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(71) Applicant: AVENTIS PHARMA S.A. [FR/FR]; 20, avenue Raymond Aron, F-92160 Antony (FR).

(72) Inventors: ACHARD, Daniel; 26, rue Adrien Tessier, F-94320 Thiais (FR). BOUCHARD, Hervé; 7, allée de la Prévôté, F-94320 Thiais (FR). BOUQUEREL, Jean; 40, rue de l'Emancipation, F-93700 Drancy (FR). FILOCHE, Bruno; 9, avenue de Ceinture, F-94000 Créteil (FR). GRISONI, Serge; 17, rue Babeuf, F-94600 Choisy le Roi (FR). HITTINGER, Augustin; 11, rue Galliéni, F-91430 Igny (FR). MYERS, Michael; 3, allée du Prieuré, F-78860 Saint Nom la Bretèche (FR).

(74) Representative: MORVAN, Michèle; Aventis Pharma S.A., Direction Brevets, 20, avenue Raymond Aron, F-92165 Antony Cedex (FR).

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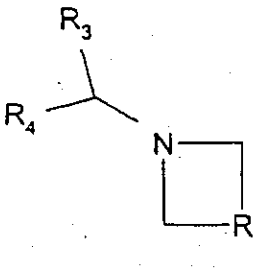
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(54) Title: AZETIDINE DERIVATIVES, PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

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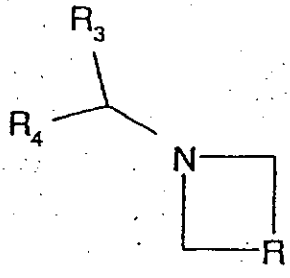
(I)

(57) Abstract: The invention concerns a compound of formula (I) wherein R represents a CR_1R_2 radical, $C{=}C(R_5)SO_2R_6$ or $C{=}C(R_7)SO_2$alk, their preparation and pharmaceutical compositions containing them.

(57) Abrégé : Composé de formule (I) dans laquelle R représente un radical CR_1R_2, $C{=}C(R_5)SO_2R_6$ ou $C{=}C(R_7)SO_2$alk, leur préparation et les compositions pharmaceutiques les contenant.

AZETIDINE DERIVATIVES, PREPARATION THEREOF AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAME

In one aspect of the present invention, there is provided a compound of formula:



(I)

in which

$C=C(R_7)SO_2alk$,

or R_1 represents a hydrogen atom and R_2 represents a radical $-C(R_8)(R_9)(R_{10})$, $-C(R_8)(R_{11})(R_{12})$, $-CO-NR_{13}R_{14}$, $-CH_2-CO-NR_{13}R_{14}$, $-CH_2-CO-R_6$, $-CO-R_6$, -CO-cycloalkyl, $-SO-R_6$, $-SO_2-R_6$, $-C(OH)(R_{12})(R_6)$, $-C(OH)(R_6)$(alkyl), $-C(=NOalk)R_6$, $-C(=NO-CH_2-CH=CH_2)R_6$, $-CH_2-CH(R_6)NR_{31}R_{32}$, $-CH_2-C(=NOalk)R_6$, $-CH(R_6)NR_{31}R_{32}$, $-CH(R_6)NHSO_2alk$, $-CH(R_6)NHCONHalk$ or $-CH(R_6)NHCOalk$,

or R_1 represents an alkyl, NH-R_{15}, cyano, -S-alk-$NR_{16}R_{17}$, -CH_2-$NR_{18}R_{19}$, or -$NR_{20}R_{21}$ radical and R_2 represents a radical -$C(R_8)(R_{11})(R_{12})$,

R_3 and R_4, which are identical or different, represent either an alkyl or cycloalkyl radical, or an aromatic chosen from phenyl, naphthyl or indenyl, these aromatics being unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, -COOalk, -$CONR_{22}R_{23}$, -CO-NH-$NR_{24}R_{25}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or -alk-$NR_{24}R_{25}$ radicals; or a heteroaromatic chosen from the benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidinyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, -COOalk, -CO-NH-$NR_{24}R_{25}$, -$CONR_{22}R_{23}$, -alk-$NR_{24}R_{25}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl radicals,

R_5 represents a hydrogen atom or an alkyl radical,

R_6 represents a radical Ar or Het,

R_7 represents a cycloalkyl, heterocycloalkyl or heterocyclenyl radical optionally substituted by a -CSO-phenyl radical,

R_8 represents a hydrogen atom or an alkyl radical,

R_9 represents a radical $-CO-NR_{26}R_{27}$, -COOH, -COOalk, $-CH_2OH$, -NH-CO-NH-alk, $-CH_2-NHR_{28}$ or -NHCOOalk,

R_{10} represents a radical Ar or Het,

R_{11} represents a radical $-SO_2$-alk, $-SO_2$-Ar or $-SO_2$-Het,

R_{12} represents a hydrogen atom or a radical Ar or Het,

R_{13} represents a hydrogen atom or an alkyl radical,

R_{14} represents a radical Ar, Het, -alk-Ar or -alk-Het,

R_{15} represents an alkyl, cycloalkyl or $-alk-NR_{29}R_{30}$ radical,

R_{16} and R_{17}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{16} and R_{17} together form with the nitrogen atom to which

they are attached a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle optionally containing one or more other heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl radicals,

R_{18} represents a hydrogen atom or an alkyl radical,

R_{19} represents a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, $-SO_2$alk, -CO-NHalk or -COOalk radical,

or alternatively R_{18} and R_{19} form with the nitrogen atom to which they are attached a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle optionally containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl radicals,

$-NR_{20}R_{21}$ represents a 3- to 8-membered saturated or unsaturated monocyclic heterocycle optionally containing another heteroatom chosen from oxygen, nitrogen and sulfur,

R_{22} and R_{23}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{22} and R_{23} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle optionally containing another

heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{24} and R_{25}, which are identical or different, represent a hydrogen atom or an alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or alternatively R_{24} and R_{25} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or $-CO-NH_2$ radicals,

R_{26} and R_{27}, which are identical or different, represent a hydrogen atom or an alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, -alk-COOalk, -alk-Ar, -alk-Het, Het or $-alk-N(alk)_2$ radical, R_{26} and R_{27} may also form with the nitrogen atom to which they are attached a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle optionally containing one or more other heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl or alkoxy radicals or halogen atoms,

R_{28} represents a $-CH_2$-alk, benzyl, $-SO_2$alk, -CONHalk, -COalk, cycloalkylalkylcarbonyl, cycloalkylcarbonyl or $-CO-(CH_2)_nOH$ radical,

n is equal to 1, 2 or 3,

R_{29} and R_{30}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{29} and R_{30} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{31} and R_{32}, which are identical or different, represent a hydrogen atom or an alkyl, Ar or -alk-Ar radical or alternatively R_{31} and R_{32} together form with the nitrogen atom to which they are attached a heterocycle chosen from aziridinyl, azetidinyl, pyrrolidinyl and piperidinyl,

alk represents an alkyl or alkylene radical,

Ar represents a phenyl or naphthyl radical optionally substituted with one or more substituents chosen from a halogen atom or an alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk, $-CONR_{22}R_{23}$, $-CO-NH-NR_{24}R_{25}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl,

alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl, -alk-$NR_{24}R_{25}$, -$NR_{24}R_{25}$, alkylthioalkyl, formyl, hydroxyl, CF_3, OCF_3, Het, -O-alk-NH-cycloalkyl or SO_2NH_2 radical,

Het represents a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, -$CONR_{22}R_{23}$, hydroxyl, hydroxyalkyl, oxo or SO_2NH_2 radicals,

the alkyl and alkylene

radicals and portions and the alkoxy radicals and portions are in the form of a straight or branched chain and contain 1 to 6 carbon atoms, the cycloalkyl radicals contain 3 to 10 carbon atoms and the heterocycloalkyl and heterocyclenyl radicals contain 3 to 10 carbon atoms, their optical isomers and their salts with an inorganic or organic acid.

Among the alkyl radicals, there may be mentioned the methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, pentyl and hexyl radicals. Among the alkoxy radicals, there may be mentioned the methoxy, ethoxy, n-propoxy, iso-propoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and pentyloxy radicals.

Among the cycloalkyl radicals, there may be mentioned the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl radicals.

The heterocycloalkyl radicals are cycloalkyl radicals in which at least one of the carbon atoms is replaced with a heteroatom chosen from nitrogen, sulfur and oxygen. Among these, there may be mentioned the pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl rings.

The heterocyclenyl radicals are cycloalkyl radicals in which at least one carbon atom is replaced with a heteroatom chosen from oxygen, sulfur and nitrogen and which contain at least one carbon-carbon or carbon-nitrogen double bond. Among the heterocyclenyl radicals, there may be mentioned the 1,2,3,4-tetrahydrohydropyridinyl, 3,6-dihydropyridyl, 1,2-dihydropyridyl, 1,4-dihydropyridyl, 1,2,3,6-tetrahydropyridinyl, 1,4,5,6-tetrahydropyrimidinyl, 2-pyrrolinyl, 3-pyrrolinyl, 2-imidazolinyl, 2-pyrazolinyl, 3,4-dihydro-2H-pyrane, dihydrofuranyl and fluorodihydrofuranyl rings. Those preferred are the 3,6-dihydropyridyl rings.

The term halogen comprises chlorine, fluorine, bromine and iodine.

Among the heterocycles representing Het, the following heterocycles may be mentioned: benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, indolinyl, indolyl, isochromanyl, isoquinolyl, piperidyl, pyrrolyl, pyridyl, pyrimidinyl, quinolyl,

1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinolyl, thiazolyl and thienyl.

When R_3 and/or R_4 represent independently a substituted phenyl, the latter is preferably mono-, di- or trisubstituted.

When R_{16} and R_{17} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is preferably an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

When R_{18} and R_{19} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is preferably an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

The heterocycle formed by $NR_{20}R_{21}$ is preferably azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl, piperazinyl or imidazolyl.

When R_{22} and R_{23} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is preferably an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

When R_{24} and R_{25} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle,

the latter is preferably an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

When R_{26} and R_{27} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is preferably an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

When R_{29} and R_{30} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is preferably an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

When R_{31} and R_{32} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is preferably an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

Preferably,

R represents a radical CR_1R_2,

either R_1 represents a hydrogen atom and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ or $C(R_8)(R_9)(R_{10})$,

or R_1 represents an alkyl radical and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$,

R_3 and R_4, which are identical or different, represent either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_{22}R_{23}$, hydroxyalkyl or $-alk-NR_{24}R_{25}$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidinyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_{22}R_{23}$, $-alk-NR_{24}R_{25}$ or hydroxyalkyl radicals,

R_8 represents a hydrogen atom,

R_9 represents a $-CO-NR_{26}R_{27}$, $-COOalk$, $-CH_2OH$, $-NH-CO-NH-alk$, $-CH_2-NHR_{28}$ or $-NHCOOalk$ radical,

R_{10} represents a radical Ar or Het,

R_{11} represents a radical $-SO_2-alk$, $-SO_2-Ar$ or $-SO_2-Het$,

R_{12} represents represents a hydrogen atom or a radical Ar or Het,

R_{22} and R_{23}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{22}

and R_{23} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{24} and R_{25}, which are identical or different, represent a hydrogen atom or an alkyl, cycloalkyl, alkylcycloalkyl or hydroxyalkyl radical or alternatively R_{24} and R_{25} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo or $-CO-NH_2$ radicals,

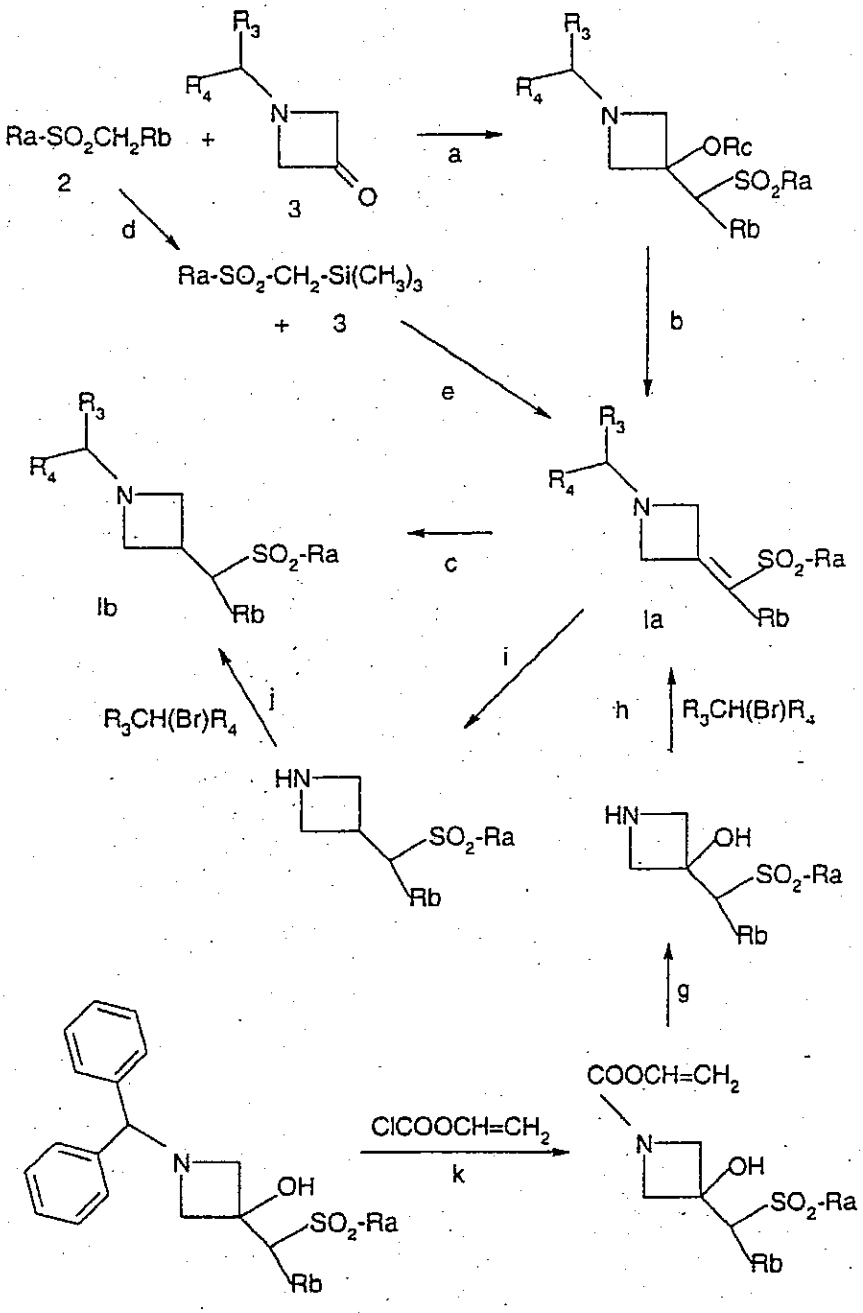
Ar represents a phenyl or naphthyl radical optionally substituted with 1 or 2 subtituents chosen from a halogen atom or an alkyl, alkoxy, -CO-alk, cyano, -COOalk, $-CONR_{22}R_{23}$, alkylsulfonyl, hydroxyalkyl, $-alk-NR_{24}R_{25}$, $-NR_{24}R_{25}$, hydroxyl, CF_3, OCF_3, -O-alk-NH-cycloalkyl or SO_2NH_2 radical,

Het represents a benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, furyl, isoquinolyl, pyrrolyl, pyridyl, quinolyl,

1,2,3,4-tetrahydroisoquinolyl,
1,2,3,4-tetrahydroquinolyl, thiazolyl or thienyl ring.

The compounds of formula (I) may be provided in the form of enantiomers and diastereoisomers. These optical isomers and mixtures thereof form part of the invention.

The compounds of formula (I) for which R represents a radical CR_1R_2, in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_{11})(R_{12})$ in which R_8 represents a hydrogen atom, R_{11} represents a radical $-SO_2-Ar$, $-SO_2-Het$ or $-SO_2alk$ and R_{12} represents a hydrogen atom or a radical Ar or Het, and the compounds of formula (I) for which R represents a radical $C=C(R_5)SO_2R_6$ or $C=C(R_7)SO_2alk$ may be prepared according to the following reaction scheme:



in these formulae, either Ra represents an alkyl, Het or Ar radical and Rb represents a hydrogen atom or a radical Ar or Het, or Ra represents a radical Ar or Het and Rb represents a hydrogen atom or an alkyl radical, or Ra represents an alkyl radical and Rb represents a cycloalkyl, heterocycloalkyl or heterocyclenyl radical optionally substituted with a radical -CSO-phenyl, Rc

represents a hydrogen atom or an acetyl radical, R_3, R_4, Ar and Het have the same meanings as in formula (I).

