98.5:1.5. One recrystallisation gives N-(R-1-phenylethyl)-S-homophenylalanine ethyl ester hydrochloride as pure SR isomer. Melting point: 181.5°-182.5°C; $[\alpha]_D^{20} = + 52.5^\circ$ (1%, methanol).

Example 12: 86.88 g of N-(R-1-phenylethyl)-S-homophenylalanine ethyl ester hydrochloride with an angle of rotation of $+52.5^\circ$ are dissolved in 870 ml of ethanol and 87 ml of deionised water and the solution is hydrogenated with 17 g of Pd/C (5%) under normal pressure for 1 hour. The hydrogenation is discontinued after a hydrogen absorption of 109%. After filtration, the filtrate is concentrated to a volume of c. 200 ml. With stirring, 750 ml of diethyl ether are added dropwise and the resultant crystalline suspension is cooled to 0°C and filtered. The filter product is washed with ice-cold ether and dried in a high vacuum, affording 55.23 g of (+)-S-homophenylalanine ethyl ester hydrochloride with an angle of rotation $[\alpha]_D^{20} = +41.1^\circ$ (1%, ethanol). A further 3.96 g of product is obtained in comparable purity from the mother liquor by concentration.

Example 13: A concentrated ethanolic hydrogenation solution (0.7 molar batch) from Example 12 is diluted with 500 ml of methanol and stirred for 36 hours at room temperature with a solution of 58.8 g of sodium hydroxide and 58.8 g of water. Precipitated sodium chloride is removed by filtration and the filtrate is concentrated to c. 300 ml, homophenylalanine sodium salt already beginning to crystallise out. The crystallisation is brought to completion by the dropwise addition of 1000 ml of acetonitrile, with stirring and subsequent cooling to 0°C . The product is isolated by filtration, washed with cold acetonitrile and dried to constant weight in a high vacuum at room temperature. The isolated sodium salt has an angle of rotation $[\alpha]_D^{20} = +37.2^\circ$ (1%, 1N hydrochloric acid).

Example 14: 10.0 g of homophenylalanine sodium salt are dissolved in 60 ml of deionised water and the solution is

added dropwise over 1 hour to 24 ml of 2N hydrochloric acid to form a white, faintly lustrous crystalline suspension. This suspension is adjusted with 1N sodium hydroxide solution to pH 4.0 and then stirred for a further 2 hours at room temperature and filtered. The filter product is washed with deionised water and dried at room temperature in a high vacuum, affording pure (+)-S-homophenylalanine with an angle of rotation $[\alpha]_D^{20} = +45.6^\circ$ (1%, 1N hydrochloric acid). Melting point: $287^\circ\text{--}290^\circ\text{C}$. Yield: 89.6%.

Example 15: In an autoclave, 78.7 g of ethyl (+)-R-2-(4-nitrobenzenesulfonyloxy)-4-phenyl-butyrate are added to 40 ml of acetonitrile and brought to reaction with 7.5 g of ammonia at 60°C under a pressure of 12-18 bar. The reaction is complete after 6 to 7 hours. The reaction solution is concentrated by evaporation and the residue is taken up in 200 ml of diethyl ether. 130 ml of hydrochloric acid in ethyl acetate (1.7N) are added to the ethereal solution, whereupon almost white crystalline (+)-S-homophenylalanine ethyl ester with an angle of rotation $[\alpha]_D^{20} = +37.8^\circ$ precipitates. Yield: 95.6%. An angle of rotation of $+37.8^\circ$ (1%, ethanol) corresponds to 93% ee.

Example 16: 1-Carboxymethyl-3S-[(1S-ethoxycarbonyl-3-phenyl-propyl)amino]-2,3,4,5-tetrahydro-1H-[1]-benzazepin-2-one

46.1 g of 1-tert-butoxycarbonylmethyl-3S-amino-2,3,4,5-tetrahydro-1H-[1]-benzazepin-2-one, 84.3 g of ethyl (+)-R-2-(4-nitrobenzenesulfonyloxy)-4-phenyl-butyrate (enriched to 90% ee) and 19.53 g of N-methylmorpholine are reacted, without a solvent, at $75^\circ\text{--}80^\circ\text{C}$ for 9 hours. The precipitated N-methylmorpholine salt of 4-nitrobenzenesulfonic acid is dissolved by addition of 250 ml of ethyl acetate and 150 ml of water. The pH is adjusted to

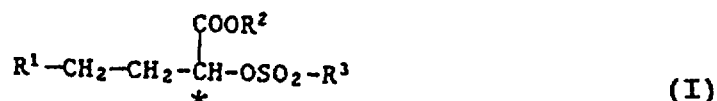
8.8 with c. 150 ml of 2N sodium carbonate solution and the ethyl acetate phase is separated and washed twice with water. Analysis by HPLC shows that the residual oil (98 g) obtained after distilling off the ethyl acetate has a diastereoisomer ratio of SS:SR = 96:4.

The preparation of the crude active substance is effected by introducing 54 g of gaseous hydrogen chloride into a solution of 96 g of the above oil in 200 ml of ethyl acetate at 0°-10°C. After complete solvolysis of the tert-butyl ester, the crude active substance is obtained as a finely crystalline suspension. Excess hydrogen chloride is completely removed by repeatedly distilling off ethyl acetate in vacuo. The highly concentrated crystalline suspension is then diluted with 200 ml of acetone, filtered at 15°C and the filter cake is washed twice with 50 ml of ethyl acetate each time. After drying to constant weight in vacuo at 60°C, 62.5 g (85.4%) of almost white active substance with a diastereoisomer ratio of SS:SR = 99.1:0.9 are isolated. For further purification, these 62.5 g of crude active substance are suspended in 250 ml of ethyl acetate and the suspension is heated for 6 hours under reflux and filtered at 15°C. The filter product is washed and dried at 60°C in a high vacuum. Yield: 61.15 g (83.6%). Ratio of SS:SR = 99.7:0.3; $[\alpha]_D^{20} = -137.3^\circ$ (1%, abs. ethanol); m.p. 181°C.



Patent claims for the Contracting States: BE, CH, DE, FR, GB, IT, LI, NL and SE

1. Compounds of formula I



wherein R¹ is C₅-C₆cycloalkyl which is unsubstituted or substituted by C₁-C₇alkyl, or is unsubstituted or substituted phenyl, R² is C₁-C₇alkyl, R³ is phenyl which is substituted by halogen or by nitro, and the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration.

2. Compounds of formula I according to claim 1, wherein R², R³ and the asterisk are as defined in claim 1 and R¹ is phenyl that may be substituted by one or more substituents selected from the group consisting of C₁-C₇alkyl, hydroxy, C₁-C₇alkoxy, C₁-C₇alkanoyloxy, fluorine, C₁-C₇alkylenedioxy, amino, C₁-C₇alkylamino, di(C₁-C₇)alkylamino, C₁-C₇alkanoylamino, carbamoyl, C₁-C₇alkylcarbamoyl, di(C₁-C₇)alkylcarbamoyl, C₁-C₇alkanesulfonylamino, sulfamoyl, C₁-C₇alkylsulfamoyl, di(C₁-C₇)alkylsulfamoyl, C₁-C₇haloalkyl, C₁-C₇hydroxyalkyl and C₁-C₇aminoalkyl.

3. Compounds of formula I according to claim 1, wherein R², R³ and the asterisk are as defined in claim 1 and R¹ is C₅-C₆cycloalkyl, phenyl or phenyl which is substituted by C₁-C₇alkyl, hydroxy, C₁-C₇alkoxy, C₁-C₇alkanoyloxy, fluorine, trifluoromethyl or by C₁-C₇alkylenedioxy.