Reactions d and e can only be used when Rb is a hydrogen atom.

The reaction is generally carried out in an inert solvent such as an ether (for example tetrahydrofuran), in the presence of a strong base such as tert-butyllithium, n-butyllithium, lithium diisopropylamide or potassium tert-butoxide, at a temperature of between -70°C and -15°C.

The dehydration reaction b is generally carried out by any dehydration method known to a person skilled in the art which makes it possible to dehydrate an alcohol in order to obtain the corresponding alkene. Preferably, the acetyloxy derivative is prepared by the action of acetyl chloride, in an inert solvent such as pyridine, tetrahydrofuran, dioxane, a chlorinated solvent (for example dichloromethane or chloroform), at a temperature of between 5°C and 20°C and then the medium is treated with a base such as an alkali metal hydroxide (for example sodium hydroxide), an alkali metal carbonate (for example sodium or potassium carbonate), an amine such as a trialkylamine (for example triethylamine, 4-dimethylaminopyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene, at a temperature of between 0°C and the boiling point of the reaction medium. The acetyloxy intermediate may be isolated or otherwise. The acetyloxy may also be prepared directly in the reaction medium of reaction a.

Reduction c is generally carried out in an inert solvent such as a (1-4C) aliphatic alcohol (for example methanol), a chlorinated solvent (for example chloroform or dichloromethane) or a mixture of these solvents, in the presence of $NaBH_4$, at a temperature of between 0°C and the boiling point of the reaction medium.

Reaction d is carried out by the action of trimethylsilyl chloride, in an inert solvent such as an ether (for example tetrahydrofuran), in the presence of n-butyllithium, at a temperature of -70°C.

Reaction e is generally carried out in an inert solvent such as an ether (for example tetrahydrofuran), in the presence of a strong base such as tert-butyllithium, n-butyllithium, lithium diisopropylamide or potassium tert-butoxide, at a temperature of between -70°C and -15°C.

Reaction f is generally carried out in a chlorinated solvent (for example dichloromethane or chloroform), at a temperature of 0°C at the boiling point of the reaction medium.

The hydrolysis g is carried out in an inert solvent such as an ether (for example dioxane), by means of hydrochloric acid, at a temperature in the region of 20°C.

The reactions h and j are preferably carried out in an inert solvent such as acetonitrile, in the presence of a base such as an alkali metal carbonate

(for example potassium carbonate), at the boiling point of the reaction medium.

Reaction i is carried out under a hydrogen atmosphere, in the presence of a catalyst such as palladium or one of its derivatives, in an inert solvent such as methanol or ethanol, at a temperature of between 15°C and 60°C.

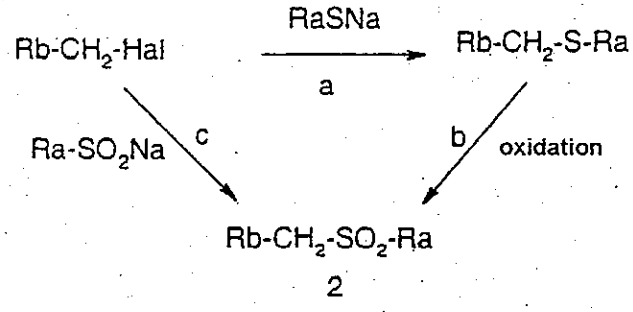
Reaction k is carried out in an inert solvent such as a chlorinated solvent (for example dichloromethane or chloroform) at a temperature of between 0°C and the boiling point of the reaction mixture.

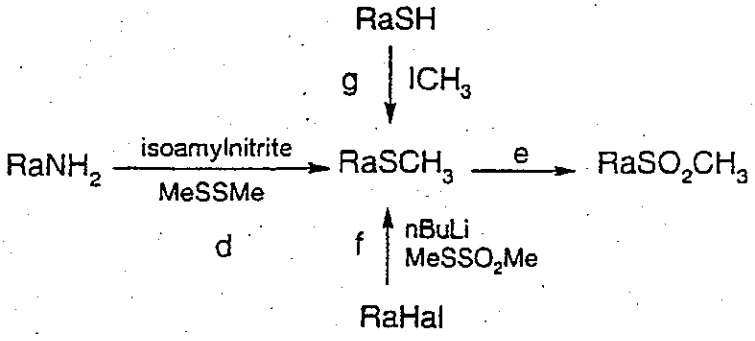
The derivatives $R_3CH(Br)R_4$ are commercially available or may be obtained by application or adaptation of the method described by BACHMANN W.E., J. Am. Chem. Soc., 2135 (1933). Generally, the corresponding alcohol R_3CHOHR_4 is brominated by means of hydrobromic acid, in acetic acid, at a temperature of between 0°C and the boiling point of the reaction medium.

The corresponding alcohols R_3CHOHR_4 are commercially available or may be obtained by application or adaptation of the methods described by PLASZ A.C. et al., J. Chem. Soc. Chem. Comm., 527 (1972).

The intermediates of formula 2 may be obtained by application or adaptation of the methods described in the examples. In particular, the procedure is

carried out according to the following reaction schemes:





in these formulae Hal represents a halogen atom and, preferably, chlorine, bromine or iodine, Ra and Rb have the same meanings as previously mentioned for derivative 2.

Reaction a is generally carried out in an inert solvent such as dimethylformamide or a 1-4C aliphatic alcohol, at a temperature of between 20°C and 30°C.

Reactions b and e are carried out by any known method which makes it possible to oxidize a sulfur-containing derivative without affecting the rest of the molecule such as those described by M. HUDLICKY, Oxidations in Organic Chemistry, ACS Monograph, 186, 252-263 (1990). For example, the procedure is carried

out by the action of an organic peroxy acid or a salt of such a peroxy acid (peroxycarboxylic or peroxysulfonic acids, in particular peroxybenzoic acid, 3-chloroperoxybenzoic acid, 4-nitroperoxybenzoic acid, peroxyacetic acid, trifluoroperoxyacetic acid, peroxyformic acid or monoperoxyphthalic acid) or inorganic peracids or a salt of such an acid (for example periodic or persulfuric acid), in an inert solvent such as a chlorinated solvent (for example chloroform or dichloromethane), at a temperature of between 0 and 25°C. It is also possible to use hydrogen peroxide, optionally in the presence of a metal oxide (sodium tungstate) or a periodate (for example sodium periodate), in an inert solvent such as a 1-4C aliphatic alcohol (for example methanol or ethanol), acetic acid, water or a mixture of these solvents, at a temperature of between 0 and 60°C. It is also possible to carry out the procedure by means of tert-butyl hydroperoxide in the presence of titanium tetraisopropoxide in a 1-4C aliphatic alcohol (for example methanol or ethanol) or a water-alcohol mixture, at a temperature in the region of 25°C or by means of oxone^{R} (potassium peroxymonosulfate), in a 1-4C aliphatic alcohol (for example methanol or ethanol), in the presence of water, acetic acid or sulfuric acid, at a temperature in the region of 20°C.

Reaction c is preferably carried out in an inert solvent such as a 1-4C aliphatic alcohol (for example methanol or ethanol), at a temperature of

between 20°C and the boiling point of the reaction medium.

Reaction d is carried out under an inert atmosphere (argon), at a temperature of between 50°C and the boiling point of the reaction medium.

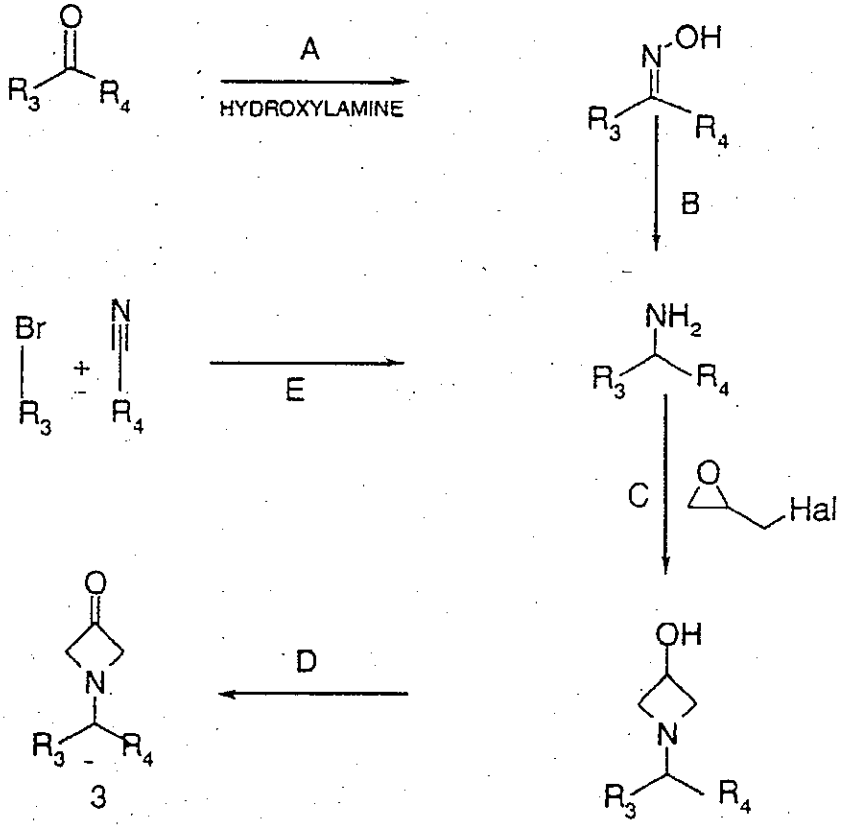
Reaction f is generally carried out in an inert solvent such as tetrahydrofuran or an aliphatic ether (for example ethyl ether), at a temperature in the region of -70°C.

Reaction g is generally carried out in an inert solvent such as dimethylformamide, an aliphatic ether (for example ethyl ether) or a 1-4C aliphatic alcohol in the presence of a base (for example sodium hydride), at a temperature of between 0°C and 60°.

The derivatives of formula Rb-CH_2-Hal are commercially available or may be obtained by application or adaptation of the methods described in the examples. In particular, the methylated derivative or the corresponding alcohol is halogenated using a halogenating agent such as hydrobromic acid, in acetic acid, at a temperature close to 20°C or N-bromo- or N-chlorosuccinimide in the presence of benzoyl peroxide, in an inert solvent such as tetrachloromethane, at the boiling point of the reaction medium. The methylated derivatives or the corresponding alcohols are commercially available or may be obtained according to the methods described by BRINE G.A. et al., J. Heterocyl. Chem, 26, 677 (1989)

and NAGARATHNAM D., Synthesis, 8, 743 (1992) and in the examples.

The azetidinones of formula 3 may be obtained by application or adaptation of the methods described by KATRITZKY A.R. et al., J. Heterocycl. Chem., 271 (1994), or DAVE P.R., J. Org. Chem., 61, 5453 (1996) and in the examples. The procedure is generally carried out according to the following reaction scheme:



In these formulae, R_3 and R_4 have the same meanings as in formula (I) and HAL represents a chlorine or bromine atom.

In step A, the procedure is preferably carried out in an inert solvent such as a 1-4C aliphatic

alcohol (ethanol or methanol for example), optionally in the presence of an alkali metal hydroxide, at the boiling point of the reaction medium.

In step B, the reduction is generally carried out using lithium aluminum hydride, in tetrahydrofuran at the boiling point of the reaction medium.

In step C, the procedure is preferably carried out in an inert solvent such as a 1-4C aliphatic alcohol (ethanol or methanol for example) in the presence of sodium hydrogen carbonate, at a temperature of between 20°C and the boiling point of the reaction medium.

In step D, the oxidation is preferably carried out in DMSO, using the sulfurtrioxide-pyridine complex, at a temperature close to 20°C or using dimethyl sulfoxide, in the presence of oxalyl chloride and triethylamine, at a temperature of between -70 and -50°C.

In step E, the procedure is carried out according to the method described by GRISAR M. et al., in J. Med. Chem., 885 (1973). The magnesium compound of the brominated derivative is formed and then the nitrile is reacted, in an ether such as ethyl ether, at a temperature of between 0°C and the boiling point of the reaction medium. After hydrolysis with an alcohol, the intermediate imine is reduced *in situ* with sodium borohydride at a temperature of between 0°C and the boiling point of the reaction medium.

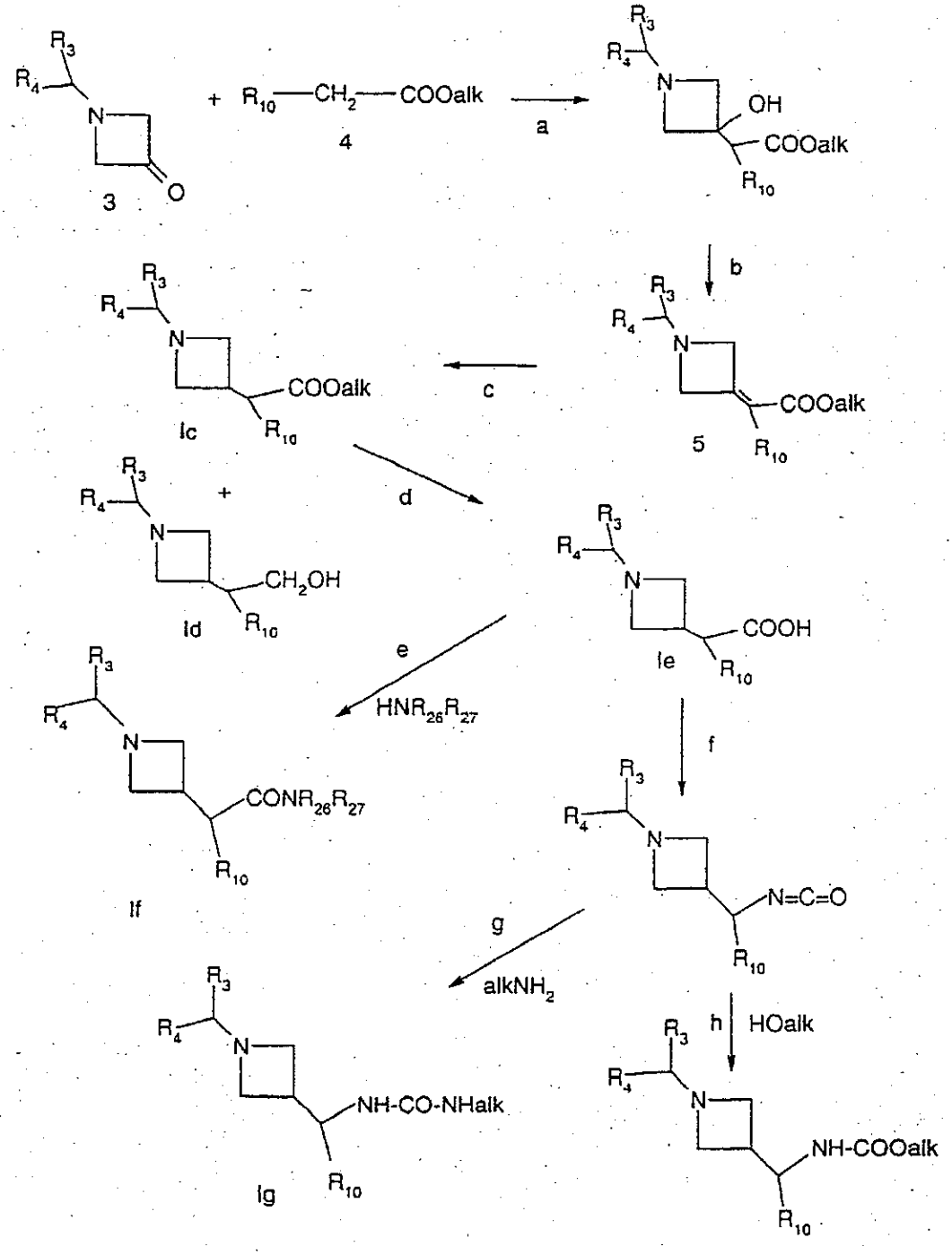
The R_3-CO-R_4 derivatives are commercially available or may be obtained by application or adaptation of the methods described by KUNDER N.G. et al. J. Chem. Soc. Perkin Trans 1, 2815 (1997); MORENO-MARRAS M., Eur. J. Med. Chem., 23 (5) 477 (1988); SKINNER et al., J. Med. Chem., 14 (6) 546 (1971); HURN N.K., Tet. Lett., 36 (52) 9453 (1995); MEDICI A. et al., Tet. Lett., 24 (28) 2901 (1983); RIECKE R.D. et al., J. Org. Chem., 62 (20) 6921 (1997); KNABE J. et al., Arch. Pharm., 306 (9) 648 (1973); CONSONNI R. et al., J. Chem. Soc. Perkin Trans 1, 1809 (1996); FR-96-2481 and JP-94-261393.