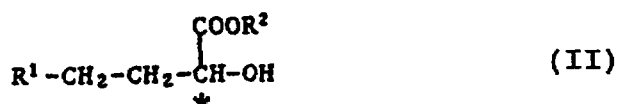
4. Compounds of formula I according to claim 1, wherein R^1 is C_5 - C_6 cycloalkyl, phenyl or phenyl which is substituted by one of the radicals selected from C_1 - C_4 -alkyl, hydroxy, C_1 - C_4 alkoxy or fluorine, R^2 is C_1 - C_4 alkyl, R^3 is 2-, 3- or 4-nitrophenyl, 2,4-dinitrophenyl or pentafluorophenyl, and the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration.

5. Compounds of formula I according to claim 1, wherein R^1 is cyclohexyl, phenyl, C_1 - C_4 alkylphenyl or C_1 - C_4 -alkoxyphenyl, R^2 is C_1 - C_4 alkyl, R^3 is 4-nitrophenyl or 2,4-dinitrophenyl, and the asterisk denotes a carbon atom that is present in the preponderant number of molecules in the R configuration.

6. Compounds of formula I according to claim 1, wherein R^1 is phenyl, R^2 is C_1 - C_4 alkyl, R^3 is 4-nitrophenyl or 2,4-dinitrophenyl and the asterisk denotes a carbon atom that is present in the preponderant number of molecules in the R configuration.

7. Ethyl (+)-R-2-(4-nitrobenzenesulfonyloxy)-4-phenylbutyrate and ethyl (-)-R-2-(2,4-dinitrobenzenesulfonyloxy)-4-phenylbutyrate.

8. A process for the preparation of compounds of the formula I as indicated in claim 1, wherein R^1 , R^2 , R^3 and the asterisk are as defined above, which comprises reacting an α -hydroxy ester of formula II



wherein R^1 and R^2 are as defined for formula I and the asterisk denotes a carbon atom that is either present in



the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration, with a compound that converts the -OH substituent into the radical of formula $-\text{OSO}_2-\text{R}^3$, wherein R^3 is as defined for formula I.

9. A process according to claim 8, wherein an R^3 -sulfonic acid anhydride is used.

10. A process according to claim 8, wherein an R^3 -sulfonyl halide is used.

11. A process according to claim 8, wherein a 4-nitrobenzenesulfonyl halide is used.

12. A process according to claim 8, wherein a 3-nitrobenzenesulfonyl halide is used.

13. A process according to claim 8, wherein a 2,4-dinitrobenzenesulfonyl halide is used.

14. A process according to claim 8, wherein a pentafluorobenzenesulfonyl halide is used.

15. A process according to claim 8, wherein an anhydride of the $\text{R}^3-\text{SO}_2-\text{O}-\text{SO}_2-\text{R}^3$ type is used.

16. A process for the preparation of compounds of the formula I as indicated in claim 1, wherein R^1 , R^2 , R^3 and the asterisk are as defined above, which comprises enantio-selectively reducing a compound of formula III





wherein R^1 and R^2 are as defined for formula I, in the presence of a platinum catalyst on a carrier as well as of a cinchona alkaloid, to a compound of formula II as defined above



and reacting the resulting compound of formula II with a compound that converts the -OH substituent into the radical of formula $\text{-OSO}_2\text{-R}^3$, wherein R^3 is as defined for formula I.

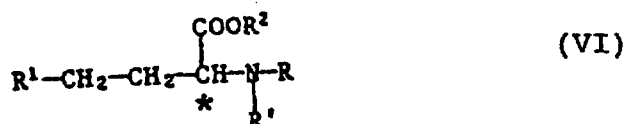
17. A process according to claim 16, wherein the carrier is carbon, alumina, calcium carbonate or barium sulfate.

18. A process according to claim 16, wherein the cinchona alkaloid is (-)-quinine, (+)-quinidine, (+)-cinchonine or (-)-cinchonidine.