The R_3Br derivatives are commercially available or may be obtained by application or adaptation of the methods described by BRANDSMA L. et al., Synth. Comm., 20 (11) 1697 and 3153 (1990); LEMAIRE M. et al., Synth. Comm., 24 (1) 95 (1994); GODA H. et al., Synthesis, 9 849 (1992); BAEUERLE P. et al., J. Chem. Soc. Perkin Trans 2, 489 (1993).

The R_4CN derivatives are commercially available or may be obtained by application or adaptation of the methods described by BOUYSSOU P. et al., J. Het. Chem., 29 (4) 895 (1992); SUZUKI N. et al., J. Chem. Soc. Chem. Comm., 1523 (1984); MARBURG S. et al., J. Het. Chem., 17 1333 (1980); PERCC V. et al., J. Org. Chem., 60 (21) 6895 (1995).

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_9)(R_{10})$

in which R_8 represents a hydrogen atom, R_9 represents a radical $-CO-NR_{26}R_{27}$, $-COOH$, $-COOalk$, $-CH_2OH$, $-NHCOOalk$ or $-NH-CO-NH-alk$ and R_{10} represents a radical Ar or Het may be prepared according to the following reaction scheme:



in these formulae R_3, R_4, R_{10}, R_{26} and R_{27} have the same

meanings as in formula (I) and alk represents an alkyl radical.

The derivatives of formula 4 are commercially available or may be obtained by esterification of the corresponding acids, optionally in an activated form such as the acid chloride. The acids are commercially available or may be obtained from the corresponding methylated derivatives according to the method described by JP. HANSEN et al., J. Heteocycl., 10, 711 (1973).

Reaction a is generally carried out in an inert solvent such as an ether (for example tetrahydrofuran), in the presence of a strong base such as tert-butyllithium, n-butyllithium, lithium diisopropylamide or potassium tert-butoxide, at a temperature of between -70°C and -15°C.

Reaction b is generally carried out by any dehydration method known to a person skilled in the art which makes it possible to dehydrate an alcohol in order to obtain the corresponding alkene and in particular the methods previously described.

The reduction c is generally carried out in an inert solvent such as an aliphatic alcohol (1-4C) such as methanol, a chlorinated solvent such as chloroform, dichloromethane or a mixture of these solvents, in the presence of $NaBH_4$, at a temperature of between 0°C and the boiling point of the reaction medium.

Reaction d is carried out by any method known to a person skilled in the art which makes it possible

to pass from an ester to the corresponding acid without affecting the rest of the molecule. The procedure is preferably carried out in an inert solvent such as dioxane, in the presence of hydrochloric acid, at the boiling point of the reaction medium.

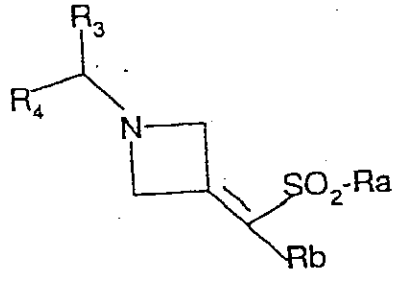
Reaction e is carried out by any method known to a person skilled in the art which makes it possible to pass from an acid or a reactive derivative of this acid to a carboxamide without affecting the rest of the molecule. Preferably, when the acid is used, the procedure is carried out in the presence of a condensing agent which is used in peptide chemistry such as a carbodiimide (for example N,N'-dicyclohexylcarbodiimide) or N,N'-carbonyldiimidazole, in an inert solvent such as an ether (for example tetrahydrofuran or dioxane), an amide (dimethylformamide) or a chlorinated solvent (for example methylene chloride, 1,2-dichloroethane or chloroform) at a temperature of between 0°C and the reflux temperature of the reaction mixture. When a reactive derivative of the acid is used, it is possible to cause the anhydride, a mixed anhydride or an ester (which may be chosen from the activated or nonactivated esters of the acid) to react; the procedure is then carried out either in an organic medium, optionally in the presence of an acid acceptor such as a nitrogen-containing organic base (for example trialkylamine, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene or 1,5-diazabicyclo[4.3.0]non-5-ene), in a

solvent as cited above, or a mixture of these solvents, at a temperature of between 0°C and the reflux temperature of the reaction mixture, or in a biphasic aqueous-organic medium in the presence of an alkaline or alkaline-earth base (sodium hydroxide or potassium hydroxide) or an alkali or alkaline-earth metal carbonate or bicarbonate at a temperature of between 0 and 40°C.

Reaction f is carried out by CURTIUS arrangement, in the presence of diphenylphosphorazide azide and triethylamine, in toluene, at a temperature in the region of 50°C.

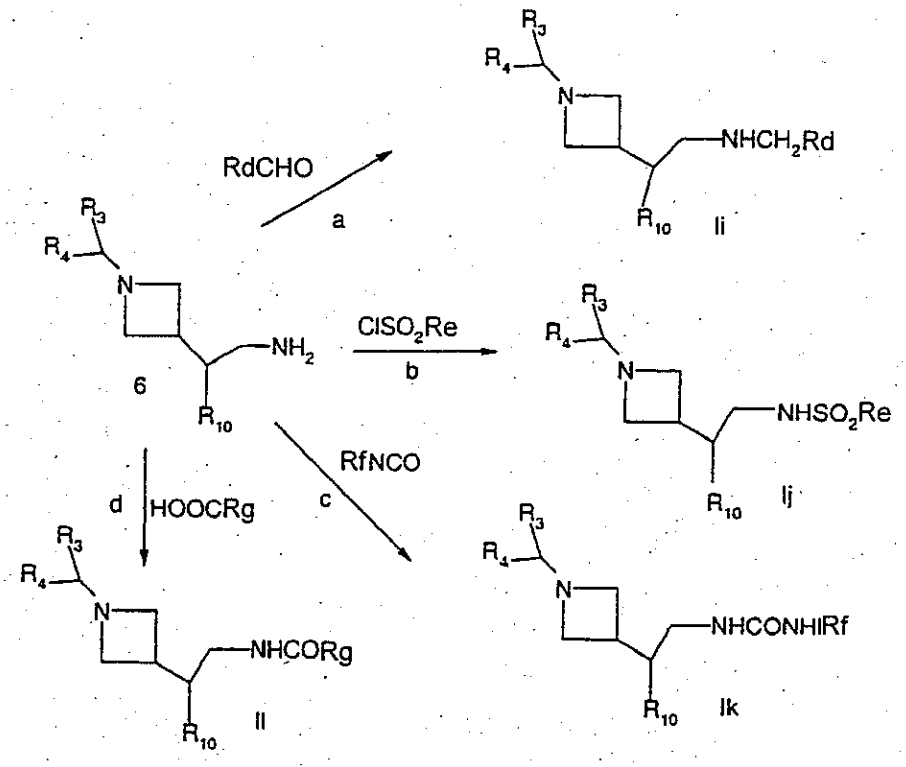
For reactions g and h, the procedure is carried out directly in the reaction medium of step g at a temperature in the region of 20°C.

In another aspect of the present invention, there is provided a process for preparing the compounds of formula (I) according to the aspect as defined above for which R represents a radical CR_1R_2, in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_{11})(R_{12})$ in which R_8 represents a hydrogen atom, R_{11} represents a radical $-SO_2-Ar$, SO_2-Het or $-SO_2alk$ and R_{12} represents a hydrogen atom or a radical Ar or Het, characterized in that a derivative of formula:



in which Ra represents an alkyl, Het or Ar radical and Rb represents a hydrogen atom or an Ar, Het or alkyl radical, Ar and Het having the same meanings as in the aspect as defined above, is reduced, the product isolated and optionally converted to a salt with an inorganic or organic acid.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-C(R_8)(R_9)(R_{10})$ for which R_8 is a hydrogen atom, R_9 is a radical $-CH_2-NHR_{28}$ and R_{10} represents a radical Ar or Het, may be prepared according to the following reaction scheme:



In these formulae, R_3, R_4 and R_{10} have the same meanings as in formula (I), Rd represents an alkyl or phenyl radical, Re represents an alkyl radical, Rf represents an alkyl radical, Rg represents an alkyl, cycloalkylalkyl, cycloalkyl, $-(CH_2)_nOH$ radical, n is equal to 1, 2 or 3.

Step a is generally carried out in an inert solvent such as an aliphatic alcohol (1-4C) (for example methanol), in a chlorinated solvent (for example dichloromethane or dichloroethane) or tetrahydrofuran, in the presence of a base such as $NaBH(OCOCH_3)_3$, at a temperature in the region of 20°C.

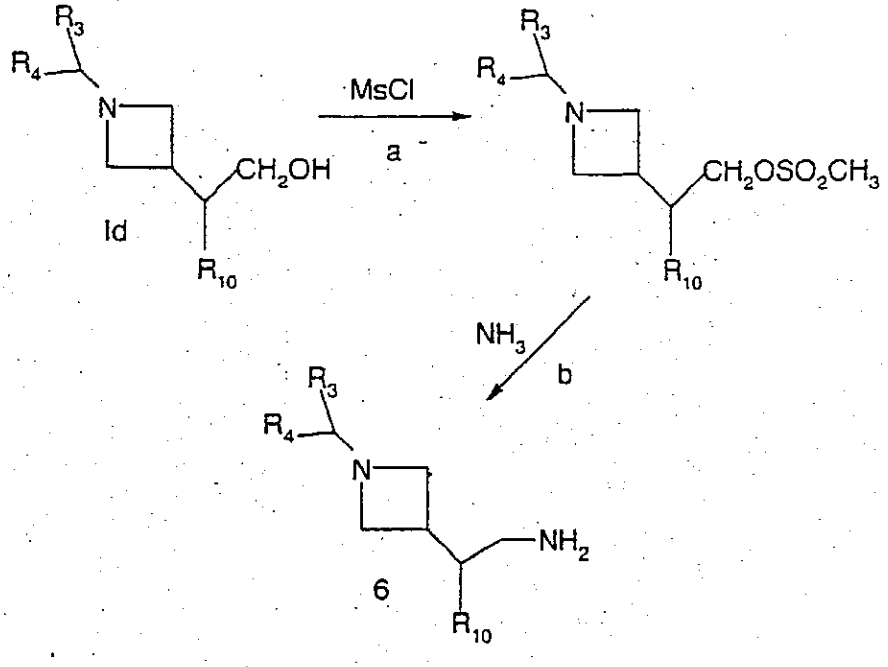
Step b is generally carried out in an inert solvent such as a halogenated solvent (for example dichloromethane), in the presence of an organic base such as triethylamine or dimethylaminopyridine, at a

temperature of between 0°C and the boiling point of the reaction medium.

Step c is generally carried out in an inert solvent such as tetrahydrofuran, dimethylformamide, a chlorinated solvent (for example chloroform or 1,2-dichloroethane), an aromatic solvent (for example benzene or toluene), at a temperature of between 10°C and the boiling point of the reaction medium.

Step d is carried out by any method known to a person skilled in the art which makes it possible to pass from an acid or a reactive derivative of this acid to a carboxamide without affecting the rest of the molecule and in particular the preferred methods previously described.

The derivatives 6 may be obtained according to the following reaction scheme:

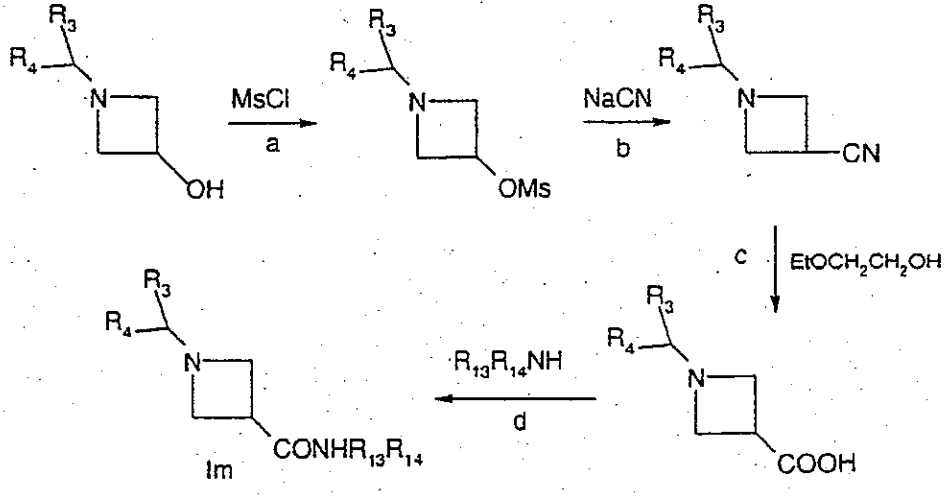


In these formulae, R_3, R_4 and R_{10} have the same meanings as in formula (I) and Ms is a methylsulfonyloxy radical.

Step a is generally carried out in an inert solvent such as tetrahydrofuran, in the presence of triethylamine, at a temperature of between 10 and 20°C.

Step b is generally carried out with liquid aqueous ammonia in methanol, in an autoclave, at a temperature in the region of 60°C.

The compounds of formula (I) in which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 is a radical $-CONR_{13}R_{14}$ may be prepared according to the following reaction scheme:



In these formulae, R_3, R_4, R_{13} and R_{14} have the same meanings as in formula (I), Ms represents a methylsulfonyloxy radical and Et represents ethyl.

Step a is carried out in the presence of triethylamine, in an inert solvent such as an ether

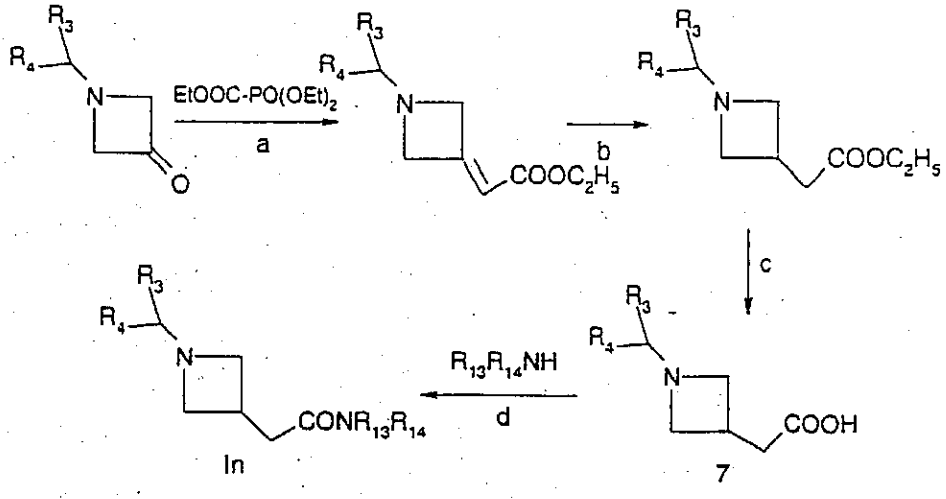
(for example tetrahydrofuran), at a temperature in the region of 0°C.

Step b is generally carried out in an inert solvent such as a mixture of water and dimethylformamide, at a temperature of between 30 and 75°C.

Step c is carried out by any method known to a person skilled in the art which makes it possible to pass from a cyanated compound to the corresponding acid without affecting the rest of the molecule. Preferably, the procedure is carried out by means of potassium hydroxide in an aliphatic alcohol (1-4C) (for example ethanol) or in an aqueous medium, at the boiling point of the reaction medium.

Step d is carried out by any method known to a person skilled in the art which makes it possible to pass from an acid or a reactive derivative of this acid to a carboxamide without affecting the rest of the molecule molecule and in particular the preferred methods previously described.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 is a radical $-CH_2-CONR_{13}R_{14}$ may be prepared according to the following reaction scheme:



In these formulae, R_3, R_4, R_{13} and R_{14} have the same meanings as in formula (I) and Et represents an ethyl radical.

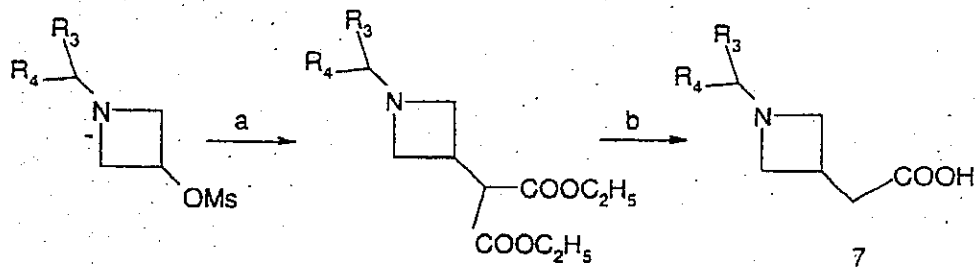
Reaction a is generally carried out in an inert solvent such as tetrahydrofuran, in the presence of a base such as sodium hydride, or an alkali metal carbonate (for example potassium carbonate), at a temperature of between 20°C and the boiling point of the reaction medium.

Reaction b is generally carried out by means of $NaBH_4$, in ethanol, at a temperature in the region of 0°C.

Reaction c is carried out by any method known to a person skilled in the art which makes it possible to pass from an ester to the corresponding acid without affecting the rest of the molecule. The procedure is preferably carried out in an inert solvent such as dioxane, in the presence of hydrochloric acid, at the boiling point of the reaction medium.

Reaction d is carried out by any method known to a person skilled in the art which makes it possible to pass from an acid or a reactive derivative of this acid to a carboxamide without affecting the rest of the molecule molecule and in particular the preferred methods previously described.

The intermediates 7 may also be obtained by malonic synthesis according to the following reaction scheme:

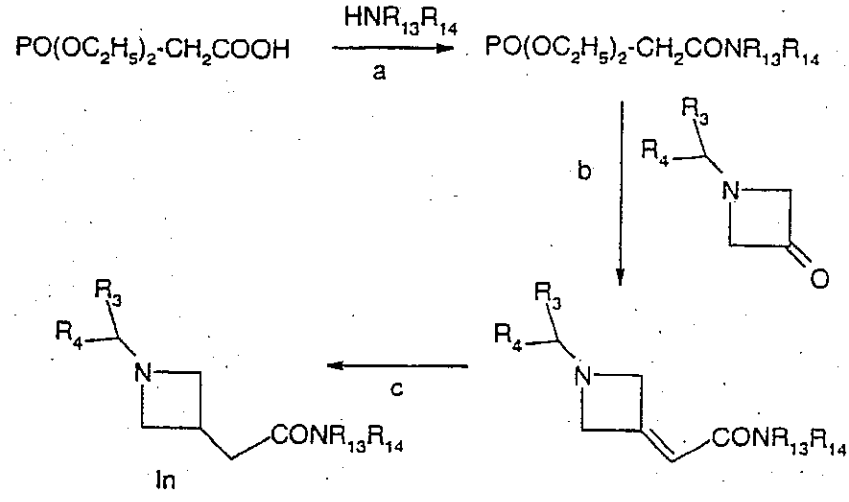


In these formulae, Ms represents a methylsulfonyloxy radical, R_3 and R_4 have the same meanings as in formula (I).

Reaction a is generally carried out by the action of diethyl malonate, in an inert solvent such as tetrahydrofuran, in the presence of freshly prepared sodium ethoxide, at the boiling point of the reaction medium.

Reaction b is generally carried out in an aqueous solution of hydrochloric acid at the boiling point of the reaction medium.

The compounds In may also be obtained according to the following reaction scheme:



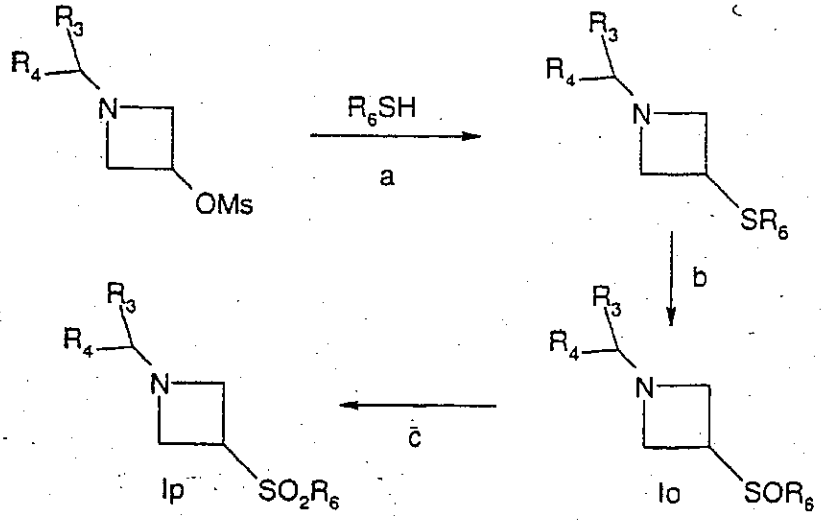
In these formulae, R_3, R_4, R_{13} and R_{14} have the same meanings as in formula (I).

Step a is carried out by any method known to a person skilled in the art which makes it possible to pass from an acid or a reactive derivative of this acid to a carboxamide without affecting the rest of the molecule molecule and in particular the preferred methods previously described.

Step b is generally carried out in an inert solvent such as tetrahydrofuran, in the presence of a base such as sodium hydride or potassium carbonate, at a temperature of between 20°C and the boiling point of the reaction medium.

The reduction of step c is generally carried out by means of $NaBH_4$, in ethanol, at a temperature in the region of 20°C.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-SOR_6$ or $-SO_2R_6$ may be prepared according to the following reaction scheme:



In these formulae, R_3, R_4 and R_6 have the same meanings as in formula (I) and Ms is a methylsulfonyloxy radical.

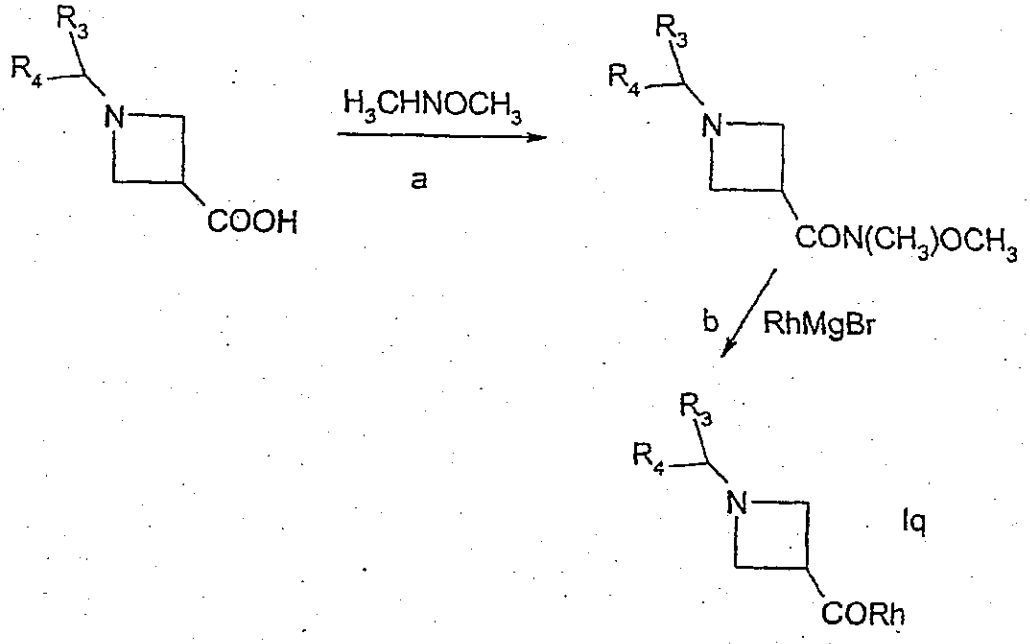
Step a is generally carried out in an inert solvent such as tetrahydrofuran, in the presence of an inorganic base such as sodium hydride, at a temperature of between 0°C and the boiling point of the reaction medium.

Step b is generally carried out by any method of persons skilled in the art for oxidizing a sulfur-containing derivative, such as those described by M. HUDLICKY, Oxidations in Organic Chemistry, ACS Monograph, 186, 252-263 (1990). For example, the procedure is carried out by the action of an organic peroxy acid or a salt of such a peroxy acid (peroxycarboxylic or peroxysulfonic acids, in particular peroxybenzoic acid, 3-chloroperoxybenzoic acid, 4-nitroperoxybenzoic acid, peroxyacetic acid,

trifluoroperoxyacetic acid, peroxyformic acid or monoperoxyphthalic acid) or inorganic peracids or a salt of such an acid (for example periodic or persulfuric acid), in an inert solvent such as a chlorinated solvent (for example chloroform or dichloromethane), at a temperature of between 0 and 25°C or alternatively by means of oxone in a water-alcohol (methanol or ethanol) mixture.

Step c is generally carried out by any method of persons skilled in the art for oxidizing a sulfinyl derivative. Preferably, the procedure is carried out by the action of an organic peroxy acid or a salt of such a peroxy acid (peroxycarboxylic or peroxysulfonic acids, in particular peroxybenzoic acid, 3-chloroperoxybenzoic acid, 4-nitroperoxybenzoic acid, peroxyacetic acid, trifluoroperoxyacetic acid, peroxyformic acid or monoperoxyphthalic acid) or alternatively by means of oxone, in a water-alcohol (methanol or ethanol) mixture.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-COR_6$ or -CO-cycloalkyl may be prepared according to the following reaction scheme:

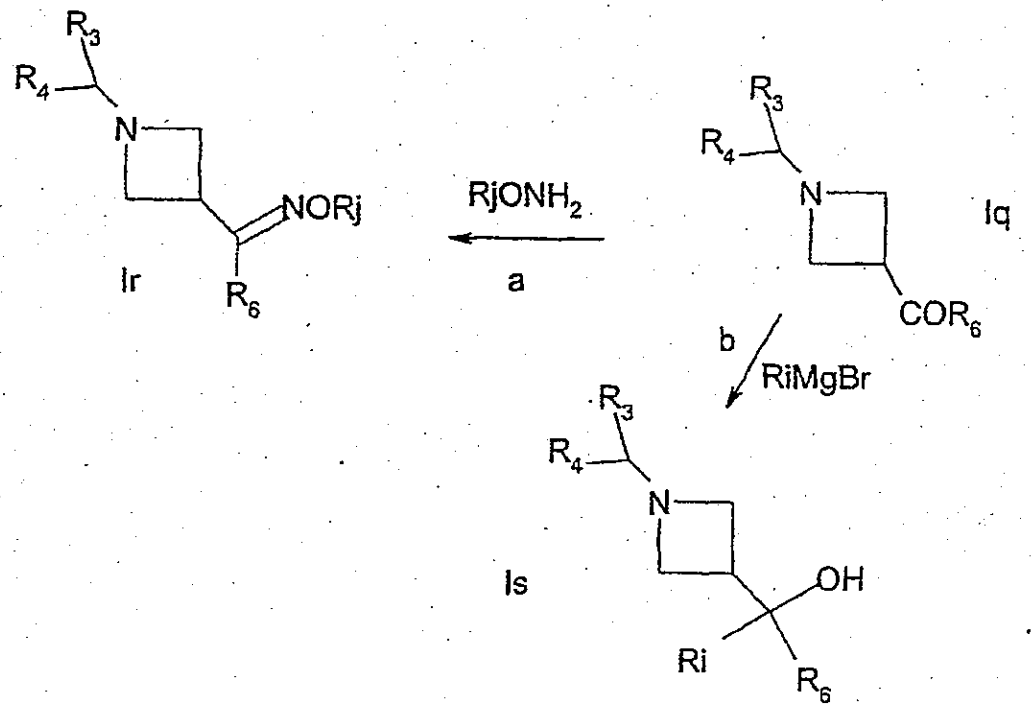


In these formulae, R_3 and R_4 have the same meanings as in formula (I) and Rh has the same meanings as R_6 or represents a cycloalkyl radical (3 to 10 carbon atoms).

Step a is carried out by any method known to a person skilled in the art which makes it possible to pass from an acid or a reactive derivative of this acid to a carboxamide without affecting the rest of the molecule molecule and in particular the preferred methods previously described.

Step b is generally carried out in an inert solvent such as an ether such as tetrahydrofuran, at a temperature in the region of 0°C. The organomagnesium compounds are prepared according to methods known to a person skilled in the art, such as those described in the examples.

The compounds of formula (I) for which R_1 is a hydrogen atom and R_2 is a radical $-C(OH)(R_6)R_{12}$, $-C(OH)(R_6)(alkyl)$, $-C(=NO-CH_2-CH=CH_2)R_6$ or $-C(=NOalk)R_6$ may be prepared according to the following reaction scheme:

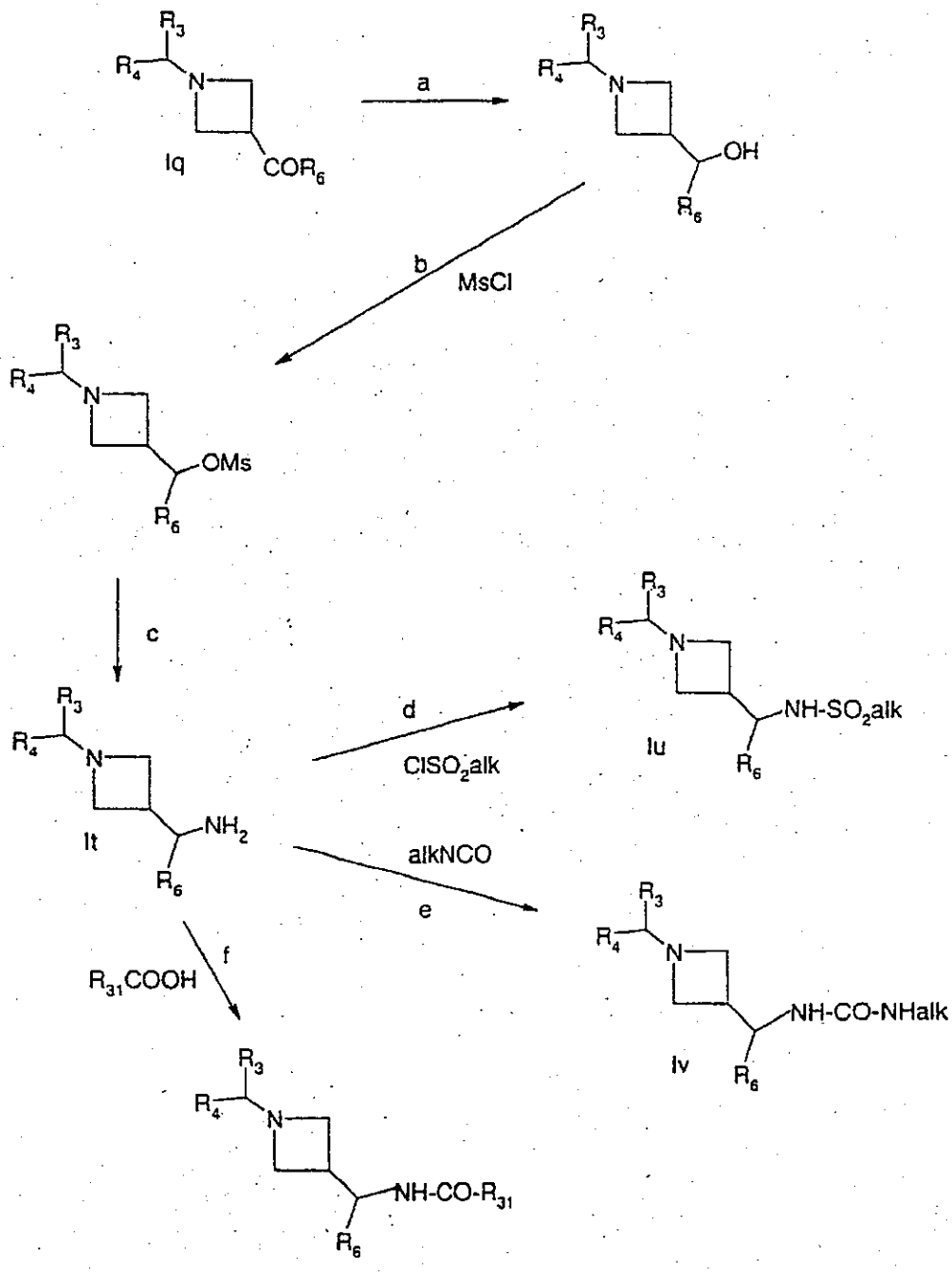


In these formulae, R_3, R_4 and R_6 have the same meanings as in formula (I), Ri has the same meanings as R_{12} or represents an alkyl radical (1 to 6 straight- or branched-chain carbon atoms) and Rj represents an alkyl radical (1 to 6 straight- or branched-chain carbon atoms) or $-CH_2-CH=CH_2$.