19. A process according to claim 16, wherein the cinchona alkaloid is (-)-cinchonidine.

20. A process according to claim 16, wherein the starting material is ethyl 4-phenyl-2-oxo-butyrate.

21. Use of compounds of formula I as indicated in claim 1 for the preparation of compounds of formula VI

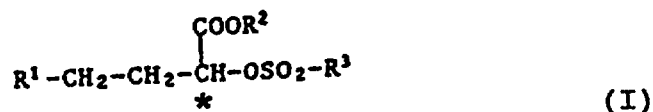


which comprises alkylating a compound of formula VII

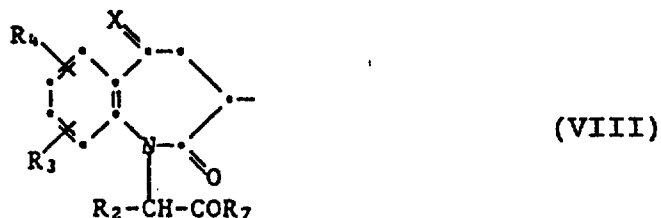




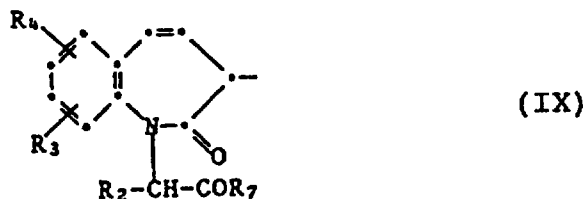
with inversion, with a compound of formula I



wherein R^1 , R^2 and R^3 are as defined above, the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration, and R^1 is hydrogen or $\text{C}_1\text{-C}_7$ alkyl and R is the radical of partial formula VIII

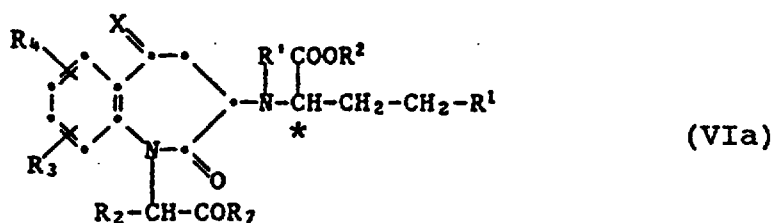


wherein, in this partial formula VIII, the radicals R_2 , R_3 , R_4 , R_7 and X are as defined in European patent application 72 352, or wherein R^1 is hydrogen or $\text{C}_1\text{-C}_7$ alkyl and R is the radical of partial formula IX



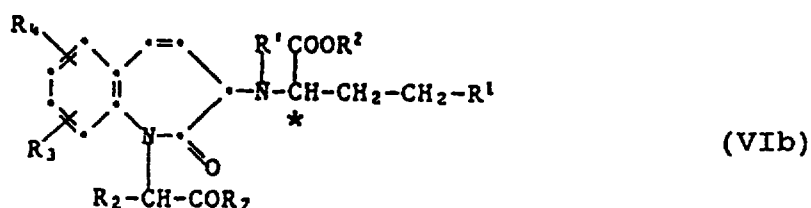
wherein, in this partial formula IX, the radicals R_2 , R_3 , R_4 and R_7 are as defined in European patent application 72 352, or wherein R^1 is hydrogen and R is 1-aryl- $\text{C}_1\text{-C}_7$ -alkyl, or wherein R^1 and R are hydrogen.

22. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of compounds of formula VIa



wherein R^1 , R^2 , R' , the asterisk and R_2 , R_3 , R_4 , R_7 and X are as defined in claim 21.

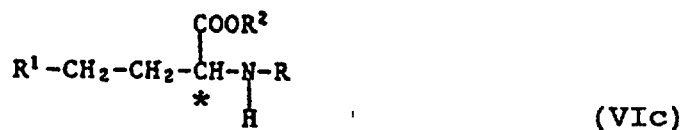
23. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of compounds of formula VIb



wherein R^1 , R^2 , R' , the asterisk and R_2 , R_3 , R_4 and R_7 are as defined in claim 21.