Step a is generally carried out in an inert solvent such as an aliphatic alcohol (for example ethanol), in the presence of sodium acetate, at a temperature of between 20°C and the boiling point of the reaction medium.

Step b is generally carried out in an inert solvent such as an ether such as tetrahydrofuran, at a temperature in the region of 0°C. The organomagnesium compounds are prepared according to methods known to a person skilled in the art such as those described in the examples.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, in which R_{31} and R_{32} are hydrogen atoms or radicals $-CH(R_6)NHSO_2alk$, $-CH(R_6)NHCONHalk$ or $-CH(R_6)NHCOR_{31}$, may be prepared according to the following reaction scheme:



In these formulae, R_3, R_4, R_6 and R_{31} have the same meanings as in formula (I), Ms represents a methylsulfonyloxy radical and alk represents an alkyl radical.

Reaction a is generally carried out by means of $NaBH_4$ in ethanol, at a temperature in the region of 20°C.

Step b is carried out in the presence of triethylamine, in an inert solvent such as an ether (for example tetrahydrofuran), at a temperature in the region of 0°C.

Step c is carried out by means of liquid aqueous ammonia in methanol, in an autoclave at a temperature in the region of 60°.

Step d is generally carried out in an inert solvent such as a halogenated solvent (for example dichloromethane) or tetrahydrofuran, in the presence of an organic base such as triethylamine, dimethylaminopyridine, at a temperature in the region of 20°C.

Step e is carried out by any method known to a person skilled in the art which makes it possible to pass from an acid or a reactive derivative of this acid to a carboxamide without affecting the rest of the molecule and in particular the preferred methods previously described.

Step f is generally carried out by means of an inert solvent such as tetrahydrofuran, dimethylformamide, a chlorinated solvent (for example chloroform or dichloroethane), an aromatic solvent (for example benzene or toluene), at a temperture of between 10°C and the boiling point of the reaction medium.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is an alkyl, Ar or -alk-Ar radical

may be prepared by the action of a halide $HalR_{31}$ on a compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} are hydrogen atoms.

This reaction is carried out in an inert polar solvent such as acetonitrile, tetrahydrofuran or dimethylformamide, in the presence of an organic or inorganic base (alkali metal (for example sodium or potassium) carbonate, trialkylamine (for example triethylamine or dimethylaminopyridine)), at a temperature of between 0°C and the boiling point of the solvent, optionally in the presence of palladium or one of its salts or complexes.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is an alkyl radical may also be prepared by the action of a corresponding compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CO-R_6$ on an amine $HNR_{31}R_{32}$ for which R_{31} is a hydrogen atom and R_{32} is an alkyl radical.

This reaction is generally carried out in an inert solvent such as a chlorinated solvent (for example dichloromethane or dichloroethane), in the presence of a reducing agent such as sodium triacetoxyborohydride, at a temperature of between 0°C and 70°C.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} are alkyl, Ar or -alk-Ar radicals may be prepared by the action of a halide $HalR_{32}$ on a compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is an alkyl, Ar or -alk-Ar radical.

This reaction is carried out in an inert polar solvent such as acetonitrile, tetrahydrofuran or dimethylformamide, in the presence of an organic or inorganic base (alkali metal (for example sodium or potassium) carbonate, trialkylamine (for example triethylamine or dimethylaminopyridine)), at a temperature of between 0°C and the boiling point of the solvent, optionally in the presence of palladium or one of its salts or complexes.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is a (2-6C) alkyl or -(2-6C)alk-Ar radical may be prepared by the action of an aldehyde RaCHO for which Ra is an alkyl or -alk-Ar radical on a compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} are hydrogen atoms.

This reaction is carried out in an inert solvent such as dichloromethane, dichloroethane, toluene or tetrahydrofuran, at a temperature of between 0°C and 50°C in the presence of a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is an alkyl, Ar or -alk-Ar radical and R_{32} is a (2-6C) alkyl or -(2-6C)alk-Ar radical may be prepared by the action of an aldehyde RaCHO for which Ra is an alkyl or -alk-Ar radical on a compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is an alkyl, Ar or -alk-Ar radical.

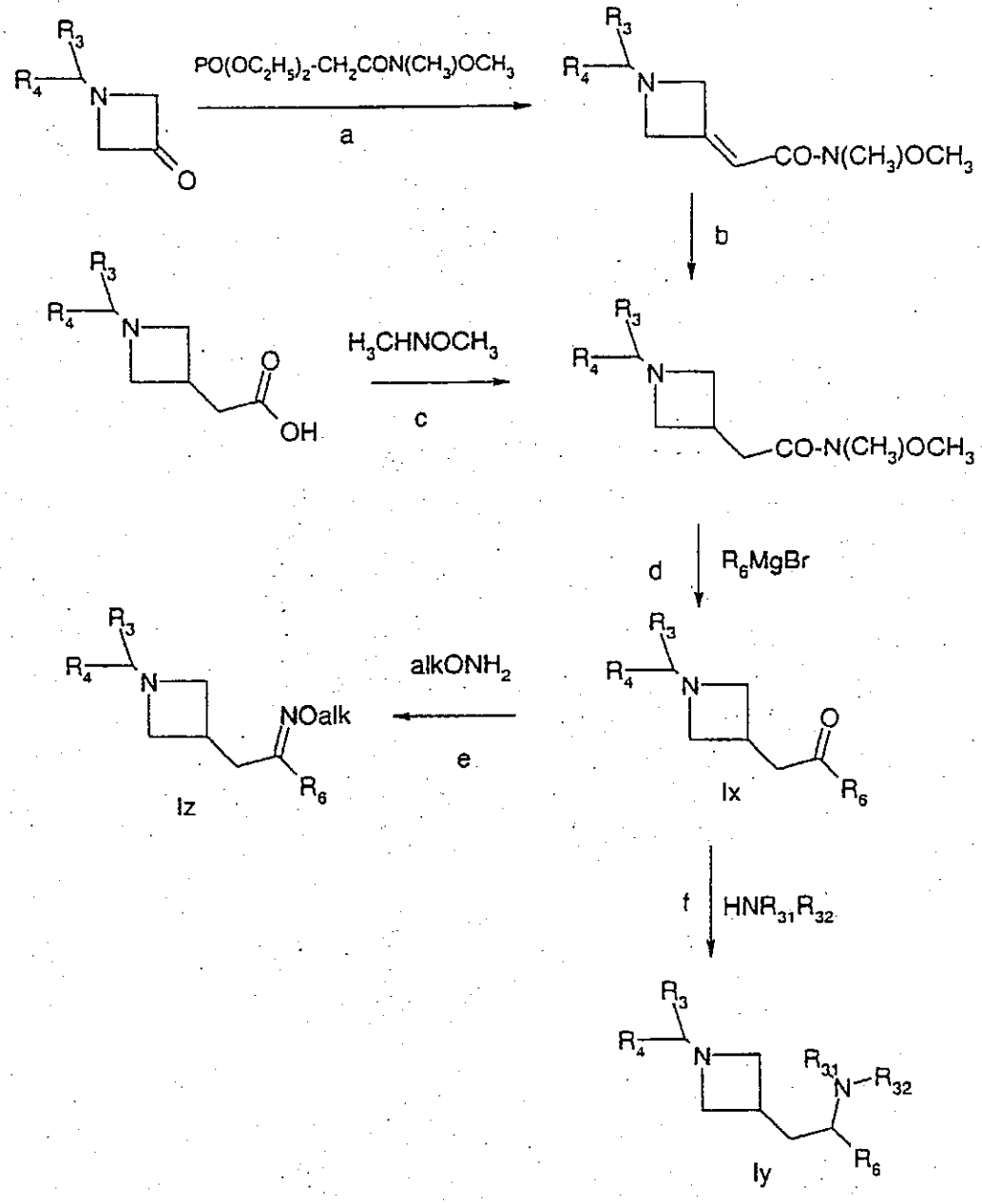
This reaction is carried out in an inert solvent such as dichloromethane, dichloroethane, toluene or tetrahydrofuran, at a temperature of between 0°C and 50°C in the presence of a reducing agent such as sodium triacetoxyborohydride or sodium cyanoborohydride.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} form with the nitrogen atom to which they are attached a heterocycle chosen from aziridinyl, azetidinyl, pyrrolidinyl or piperidinyl may be prepared

by the action of a dihalide Hal-(2-5C)alk-Hal on a compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} are hydrogen atoms.

This reaction is carried out in an inert polar solvent such as acetonitrile, tetrahydrofuran or dimethylformamide, in the presence of an organic or inorganic base (alkali metal (for example sodium or potassium) carbonate, trialkylamine (for example triethylamine or dimethylaminopyridine)), at a temperature of between 0°C and the boiling point of the solvent, optionally in the presence of palladium or one of its salts or complexes.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH_2-COR_6$, $-CH_2-CH(R_6)-NR_{31}R_{32}$ or $-CH_2-C(=NOalk)R_6$ may be prepared according to the following reaction scheme:



In these formulae, R_3, R_4, R_6, R_{31} and R_{32} have the same meanings as in formula (I) and alk represents an alkyl radical.

Step a is generally carried out in a solvent such as tetrahydrofuran, at a temperature of between 20°C and the boiling point of the reaction medium.

Step b is generally carried out in an inert solvent such as an aliphatic alcohol (for example methanol), a chlorinated solvent (chloroform or

dichloromethane) or a mixture of these solvents, in the presence of a reducing agent such as $NaBH_4$, at a temperature of between 0°C and the boiling point of the reaction medium.

Step c is carried out by any method known to a person skilled in the art which makes it possible to pass from an acid or a reactive derivative of this acid to a carboxamide without affecting the rest of the molecule and in particular the preferred methods previously described.

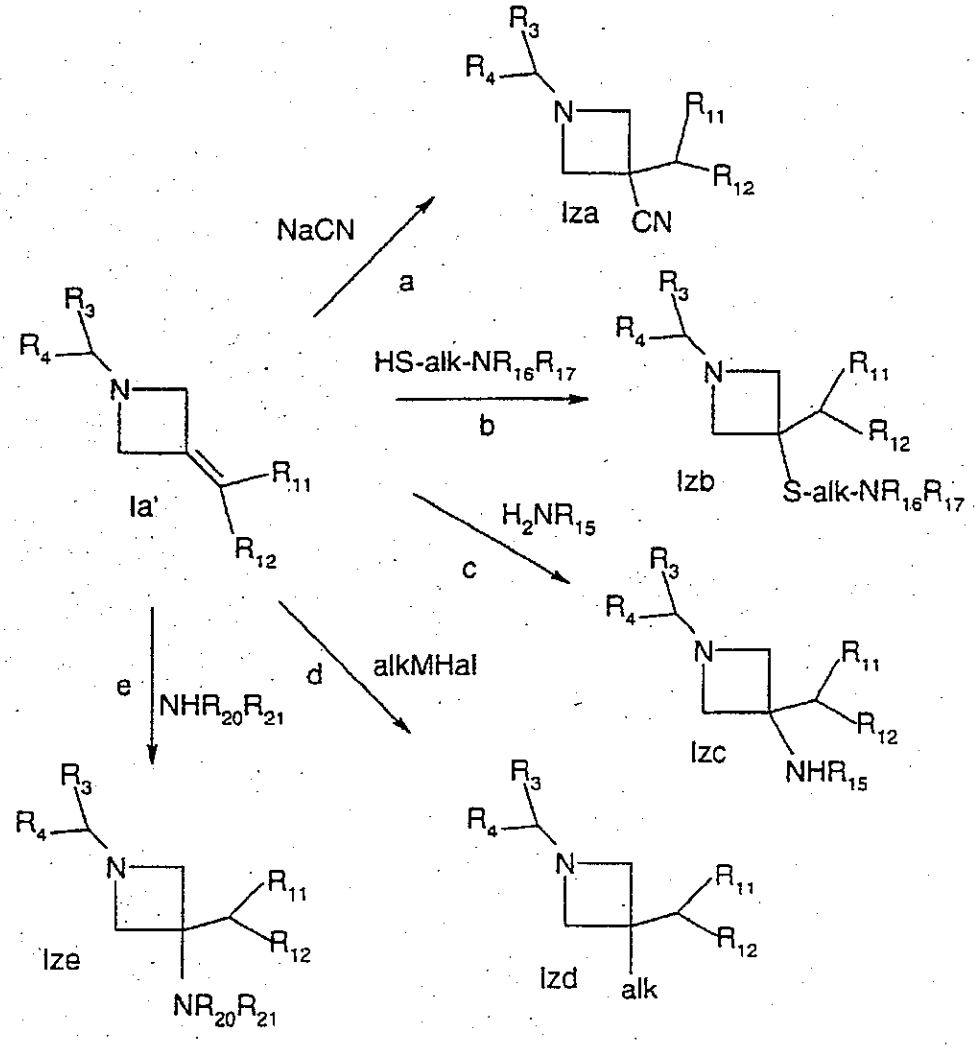
Step d is generally carried out in an inert solvent such as an ether such as tetrahydrofuran, at a temperature in the region of 0°C. The organomagnesium compounds are prepared according to the methodes known to a person skilled in the art such as those described in the examples.

Step e is generally carried out in an inert solvent such as a 1-4C aliphatic alcohol such as methanol, in the presence of sodium acetate, at a temperature of between 20°C and the boiling point of the reaction medium.

Step f is carried out in an inert solvent such as a chlorinated solvent (for example dichloromethane or dichloroethane), in the presence of a reducing agent such as sodium triacetoxyborohydride, at a temperature of between 0°C and 70°C.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a cyano, -S-alk-$NR_{16}R_{17}$, -NHR_{15}, alkyl or -$NR_{20}R_{21}$ radical

and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ in which R_8 is a hydrogen atom may be prepared according to the following reaction scheme:



In these formulae, R_3, R_4, R_{11}, R_{12}, R_{15}, R_{16} and R_{17} have the same meanings as in formula (I), alk represents an alkyl radical, Hal represents a halogen atom and M represents a metal and preferably copper.

Step a is preferably carried out in a polar solvent such as dimethyl sulfoxide, at a temperature of between 20 and 50°C.

Step b is preferably carried out in an inert solvent such as dimethyl sulfoxide, tetrahydrofuran or acetonitrile, in the presence of a base such as an alkali metal carbonate (for example potassium carbonate) or ammonium hydroxide, at a temperature of between 20°C and the boiling point of the reaction medium.

Step c is preferably carried out in an inert solvent such as dimethyl sulfoxide, tetrahydrofuran or acetonitrile, in the presence of a base such as an alkali metal carbonate (for example potassium carbonate) or ammonium hydroxide, at a temperature of between 20°C and the boiling point of the reaction medium.

Step d is preferably carried out in an inert solvent such as an ether (ethyl ether) or tetrahydrofuran, at a temperature of between -78°C and 20°C.

Step e is preferably carried out in an inert solvent such as dimethyl sulfoxide, tetrahydrofuran, acetonitrile, dichloromethane or dichloroethane in the presence of a base such as an alkali metal carbonate (for example potassium carbonate) or ammonium hydroxide, at a temperature of between 20°C and the boiling point of the reaction medium.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} and R_{19} represent a hydrogen atom may be prepared by reducing the corresponding

compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a cyano radical.