24. Use of compounds of formula VIb as indicated in claim 23 for the preparation of compounds of formula VIA as indicated in claim 22, wherein X denotes two hydrogen atoms, which comprises hydrogenolysing a compound of formula VIb.

25. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of compounds of formula VIC



wherein R^1 , R^2 and the asterisk are as defined above and R is 1-aryl- C_1 - C_7 alkyl, for example benzyl, 1-phenyl-



ethyl or 1-naphthylethyl.

26. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of compounds of formula VI_d



wherein R¹, R² and the asterisk are as defined above.

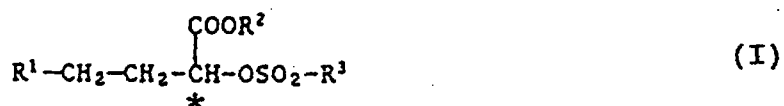
27. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of 1-carboxymethyl-3S-[(1S-ethoxycarbonyl-3-phenyl-propyl)amino]-2,3,4,5-tetrahydro-1H-[1]-benzazepin-2-one.

28. Ethyl (+)-R-2-(3-nitrobenzenesulfonyloxy)-4-phenylbutyrate.



Patent claims for the Contracting State: AT

1. A process for the preparation of compounds of formula I



wherein R^1 is $\text{C}_5\text{-C}_6$ cycloalkyl which is unsubstituted or substituted by $\text{C}_1\text{-C}_7$ alkyl, or is unsubstituted or substituted phenyl, R^2 is $\text{C}_1\text{-C}_7$ alkyl, R^3 is phenyl which is substituted by halogen or by nitro, and the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration, which comprises reacting an α -hydroxy ester of formula II



wherein R^1 and R^2 are as defined for formula I and the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration, with a compound that converts the -OH substituent into the radical of formula $\text{-OSO}_2\text{-R}^3$, wherein R^3 is as defined for formula I.

2. A process according to claim 1 for the preparation of compounds of formula I, wherein R^2 , R^3 and the asterisk are as defined in claim 1 and R^1 is phenyl that may be substituted by one or more substituents selected from the group consisting of $\text{C}_1\text{-C}_7$ alkyl, hydroxy, $\text{C}_1\text{-C}_7$ alkoxy, $\text{C}_1\text{-C}_7$ alkanoyloxy, fluorine, $\text{C}_1\text{-C}_7$ alkylenedioxy, amino,



C₁-C₇alkylamino, di(C₁-C₇)alkylamino, C₁-C₇alkanoyl-amino, carbamoyl, C₁-C₇alkylcarbamoyl, di(C₁-C₇)alkylcarbamoyl, C₁-C₇alkanesulfonylamino, sulfamoyl, C₁-C₇alkylsulfamoyl, di(C₁-C₇)alkylsulfamoyl, C₁-C₇haloalkyl, C₁-C₇hydroxyalkyl and C₁-C₇aminoalkyl.

3. A process according to claim 1 for the preparation of compounds of formula I, wherein R², R³ and the asterisk are as defined in claim 1 and R¹ is C₅-C₆cycloalkyl, phenyl or phenyl which is substituted by C₁-C₇alkyl, hydroxy, C₁-C₇alkoxy, C₁-C₇alkanoyloxy, fluorine, trifluoromethyl or by C₁-C₇alkylenedioxy.

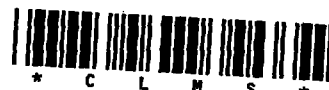
4. A process according to claim 1 for the preparation of compounds of formula I, wherein R¹ is C₅-C₆cycloalkyl, phenyl or phenyl which is substituted by one of the radicals selected from C₁-C₄alkyl, hydroxy, C₁-C₄alkoxy or fluorine, R² is C₁-C₄alkyl, R³ is 2-, 3- or 4-nitrophenyl, 2,4-dinitrophenyl or pentafluorophenyl, and the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration.

5. A process according to claim 1 for the preparation of compounds of formula I, wherein R¹ is cyclohexyl, phenyl, C₁-C₄alkylphenyl or C₁-C₄alkoxyphenyl, R² is C₁-C₄alkyl, R³ is 4-nitrophenyl or 2,4-dinitrophenyl, and the asterisk denotes a carbon atom that is present in the preponderant number of molecules in the R configuration.

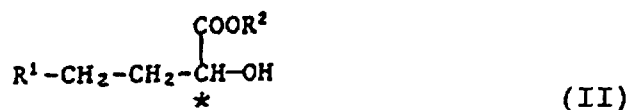
6. A process according to claim 1 for the preparation of compounds of formula I, wherein R¹ is phenyl, R² is C₁-C₄alkyl, R³ is 4-nitrophenyl or 2,4-dinitrophenyl and the asterisk denotes a carbon atom that is present in the preponderant number of molecules in the R configuration.



7. A process according to claim 1 for the preparation of ethyl (+)-R-2-(4-nitrobenzenesulfonyloxy)-4-phenylbutyrate or ethyl (-)-R-2-(2,4-dinitrobenzenesulfonyloxy)-4-phenylbutyrate.
8. A process according to claim 1 for the preparation of ethyl (+)-R-2-(3-nitrobenzenesulfonyloxy)-4-phenylbutyrate.
9. A process according to claim 1, wherein an R³-sulfonic acid anhydride is used.
10. A process according to claim 1, wherein an R³-sulfonyl halide is used.
11. A process according to claim 1, wherein a 4-nitrobenzenesulfonyl halide is used.
12. A process according to claim 1, wherein a 3-nitrobenzenesulfonyl halide is used.
13. A process according to claim 1, wherein a 2,4-dinitrobenzenesulfonyl halide is used.
14. A process according to claim 1, wherein a pentafluorobenzenesulfonyl halide is used.
15. A process according to claim 1, wherein an anhydride of the R³-SO₂-O-SO₂-R³ type is used.
16. A process for the preparation of compounds of the formula I as indicated in claim 1, wherein R¹, R², R³ and the asterisk are as defined above, which comprises enantio-selectively reducing a compound of formula III



wherein R^1 and R^2 are as defined for formula I, in the presence of a platinum catalyst on a carrier as well as of a cinchona alkaloid, to a compound of formula II as defined above



and reacting the resulting compound of formula II with a compound that converts the -OH substituent into the radical of formula $-\text{OSO}_2-\text{R}^3$, wherein R^3 is as defined for formula I.

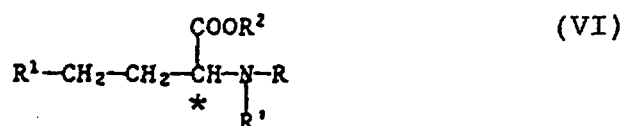
17. A process according to claim 16, wherein the carrier is carbon, alumina, calcium carbonate or barium sulfate.

18. A process according to claim 16, wherein the cinchona alkaloid is (-)-quinine, (+)-quinidine, (+)-cinchonine or (-)-cinchonidine.

19. A process according to claim 16, wherein the cinchona alkaloid is (-)-cinchonidine.

20. A process according to claim 16, wherein the starting material is ethyl 4-phenyl-2-oxo-butyrate.

21. Use of compounds of formula I as indicated in claim 1 for the preparation of compounds of formula VI

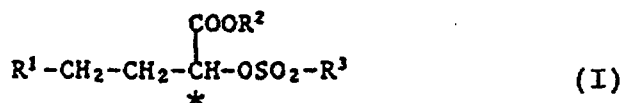




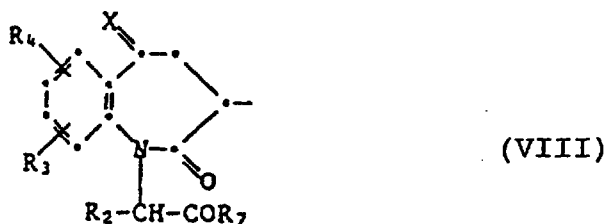
which comprises alkylating a compound of formula VII