This reaction is generally carried out in an inert solvent such as tetrahydrofuran, ethyl ether or toluene, at a temperature of between 0°C and the boiling point of the reaction medium, in the presence of a reducing agent such as aluminum hydride.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} represents a hydrogen atom and R_{19} represents an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, -SO_2alk, -CO-NHalk or -COOalk radical may be prepared by the action of a halide $HalR_{19}$, Hal represents a halogen, on a compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} and R_{19} represent a hydrogen atom.

This reaction is carried out in an inert polar solvent such as acetonitrile, tetrahydrofuran or dimethylformamide, in the presence of an organic or inorganic base (alkali metal (for example sodium or potassium) carbonate, trialkylamine (for example triethylamine or dimethylaminopyridine)), at a temperature of between 0°C and the boiling point of the solvent, optionally in the presence of palladium or one of its salts or complexes.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} represents an alkyl radical and

R_{19} represents an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, $-SO_2alk$, -CO-NHalk or -COOalk radical may be prepared by the action of an alkyl halide on a compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a radical $-alk-NR_{18}R_{19}$, R_{18} represents a hydrogen atom and R_{19} represents an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, $-SO_2alk$, -CO-NHalk or -COOalk radical.

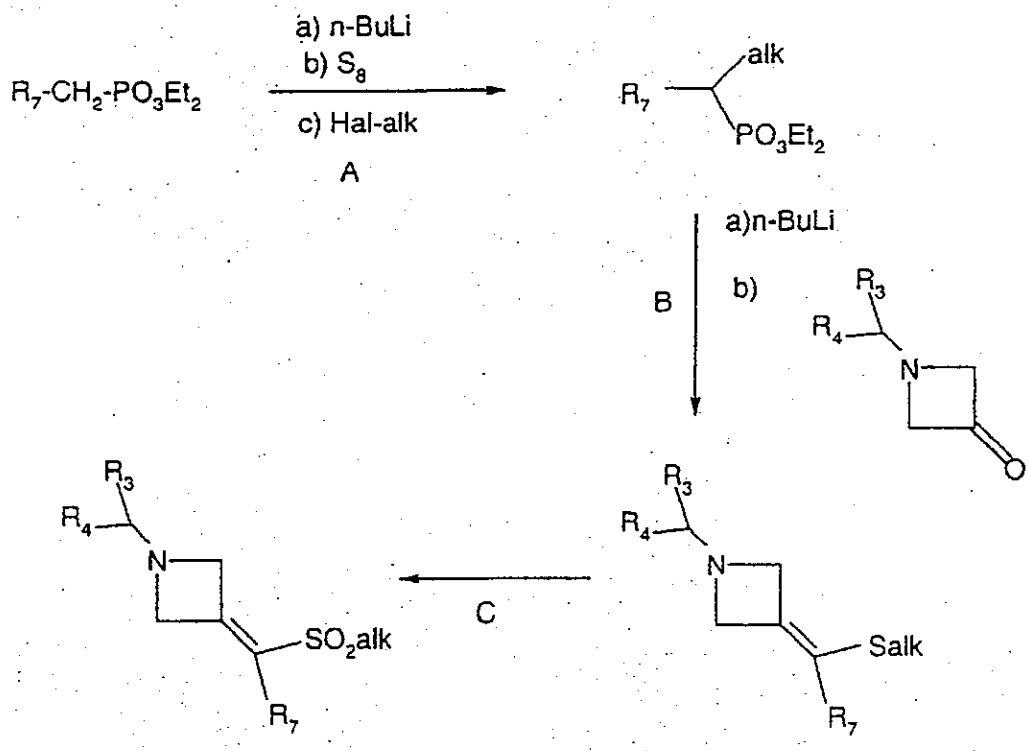
This reaction is carried out in an inert polar solvent such as acetonitrile, tetrahydrofuran or dimethylformamide, in the presence of an organic or inorganic base (alkali metal (for example sodium or potassium) carbonate, trialkylamine (for example triethylamine or dimethylaminopyridine)), at a temperature of between 0°C and the boiling point of the solvent, optionally in the presence of palladium or one of its salts or complexes.

The compounds of formula (I) for which R represents a radical CR_1R_2 in which either R_1 represents a hydrogen atom and R_2 represents a radical $-C(R_8)(R_9)(R_{10})$ or $-C(R_8)(R_{11})(R_{12})$, or R_1 represents an alkyl, NH-R_{15}, cyano, $-S-alk-NR_{16}R_{17}$, $-alk-NR_{18}R_{19}$ or $-NR_{20}R_{21}$ radical and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ and R_8 represents an alkyl radical may be prepared by alkylation of a corresponding compound of formula (I) for which R_8 is a hydrogen atom.

This reaction is preferably carried out by means of a base such as an alkali metal hydride (for

example sodium hydride), an alkali metal amide (for example sodium amide) or an organometallic derivative, in an inert solvent such as an aliphatic ether (ethyl ether) or tetrahydrofuran, at a temperature of between -78°C and 30°C, by means of an alkylating agent such as an alkyl halide or an alkyl sulfonate.

The compounds of formula (I) for which R represents a radical $C=C(R_7)SO_2alk$ may also be prepared according to the following reaction scheme:



In these formulae, R_3, R_4 and R_7 have the same meanings as in formula (I), alk represents an alkyl radical and Hal represents a halogen atom.

Reaction A is generally carried out in an inert solvent such as an ether (for example ethyl ether), in the presence of a strong base such as tert-butyllithium

or n-butyllithium, at a temperature of between -70°C and -50°C, followed by the addition of sulfur and then an alkyl halide (for example iodide or bromide).

Reaction B is generally carried out in an inert solvent such as an ether (for example tetrahydrofuran), in the presence of a strong base such as tert-butyllithium or n-butyllithium, at a temperature of between -70°C and -50°C, followed by the addition of azeditin-3-one, a return to room temperature and hydrolysis.

Reaction C is carried out by any known method which makes it possible to oxidize a sulfur-containing derivative without affecting the rest of the molecule, such as those previously described.

It is understood for persons skilled in the art that, to carry out the processes according to the invention which are described above, it may be necessary to introduce groups protecting amino, hydroxyl and carboxyl functions in order to avoid side reactions. These groups are those which allow removal without affecting the rest of the molecule. As examples of groups protecting the amino function, there may be mentioned tert-butyl or methyl carbamates which may be regenerated using iodotrimethylsilane or allyl using palladium catalysts. As examples of groups protecting the hydroxyl function, there may be mentioned triethylsilyl and tert-butyldimethylsilyl which may be regenerated using tetrabutylammonium fluoride or alternatively asymmetric acetals (methoxymethyl or

tetrahydropyranyl for example) with regeneration using hydrochloric acid. As groups protecting carboxyl functions, there may be mentioned esters (allyl or benzyl for example), oxazoles and 2-alkyl-1,3-oxazolines. Other protecting groups which can be used are described by GREENE T.W. et al., Protecting Groups in Organic Synthesis, second edition, 1991, John Wiley & Sons.

The compounds of formula (I) may be purified by the customary known methods, for example by crystallization, chromatography or extraction.

The enantiomers of the compounds of formula (I) may be obtained by resolution of the racemates for example by chromatography on a chiral column according to PIRCKLE W.H. et al., Asymmetric synthesis, Vol. 1, Academic Press (1983) or by formation of salts or by synthesis from chiral precursors. The diastereoisomers may be prepared according to known conventional methods (crystallization, chromatography or from chiral precursors).

The compounds of formula (I) may be optionally converted to addition salts with an inorganic or organic acid by the action of such an acid in an organic solvent such as an alcohol, a ketone, an ether or a chlorinated solvent. These salts also form part of the invention.

As examples of pharmaceutically acceptable salts, the following salts may be mentioned: benzenesulfonate, hydrobromide, hydrochloride, citrate,

ethanesulfonate, fumarate, gluconate, iodate, isethionate, maleate, methane sulfonate, methylene-bis-β-oxynaphthoate, nitrate, oxalate, pamoate, phosphate, salicylate, succinate, sulfate, tartrate, theophyllineacetate and p-toluenesulfonate.

In yet another aspect of the present invention, there is provided a pharmaceutical composition containing as active ingredient, at least one compound of formula (I) according to the aspect as defined above.

The compounds of formula (I) exhibit advantageous pharmacological properties. These compounds possess a high affinity for the cannabinoid receptors and particularly those of the CB1 type. They are CB1 receptor antagonists and are therefore useful in the treatment and prevention of disorders affecting the central nervous system, the immune system, the cardiovascular or endocrine system, the respiratory system, the gastrointestinal apparatus and reproductive disorders (Hollister, Pharm. Rev.; 38, 1986, 1-20, Reny and Sinha, Prog. Drug Res., 36, 71-114 (1991), Consroe and Sandyk, in Marijuana/Cannabinoids, Neurobiology and Neurophysiology, 459, Murphy L. and Barthe A. Eds, CRC Press, 1992).

Accordingly, these compounds may be used for the treatment or prevention of psychoses including schizophrenia, anxiety disorders, depression, epilepsy,

neurodegeneration, cerebellar and spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheral neuropathies, glaucomas, migraine, Parkinson's disease, Alzheimer's disease, Huntington's chorea, Raynaud's syndrome, tremor, obsessive-compulsive disorder, senile dementia, thymic disorders, Tourette's syndrome, tardive dyskinesia,

bipolar disorders, cancers, movement disorders induced by medicaments, dystonia, endotoxemic shocks, hemorrhagic shocks, hypotension, insomnia, immunological diseases, multiple sclerosis, vomiting, asthma, appetite disorders (bulimia, anorexia), obesity, memory disorders, in weaning from chronic treatments and alcohol or drug abuse (opioids, barbiturates, cannabis, cocaine, amphetamine, phencyclide, hallucinogens, benzodiazepines for example), as analgesics or potentiators of the analgesic activity of the narcotic and nonnarcotic drugs. They may also be used for the treatment or prevention of intestinal transit.

The affinity of the compounds of formula (I) for the cannabis receptors has been determined according to the method described by KUSTER J.E., STEVENSON J.I., WARD S.J., D'AMBRA T.E., HAYCOCK D.A. in J. Pharmacol. Exp. Ther., 264 1352-1363 (1993).

In this test, the IC_{50} of the compounds of formula (I) is less than or equal to 1000 nM.

Their antagonist activity has been shown by means of the model of hypothermia induced by an agonist of the cannabis receptors (CP-55940) in mice, according to the method described by Pertwee R.G. in Marijuana, Harvey D.J. eds, 84 Oxford IRL Press, 263-277 (1985).

In this test, the DE50 of the compounds of formula (I) is less than or equal to 50 mg/kg.

The compounds of formula (I) exhibit low toxicity. Their LD_{50} is greater than 40 mg/kg by the subcutaneous route in mice.

The preferred compounds of formula (I) are the following:

(RS)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine,

(R)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine,

(S)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine,

(RS)-1-[bis(4-chlorophenyl)methyl)]-3-[(pyrid-3-yl)-(methylsulfonyl)methyl]azetidine,

(R)-1-[bis(4-chlorophenyl)methyl)]-3-[(pyrid-3-yl)-(methylsulfonyl)methyl]azetidine,

(S)-1-[bis(4-chlorophenyl)methyl)]-3-[(pyrid-3-yl)-(methylsulfonyl)methyl]azetidine,

(RS)-1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(R)-1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(S)-1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluoro-phenyl)methylsulfonylmethyl]azetidine,

1-[bis(4-chlorophenyl)methyl]-3-(RS)-{[3-azetidin-1-yl-phenyl]methylsulfonylmethyl}azetidine,

1-[bis(4-chlorophenyl)methyl]-3-(R)-{[3-azetidin-1-yl-phenyl]methylsulfonylmethyl}azetidine,

1-[bis(4-chlorophenyl)methyl]-3-(S)-{[3-azetidin-1-yl-phenyl]methylsulfonylmethyl}azetidine,

(RS)-1-[3({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]pyrrolidine,

(R)-1-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]pyrrolidine,

(S)-1-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]pyrrolidine,

(RS)-N-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethyl)phenyl]-N-methylamine,

(R)-N-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]-N-methylamine,

(S)-N-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]-N-methylamine,

(RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bistrifluoromethylphenyl)methylsulfonylmethyl]azetidine,

(R)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bistrifluoromethylphenyl)methylsulfonylmethyl]azetidine,

(S)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bistrifluoromethylphenyl)methylsulfonylmethyl]azetidine,

1-[bis(4-chlorophenyl)methyl]-3-(phenylsulfonylmethyl)-azetidine,

(RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-3-methylazetidine,

(R)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-3-methylazetidine,

(S)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-3-methyl-azetidine,

(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylacetamide,

(R)-2-{1-[bis(4-chlorophenyl)methyl]azeditin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylacetamide,

(S)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylacetamide,

(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isobutylacetamide,

(R)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isobutylacetamide,

(S)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isobutylacetamide,

(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylmethylacetamide,

(R)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylmethylacetamide,

(S)-2-{1-bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylmethylacetamide,

(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isopropylacetamide,

(R)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isopropylacetamide,

(S)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isopropylacetamide,

(RS)-1-[bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluorophenyl)-1-methylsulfonylethyl]azetidine,

(R)-1-[bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluorophenyl)-1-methylsulfonylethyl]azetidine,

(S)-1-[bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluorophenyl)-1-methylsulfonylethyl]azetidine,

(RS)-1-[bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(R)-1-[bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(S)-1-[bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RS)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SS)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RR)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SR)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RS)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SS)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RR)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SR)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RS)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine,

(SR)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine,

(RR)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine,

(SS)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine,

(SS)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RR)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RS)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SR)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

their optical isomers and their pharmaceutically acceptable salts.

The following examples illustrate the invention.

Example 1

(RS)-1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonylmethyl]azetidin may be prepared from 1.0 g of 1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]-azetidine in 40 cm^3 of methanol, 96 mg of sodium borohydride are added and the mixture is stirred for 3 hours at 20°C. After addition of 100 cm^3 of dichloromethane, the reaction mixture is washed twice with 50 cm^3 of water and dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The crude product is

chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 6 cm, diameter 3 cm), eluting under an argon pressure of 0.8 bar with dichloromethane and then the mixture dichloromethane + 1% methanol and collecting 80-cm^3 fractions. Fractions 13 to 15 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.55 g of a white solid is obtained which is taken up in 50 cm^3 of diisopropyl ether, filtered and dried to give 0.47 g of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine in the form of a white solid [^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6 with addition of a few drops of CD_3COOD d4, at a temperature of 353 K, δ in ppm) : 2.46 (t, J = 7.5 Hz : 1H); 2.77 (s : 3H); 3.15 (mt : 2H); 3.40 (mt : 1H); 3.49 (broad t, J = 7.5 Hz : 1H); 4.46 (s : 1H); 4.81 (d, J = 9 Hz : 1H); from 7.05 to 7.20 (mt : 3H); from 7.15 to 7.45 (mt : 8H)].

1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine may be prepared according to two methods:

Method 1

0.65 cm^3 of methylsulfonyl chloride is added to a solution of 2.94 g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]-azetidin-3-ol in 250 cm^3 of dichloromethane at 22°C, followed, in small portions over 15 minutes by 2.42 g of 4-dimethylaminopyridine; the orange-colored solution is stirred for 2 hours at room temperature. The

reaction mixture is washed 3 times with 150 cm^3 of distilled water and once with 150 cm^3 of a saturated sodium chloride solution, then dried with magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 5.5 cm, height 15 cm), under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (1/9 by volume) as eluent and collecting 70-cm^3 fractions. Fractions 15 to 36 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 1.86 g of a white foam are obtained, which foam is crystallized from isopropyl ether to give a solid melting at 190°C.

Recrystallization from 45 cm^3 of ethanol gives 1.08 g of 1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine melting at 206°C [NMR spectrum in DMSO-d6, T=300K, δ in ppm (300 MHz) : 3.00 (3H,s, SCH_3), 3.87 (2H, s, NCH_2), 4.20 (2H, s, NCH_2), 4.75 (1H, s, NCH), 7.15 (2H, d, J=8Hz, 2CH arom.), 7.30 (5H, m, 5CH arom.), 7.45 (4H, d, J=7Hz, 4CH arom.)].

6.75 g of 3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]azetidin-3-ol hydrochloride are added to a solution of 6.8 g of bis(4-chlorophenyl)-bromomethane in 300 cm^3 of acetonitrile, followed by 2.97 g of potassium carbonate. The reaction mixture is heated for 1 hour under reflux, cooled to room temperature, filtered and concentrated to dryness under

reduced pressure (2.7 kPa). The residue obtained is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 8.5 cm, height 22 cm), under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (25/75 by volume) as eluent and collecting 250-cm^3 fractions. Fractions 11 to 48 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 5.3 g of 1-[bis(4-chlorophenyl)-methyl]-3-[(3,5-difluorophenyl)methylsulfonyl)methyl-(RS)]azetidin-3-ol are obtained. [^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 2.00 (s : 3H); 2.94 (s : 3H); 3.25 (mt : 2H); 3.48 (d, J = 9Hz : 1H); 3.80 (d, J = 9 Hz : 1H); 4.54 (s : 1H); 5.34 (s : 1H); 7.15 (d, J = 8.5 Hz : 2H); from 7.20 to 7.40 (mt : 8H); 7.50 (broad t, J = 9 Hz : 1H)].

Bis(4-chlorophenyl)bromomethane may be prepared according to the procedure described by BACHMANN W.E., J. Am. Chem. Soc., 2135 (1933).

3-[(3,5-Difluorophenyl)methylsulfonyl)methyl-(RS)]azetidin-3-ol hydrochloride may be obtained in the following manner: 160 cm^3 of a 6.2 N hydrochloric acid solution in dioxane are added to a solution of 37 g of 3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]-1-(vinyloxycarbonyl)azetidin-3-ol in 160 cm^3 of dioxane. After 16 hours at room temperature, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is taken up in 320 cm^3 of ethanol, heated for 1 hour under reflux and cooled on an ice-cold bath. The solid which appears is

filtered, washed with ethyl ether and dried at 40°C under reduced pressure (2.7 kPa). 29.85 g of white crystals are obtained whose melting point is greater than 260°C.

3-[(3,5-Difluorophenyl)(methylsulfonyl)methyl-(RS)]-1-(vinyloxycarbonyl)azetidin-3-ol may be obtained in the following manner: a solution of 14 cm^3 of vinyl chloroformate in 35 cm^3 of dichloromethane is added at 5°C to a solution of 60.18 g of 1-benzhydryl-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]azetidin-3-ol in 100 cm^3 of dichloromethane. After 20 hours at room temperature, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 11 cm, height 32 cm), under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (3/7 by volume) as eluent and collecting 1000-cm^3 fractions. Fractions 8 to 18 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 37 g of 3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]-1-(vinyloxycarbonyl)azetidin-3-ol are obtained in the form of white crystals melting at 195°C.

1-Benzhydryl-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]azetidin-3-ol may be obtained in the following manner: 29.5 cm^3 of 1.6 N n-butyllithium in solution in hexane are added to a solution of 6.73 cm^3 of diisopropylamine in 110 cm^3 of tetrahydrofuran, under an argon atmosphere, cooled to

-70°C. After 30 minutes, a mixture of 8.7 g of 3,5-difluorobenzyl methyl sulfone in 200 cm^3 of tetrahydrofuran is then added and the stirring is maintained for 45 minutes at -70°C. 10 g of 1-benzhydrylazetidin-3-one dissolved in 60 cm^3 of tetrahydrofuran are added and then the medium is stirred for 20 minutes while allowing the mixture to return to room temperature. The reaction mixture is hydrolyzed with 400 cm^3 of a saturated ammonium chloride solution, extracted with dichloromethane, washed 3 times with 500 cm^3 of water and then a saturated sodium chloride solution. The organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue (19 g) is taken up in isopropyl ether from which it crystallizes. After filtration and drying, 15.35 g of 1-benzhydryl-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]azetidin-3-ol are obtained in the form of white crystals.

1-Benzhydrylazetidin-3-one may be prepared according to the procedure described by KATRITZKY A.R. et al. in J. Heterocycl. Chem., 271 (1994).

3,5-Difluorobenzyl methyl sulfone may be prepared in the following manner: starting with 33.46 g of 3,5-difluorobenzyl methyl sulfide in 318 cm^3 of water, 318 cm^3 of acetic acid and 318 cm^3 of ethanol, 129.9 g of oxone® are added at 5°C. After 16 hours at room temperature, the reaction mixture is diluted with dichloromethane, washed with water and with a saturated

sodium chloride solution, dried, filtered and concentrated to dryness under reduced pressure (2.7 kPa). 35.57 g of 3,5-difluorobenzyl methyl sulfone are obtained in the form of white crystals, m.p. = 135°C.

3,5-Difluorobenzyl methyl sulfide may be prepared in the following manner: starting with 40 g of 3,5-difluorobenzyl bromide and 16.25 g of sodium methyl thiolate in DMF at 60°C, 33.46 g of 3,5-difluorobenzyl methyl sulfide are obtained after treatment in the form of a yellow oil.

Method 2

0.80 g of crushed sodium hydroxide is added to a solution of 2.2 g of 3-acetoxy-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]azetidine in 25 cm^3 of dioxane at room temperature. After 16 hours at room temperature, 50 cm^3 of water and 100 cm^3 of ethyl acetate are added. The mixture is separated after settling, the organic phase washed again with 100 cm^3 of water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). A white foam is obtained which is crystallized from isopropyl ether to give 0.85 g of a solid melting at 190°C.

Crystallization from 20 cm^3 of ethanol gives 0.70 g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-(methylsulfonyl)methylene]azetidine melting at 205°C.

14 cm^3 of a 1.6 N solution of n-butyllithium in hexane are added at -70°C to a solution of 4.77 g of

[Bis(4-chlorophenyl)methyl]amine hydrochloride may be prepared according to the method described by GRISAR M. et al., J. Med. Chem., 885 (1973).

Example 2

(-)-1-[Bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine and (+)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine may be prepared by CLHP separation on a CHIRALPAK AS chiral column (particle size 20 μm, height 23 cm, diameter 6 cm) of 0.52 g of the racemate prepared in Example 1. By eluting with the heptane/ethanol (90/10) mixture at a flow rate of 80 cm^3/min and after having concentrated the collected fractions to dryness under reduced pressure (2.7 kPa), there are obtained 110 mg of (-)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine $[\alpha_D]$ = 6.3° (C = 0.5 M in methanol) in the form of a white solid melting at 178°C and 134 mg of (+)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine $[\alpha_D]$ = +5.8° (C = 0.5 M in methanol) in the form of a white solid melting at 178°C.

Example 3

The mixture of the 2 A diastereoisomer forms 1-[4-[(R*)-(4-chlorophenyl)-{3-[3,5-difluorophenyl)-methylsulfonylmethyl-(R)]azetidin-1-yl}methyl]benzyl]-pyrrolidine and 1-[4-[(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl-(S)]azetidin-1-

yl}methyl]benzyl]pyrrolidone may be prepared by carrying out the procedure in the following manner: 20 mg of sodium borohydride are added to a solution of 60 mg of 1-(R*)-[4-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)-benzyl]pyrrolidone, A isomer form, in 2 cm^3 of ethanol and 2 cm^3 of dichloromethane. After stirring for 20 hours at 20°C, 0.25 cm^3 of water and 20 cm^3 of dichloromethane are added and the mixture is stirred and dried over magnesium sulfate and then filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 7 cm, diameter 1 cm), eluting under an argon pressure of 0.1 bar with dichloromethane and then with a mixture of dichloromethane and methanol (95/5 by volume) and collecting 5-cm^3 fractions. Fractions 13 to 18 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 38 mg of the mixture of the 2 A diastereoisomer forms 1-[4-[(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl-(R)]azetidin-1-yl}methyl]benzyl]pyrrolidine and 1-[4-[(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonyl-methyl-(S)]azetidin-1-yl}methyl]benzyl]pyrrolidine are obtained in the form of a white foam [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm) : 1.77 (mt : 4H); from 2.40 to 2.60 (mt :5H); 2.67 (s : 3H); from 3.10 to 3.25 (mt : 2H); 3.38 (mt : 1H); from 3.50 to 3.70 (mt : 3H); 4.24 (s : 1H); 4.25 (d, J = 11 Hz : 1H); 6.83 (broad t,

J = 9 Hz : 1H); 6.94 (mt : 2H) from 7.10 to 7.35 (mt : 8H)].

1-(R*)-[4-(4-Chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)-benzyl]pyrrolidine, A isomer form, may be prepared by carrying out the procedure in the following manner: 50 mm^3 of pyrrolidine are added to a solution of 0.32 g of 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)-methyl}-3-[(3,5-difluorophenyl)methylsulfonyl-methylene]azetidine, A isomer form, and 5 mg of sodium iodide in 10 cm^3 of dichloromethane. After stirring for 20 hours at 20°C, 50 mm^3 of pyrrolidine are added to the mixture, the mixture is stirred for 8 hours and then 50 mm^3 of pyrrolidine are again added and the mixture is stirred for 20 hours at 20°C. The reaction mixture is washed with water and then the organic phase is dried over magnesium sulfate and concentrated to dryness under vacuum (2.7 kPa). The residue obtained is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 1.2 cm, height 30 cm), under an argon pressure of 0.1 bar, eluting with dichloromethane and then with a dichloromethane and methanol (97.5/2.5 by volume) mixture and collecting 3-cm^3 fractions. Fractions 12 to 40 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 0.18 g of 1-(R*)-[4-(4-Chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethylene]azetidin-1-yl}methyl)benzyl]-pyrrolidine, A isomer form, is obtained in the form of a white foam $[\alpha]^{20}365nm$ = -22.5° +/- 0.7 (c = 0.5%;

dichloromethane) [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 1.78 (mt : 4H); 2.51 (mt : 4H); 2.81 (s : 3H); 3.58 (s : 2H); 3.84 (mt : 2H); 4.33 (mt : 2H); 4.50 (2 : 1H); 6.84 (tt, J = 9 and 2.5 Hz : 1H); 6.98 (mt : 2H); from 7.20 to 7.40 (mt : 8H)].

1-{(R*)-[(4-Chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidine, A isomer form, may be prepared by carrying out the procedure in the following manner:

12.4 cm^3 of methylsulfonyl chloride are added to a solution of 28.0 g of the mixture of the 2 diastereoisomers (A forms) 1-{(R*)-[(4-chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(R)-(3,5-difluorophenyl)methylsulfonylmethyl)]azetidin-3-ol and 1-{(R*)-[(4-chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(S)-(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ol and 32 g of 4-dimethylaminopyridine in 500 cm^3 of dichloromethane. After stirring for one hour at 10°C and then one hour at 20°C, the reaction mixture is washed with 500 cm^3 of water, the organic phase is dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 6 cm, height 30 cm), under an argon pressure of 0.2 bar, eluting with dichloromethane and collecting 250-cm^3 fractions. Fractions 9 to 25 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 6.3 g of 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-

3-[(3,5-difluorophenyl)methylsulfonylmethylene]-azetidine, A isomer form, are obtained in the form of a white foam.

The mixture of the 2 diastereoisomers (A forms) 1-{(R*)-[4-chloromethyl)phenyl]-(4-chlorophenyl)-methyl}-3-[(R)-(3,5-difluorophenyl)methylsulfonyl-methyl)]azetidin-3-ol and 1-{(R*)-[4-chloromethyl)-phenyl](4-chlorophenyl)methyl}-3-[(S)-(3,5-difluorophenyl)methylsulfonylmethyl)]azetidin-3-ol may be prepared by carrying out the procedure in the following manner: 6 cm^3 of thionyl chloride are added to a solution of 0.20 g of the mixture of the 2 diastereoisomers (A forms) 1-{(R*)-(4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl}-3-[(R)-(3,5-difluoro-phenyl)methylsulfonylmethyl)]azetidin-3-ol, and 1-{(R*)-(4-chlorophenyl)[4-(hydroxymethyl)phenyl]-methyl}-3-[(S)-(3,5-difluorophenyl)methylsulfonyl-methyl)]azetidin-3-ol in 10 cm^3 of dichloromethane. After stirring for 20 hours at 20°C, 5 cm^3 of a saturated aqueous sodium hydrogencarbonate solution are added to the reaction mixture and then stirred for 15 minutes. The mixture is separated after settling, the organic phase is washed with water, dried over magnesium sulfate and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 1.0 cm, height 20 cm), under an argon pressure of 0.2 bar, eluting with a cyclohexane and ethyl acetate (75/25 by volume) mixture and

collecting 20-cm^3 fractions. Fractions 4 to 7 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.17 g of the mixture of the 2 diastereoisomers (A forms) 1-{(R*)-[4-(chloromethyl)-phenyl]-(4-chlorophenyl)methyl}-3-[(R)-(3,5-difluoro-phenyl)methylsulfonylmethyl)]azetidin-3-ol and 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(S)-(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ol, are obtained in the form of a white foam.

The mixture of the 2 diastereoisomers (A forms) 1-{(R*)-(4-chlorophenyl)[4-(hydroxymethyl)phenyl]-methyl}-3-[(R)-(3,5-difluorophenyl)methylsulfonyl-methyl)]azetidin-3-ol, and 1-{(R*)-(4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl}-3-[(S)-(3,5-difluoro-phenyl)methylsulfonylmethyl)]azetidin-3-ol may be prepared by carrying out the procedure in the following manner: 1.6 cm^3 of a 1.5 M solution of diisobutylaluminum hydride in toluene are added to a solution, kept under argon and cooled to -30°C, of 0.58 g of the mixture of the 2 diastereoisomers (A forms) 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxy-carbonyl)phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)-methylsulfonylmethyl)]azetidine and 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]methyl}-3-[(S)-(3,5-difluorophenyl)methylsulfonylmethyl)]-azetidine, in 10 cm^3 of anhydrous toluene. After stirring for 15 minutes at -30°C, 1.0 cm^3 of the same hydride solution is again added and the mixture is allowed to return to 0°C. After stirring for

30 minutes, the stirred mixture is supplemented with 3 cm^3 of water and 6 cm^3 of 1 N sodium hydroxide and then extracted with 25 cm^3 of dichloromethane. The organic phase is washed with 5 cm^3 of water, 5 cm^3 of brine and then dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 1.2 cm, height 30 cm), under an argon pressure of 0.1 bar, eluting with a cyclohexane and ethyl acetate (50/50 by volume) mixture and collecting 30-cm^3 fractions. Fractions 4 to 12 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 0.42 g of the mixture of the 2 diastereoisomers (A forms) 1-{(R*)-(4-chlorophenyl)-[4-(hydroxymethyl)phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)methylsulfonylmethyl)]azetidin-3-ol and 1-{(R*)-(4-chlorophenyl)[4-(hydroxymethylphenyl]methyl}-3-[(S)-(3,5-difluorophenyl)methylsulfonylmethyl)]azetidin-3-ol, are obtained in the form of a white lacquer.

The mixture of the 2 diastereoisomers (A forms) 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)-phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)methyl-sulfonylmethyl)]azetidine and 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]methyl}-3-[(S)-(3,5-difluorophenyl)methylsulfonylmethyl)]azetidine may be prepared by carrying out the procedure in the following manner: 3 cm^3 of a 1.6 N solution of n-butyllithium in hexane are poured under argon over

5 minutes, into a solution, cooled to -60°C, of 1.0 g of (3,5-difluorobenzyl)methyl sulfone in 30 cm^3 of tetrahydrofuran. After stirring for 1 hour at -60°C and then for 30 minutes at -30°C, a solution, previously cooled to -60°C, of 1.45 g of 1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]methyl}azetidin-3-one, A isomer form, in 15 cm^3 of tetrahydrofuran is added dropwise to this mixture. After stirring for 30 minutes at -60°C and then for 30 minutes at -30°C, 0.43 cm^3 of acetyl chloride is added and the reaction mixture is allowed to return to 0°C. 40 cm^3 of water and 40 cm^3 of dichloromethane are then added to the medium, with stirring, and then the medium is allowed to return to room temperature and it is separated after settling. The organic phase is washed with 20 cm^3 of water and is then dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.040-0.063 mm, diameter 3 cm, height 30 cm), eluting under an argon pressure of 0.5 bar with a cyclohexane and ethyl acetate (75/25 by volume) mixture and collecting 30-cm^3 fractions. Fractions 21 to 35 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 1.28 g of the mixture of the 2 diasterisomers (A forms) 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)methylsulfonylmethyl)]azetidine and 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)-

phenyl]methyl}-3-[(S)-(3,5-difluorophenyl)methyl-sulfonylmethyl)]azetidine are obtained in the form of a cream-colored foam.