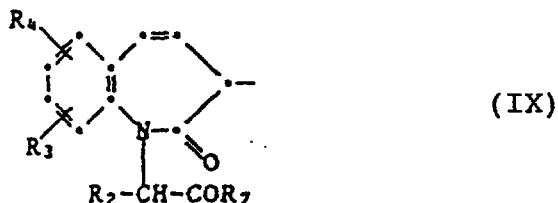
with inversion, with a compound of formula I



wherein R^1 , R^2 and R^3 are as defined above, the asterisk denotes a carbon atom that is either present in the preponderant number of molecules in the S configuration or in the preponderant number of molecules in the R configuration, and R' is hydrogen or C_1 - C_7 alkyl and R is the radical of partial formula VIII



wherein, in this partial formula VIII, the radicals R_2 , R_3 , R_4 , R_7 and X are as defined in European patent application 72 352, or wherein R' is hydrogen or C_1 - C_7 alkyl and R is the radical of partial formula IX

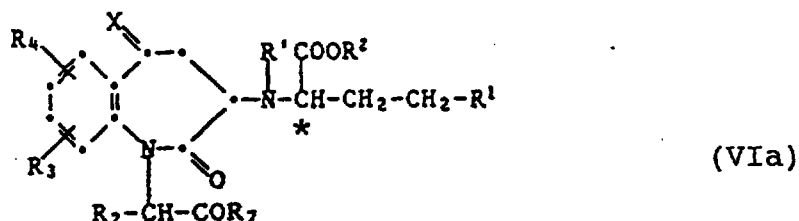


wherein, in this partial formula IX, the radicals R_2 , R_3 , R_4 and R_7 are as defined in European patent application 72 352, or wherein R' is hydrogen and R is 1-aryl- C_1 - C_7 -alkyl, or wherein R' and R are hydrogen.

22. Use of compounds of formula I as indicated in claim 1

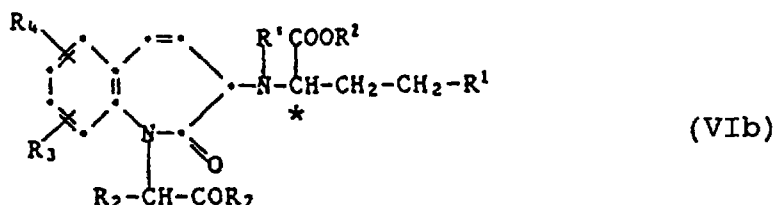


according to claim 21 for the preparation of compounds of formula VIa



wherein R^1 , R^2 , R' , the asterisk and R_2 , R_3 , R_4 , R_7 and X are as defined in claim 21.

23. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of compounds of formula VIb



wherein R^1 , R^2 , R' , the asterisk and R_2 , R_3 , R_4 and R_7 are as defined in claim 21.

24. Use of compounds of formula VIb as indicated in claim 23 for the preparation of compounds of formula VIa as indicated in claim 22, wherein X denotes two hydrogen atoms, which comprises hydrogenolysing a compound of formula VIb.

25. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of compounds of formula VIc





wherein R¹, R² and the asterisk are as defined above and R is 1-aryl-C₁-C₇alkyl, for example benzyl, 1-phenylethyl or 1-naphthylethyl.

26. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of compounds of formula VIId



wherein R¹, R² and the asterisk are as defined above.

27. Use of compounds of formula I as indicated in claim 1 according to claim 21 for the preparation of 1-carboxymethyl-3S-[(1S-ethoxycarbonyl-3-phenyl-propyl)amino]-2,3,4,5-tetrahydro-1H-[1]-benzazepin-2-one.