1-{(R*)-(4-Chlorophenyl)[4-methoxycarbonyl)-phenyl]methyl}azetidin-3-one, A isomer form, may be prepared by carrying out the procedure in the following manner: 0.90 cm^3 of dimethyl sulfoxide is poured over 10 minutes into a solution, cooled to -60°C, of 0.55 cm^3 of oxalyl chloride in 5 cm^3 of dichloromethane. After stirring for 30 minutes at -60°C, a solution of 1.75 g of 1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)-phenyl]methyl}azetidin-3-ol, A isomer form, in 20 cm^3 of dichloromethane is added to the mixture over 15 minutes. After stirring for 3 hours at -60°C, 2.7 cm^3 of triethylamine are poured in and then the reaction medium is allowed to return to 0°C. 20 cm^3 of water are then added, the mixture is stirred and then separated after settling. The organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The orange-colored oil obtained is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 2 cm, height 30 cm), under an argon pressure of 0.5 bar, eluting with a cyclohexane and ethyl acetate (75/25 by volume) mixture and collecting 30-cm^3 fractions. Fractions 2 to 15 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 1.45 g of 1-{(R*)-(4-chlorophenyl)[4-

(methoxycarbonyl)phenyl]methyl}azetidin-3-one, A isomer form, are obtained in the form of a yellow foam.

1-{(R*)-(4-Chlorophenyl)[4-methoxycarbonyl)-phenyl]methyl}azetidin-3-ol, A isomer form, may be prepared by carrying out the procedure in the following manner: 0.605 g of sodium hydrogen carbonate is added to a suspension of 2.0 g of methyl (+)-4-[(R*)-amino-(4-chlorophenyl)methyl]benzoate in 30 cm^3 of ethanol followed by 0.60 cm^3 of epibromohydrin. After stirring for 20 hours at 60°C, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 3 cm, height 35 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (70/30 by volume for fractions 6 to 10 and then 60/40 for fractions 18 to 27, and then 50/50) and collecting 60-cm^3 fractions. Fractions 15 to 40 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up in 30 cm^3 of ethanol and is then supplemented with 0.20 g of sodium hydrogen carbonate and 0.2 cm^3 of epibromohydrin. After stirring for 48 hours at 20°C and then 24 hours at 35°C, the mixture is filtered and the filtrate is concentrated to dryness at 60°C under reduced pressure (2.7 kPa). 1.76 g of 1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)-phenyl]methyl}azetidin-3-ol, A isomer form, are obtained in the form of a pasty solid.

Methyl (+)-4-[(R*)-amino-(4-chlorophenyl)-methyl]benzoate may be prepared by carrying out the procedure in the following manner: 2.51 g of D-(-)-tartaric acid are added to a solution of 9.2 g of methyl 4-[(RS)-amino-(4-chlorophenyl)methyl]benzoate in 10 cm^3 of methanol. The solution is concentrated to dryness under reduced pressure (2.7 kPa). The cream-colored foam obtained is dissolved in 50 cm^3 of ethanol containing 5% of water and the resulting solution is allowed to crystallize for 20 hours at 20°C. The crystals are filtered, washed with ethanol containing 5% of water, drained and then dried under reduced pressure (2.7 kPa). 3.4 g of white crystals are obtained, which crystals are named "A crystals" [and which are stored for the subsequent preparation of the second enantiomer methyl (-)-4-[(R*)-amino-(4-chlorophenyl)methyl]benzoate)]. The mother liquors are concentrated to dryness and a white foam is obtained (8.1 g) which is dissolved in 100 cm^3 of ethyl acetate. The solution obtained is supplemented with 50 cm^3 of 1 N sodium hydroxide, stirred and separated after settling. The organic phase is washed with 50 cm^3 of water and then dried over magensium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). A yellow solid is obtained which is dissolved in 100 cm^3 of methanol. The solution obtained is supplemented with 1.85 g of L-(+)-tartaric acid and the resulting solution is concentrated to dryness under reduced pressure (2.7 kPa). A cream-colored foam is

obtained which, once dissolved in 27 cm^3 of ethanol containing 4% of water, is allowed to crystallize for 20 hours at 20°C. The crystals are filtered, washed with ethanol containing 4% of water, drained and then dried under reduced pressure (2.7 kPa). 3.4 g of crystals of methyl (+)-4-[(R*)-amino-(4-chlorophenyl)-methyl]benzoate L-(+)-tartrate are obtained which are recrystallized from 60 cm^3 of ethanol containing 5% of water. After draining and then drying, 2.78 g of white crystals are obtained which are dissolved in 50 cm^3 of ethyl acetate. The solution obtained is supplemented with 100 cm^3 of 1 N sodium hydroxide, stirred and separated after settling. The organic phase is washed with 50 cm^3 of water and then dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). 2.1 g of methyl (+)-4-[(R*)-amino-(4-chlorophenyl)methyl]benzoate are obtained in the form of a white solid.

Methyl 4-[(RS)-amino-(4-chlorophenyl)methyl]-benzoate may be prepared by carrying out the procedure in the following manner: 3.9 cm^3 of hydrazine hydrate are added to a suspension of 16.3 g of methyl 4-[(RS)-phthalimido-(4-chlorophenyl)methyl]benzoate in 200 cm^3 of methanol. After stirring for 5 hours at the reflux temperature and then for 20 hours at 20°C, the reaction mixture is filtered and the filtrate is concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is taken up in a mixture of 200 cm^3 of water and 200 cm^3 of ethyl acetate. After stirring for 15

minutes, the resulting suspension is filtered, the filtrate separated after settling in a separating funnel and the organic phase is washed with 50 cm^3 of water, dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). 8.4 g of methyl 4-[(RS)-amino-(4-chlorophenyl)methyl]benzoate are obtained in the form of a pale yellow oil.

Methyl 4-[(RS)-phthalimido-(4-chlorophenyl)-methyl]benzoate may be prepared by carrying out the procedure in the following manner: 12.6 g of potassium phthalimide are added to a solution of 11.6 g of methyl 4-[(RS)-bromo-(4-chlorophenyl)methyl]benzoate in 70 cm^3 of N,N-dimethylformamide. After stirring for 3 hours at the reflux temperature, the reaction mixture is cooled to 20°C and then supplemented with 300 cm^3 of ethyl acetate and 300 cm^3 of water. After stirring, the mixture is separated after settling, the aqueous phase reextracted with twice 100 cm^3 of ethyl acetate, the combined organic phases are washed with twice 400 cm^3 of water and then dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). 16.3 g of methyl 4-[(RS)-phthalimido-(4-chlorophenyl)methyl]benzoate are obtained in the form of a pasty yellow solid.

Methyl 4-[(RS)-bromo-(4-chlorophenyl)methyl]-benzoate may be prepared by carrying out the procedure in the following manner: 10.18 g of N,N'-carbonyl-diimidazole and 54.3 cm^3 of allyl bromide are added to a solution of 17.4 g of methyl 4-[(RS)-(4-chloro-

phenyl)(hydroxy)methyl]benzoate in 200 cm^3 of acetonitrile. After stirring for 30 minutes at 20°C, the reaction mixture is heated under reflux for 2 hours, stirred for 20 hours at 20°C and concentrated almost to dryness under reduced pressure (2.7 kPa). The mixture, taken up in dichloromethane, is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 7 cm, height 30 cm), under an argon pressure of 0.5 bar, eluting with dichloromethane, and collecting 500-cm^3 fractions. Fractions 3 to 6 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 11.6 g of methyl 4-[(RS)-bromo-(4-chlorophenyl)methyl]benzoate are obtained in the form of an oil which will be used as it is in the next step.

Methyl 4-[(RS)-(4-chlorophenyl)(hydroxy)-methyl]benzoate may be prepared by carrying out the procedure in the following manner: 1.21 g of sodium borohydride are added slowly in small fractions (the medium becomes slightly warm up to 50°C) to a suspension of 2.75 g of methyl 4-(4-chlorobenzoyl)benzoate in 200 cm^3 of methanol at 20°C. After stirring for 20 hours at 20°C, the reaction mixture is concentrated to a reduced volume and then supplemented with 150 cm^3 of dichloromethane and, with stirring, with 100 cm^3 of 0.5 N hydrochloric acid. After decantation, the organic phase is dried over magensium sulfate, concentrated to dryness under reduced pressure (2.7 kPa). 2.5 g of methyl 4-[(RS)-(4-

chlorophenyl)(hydroxy)methyl]benzoate are obtained in the form of a colorless oil which crystallizes slowly at 20°C and which will be used as it is in the next step.

Methyl 4-(4-chlorobenzoyl)benzoate may be prepared by carrying out the procedure in the following manner: 27.4 cm^3 of tri-n-butylphosphine are added, under argon, to a solution, cooled to -22°C of 19.3 g of terephthalic acid chloride monomethyl ester in 200 cm^3 of tetrahydrofuran. After stirring for 20 minutes at -22°C, a solution of 4-chlorophenyl-magnesium bromide (prepared from 19.15 g of 4-bromochlorobenzene, 2.43 g of magnesium and one iodine crystal in 100 cm^3 of diethyl ether under reflux) is poured in while maintaining this temperature. After stirring for 30 minutes at -22°C, 150 cm^3 of 1 N hydrochloric acid are added slowly, the mixture is allowed to return to 20°C and then the medium is diluted with 200 cm^3 of diethyl ether. The white suspension obtained is filtered, the solid is washed with twice 50 cm^3 of water and then with twice 50 cm^3 of diethyl ether. After draining and then drying under reduced pressure (2.7 kPa), 16.2 g of methyl 4-(4-chlorobenzoyl)benzoate are obtained in the form of a white solid melting at 170°C.

Example 4

The mixture of the 2 B diastereoisomer forms 1-[4-[(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl-(R)]azetidin-1-yl}methyl]benzyl]-

pyrrolidine and 1-[4-[(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl-(S)]azetidin-1-yl}methyl]benzylpyrrolidine may be prepared by carrying out the procedure as described in Example 3, starting with 50 mg of (+)-1-[4-(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}-methyl)benzyl]pyrrolidine, B isomer form, 1.5 cm^3 of ethanol, 1.5 cm^3 of dichloromethane and 18 mg of sodium borohydride, with stirring for 8 hours at 50°C and then for 48 hours at 20°C. 50 mg of the mixture of the 2 B diastereoisomer forms 1-[4-[(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl-(R)]azetidin-1-yl}methyl]benzyl]pyrrolidine and 1-[4-[(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonyl-methyl-(S)]azetidin-1-yl}methyl]benzylpyrrolidine are obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm). A 60/40 mixture of diastereoisomers is observed, * 1.79 (mt: 4H); from 2.45 to 2.60 (mt: 5H); 2.67 (s : 3H); from 3.10 to 3.30 (mt : 2H); 3.40 (mt : 1H); 3.57 and 3.60 (2s : 2H in total); 3.65 (broad t, J = 7.5 Hz : 1H); 4.26 and 4.30 (2s : 2H in total); 6.84 (tt, J = 9 and 2 Hz : 1H); 6.96 (mt : 2H); from 7.25 to 7.40 (mt : 8H).

(+)-1-[4-(R*)-(4-Chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)benzyl]pyrrolidine, B isomer form, may be prepared by carrying out the procedure as is described in Example 3, starting with 0.50 g of 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(3,5-

difluorophenyl)(methylsulfonyl)methylene]azetidine, B isomer form, 5 mg of sodium iodide, 15 cm^3 of dichloromethane and 0.190 g of pyrrolidine. The crude product is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 1.5 cm, height 20 cm), under an argon pressure of 0.1 bar, eluting with dichloromethane and then with a dichloromethane and methanol (95/5 by volume) mixture and collecting 25-cm^3 fractions. Fractions 20 to 40 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 0.28 g of (+)-1-[4-(R*)-(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)benzyl]pyrrolidine, B isomer form, is obtained in the form of a white foam. $[a]^{20}365nm$ = +26.8 +/- 0.8 (c = 0.5%; dichloromethane) [$^{-1}$H NMR spectrum (300 MHZ, $CDCl_3$, δ in ppm) : 1.78 (mt : 4H); 2.50 (mt : 4H); 2.80 (s : 3H); 3.57 (s : 2H); 3.84 (mt : 2H); 4.34 (mt : 2H); 4.50 (s : 1H); 6.84 (tt, J = 9 and 2.5 Hz : 1H); 6.98 (mt : 2H); from 7.20 to 7.40 (mt : 8H)].

1-{(R*)-[4-(Chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine, B isomer form, may be prepared by carrying out the procedure as described in Example 3, starting with 7.3 g of the mixture of the 2 B diastereoisomer forms 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(R)-(3,5-difluorophenyl)-(methylsulfonyl)methyl)]azetidin-3-ol and 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(S)-(3,5-difluorophenyl)(methylsulfonyl)methyl)]azetidin-3-

ol, 8.2 g of 4-dimethylaminopyridine, 150 cm^3 of dichloromethane and 3.2 cm^3 of methylsulfonyl chloride. The crude product is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 3 cm, height 30 cm) under an argon pressure of 0.2 bar, eluting with dichloromethane and collecting 100-cm^3 fractions. Fractions 15 to 30 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 2.50 g of 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(3,5-difluorophenylmethylsulfonyl)methylene]azetidine, B isomer form, are obtained in the form of a white foam.

The mixture of the 2 B diastereoisomer forms 1-{(R*)-[4-(chloromethyl)phenyl[4-chlorophenyl)methyl}-3-[(R)-(3,5-difluorophenyl)(methylsulfonyl)methyl)]-azetidin-3-ol and 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(S)-(3,5-difluorophenyl)-(methylsulfonyl)methyl)]azetidin-3-ol may be prepared by carrying out the procedure as described in Example 3, starting with 11.0 g of the mixture of the 2 B diastereoisomer forms 1-{(R*)-4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)(methylsulfonyl)methyl)]azetidin-3-ol and 1-{(R*)-(4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl}-3-[(S)-(3,5-difluorophenyl)(methylsulfonyl)methyl)]-azetidin-3-ol, 250 cm^3 of dichloromethane and 3.1 cm^3 of thionyl chloride. The crude product is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 3 cm, height 30 cm), under an argon pressure

of 0.2 bar, eluting with a cyclohexane and ethyl acetate (70/30 by volume) mixture and collecting 50-cm^3 fractions. Fractions 9 to 25 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 7.3 g of the mixture of the 2 B diastereoisomer forms 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(R)-(3,5-difluorophenyl)-(methylsulfonyl)methyl)]azetidin-3-ol and 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(S)-(3,5-difluorophenyl)(methylsulfonyl)methyl)]azetidin-3-ol are obtained in the form of a white foam.

The mixture of the 2 B diastereoisomer forms 1-{(R*)-(4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)(methylsulfonyl)methyl)]-azetidin-3-ol and 1-{(R*)-[4-(chlorophenyl)[4-(hydroxy-methyl)phenyl]methyl}-3-[(R)-3,5-difluorophenyl)-(methylsulfonyl)methyl)]azetidin-3-ol may be prepared by carrying out the procedure as described in Example 3, starting with 18.0 g of the mixture of the 2 B diastereoisomer forms 3-acetoxy-1-{(R*)-(4-chloro-phenyl)[4-(methoxycarbonyl)phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine and 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methyloxycarbonyl)-phenyl]methyl}-3-[(S)-(3,5-difluorophenyl)(methyl-sulfonyl)methyl]azetidine, 150 cm^3 of anhydrous toluene and 100 cm^3 of a 20% solution of diisobutylaluminum hydride in toluene. The crude product is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 3 cm, height 30 cm), under an

argon pressure of 0.1 bar, eluting with a cyclohexane and ethyl acetate (50/50 by volume) mixture and collecting 50-cm^3 fractions. Fractions 15 to 30 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 11.0 g of the mixture of the 2 B diastereoisomer forms 1-{(R*)-(4-chlorophenyl)[4-(hydroxymethyl)phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidin-3-ol and 1-{(R*)-[(4-chlorophenyl)[4-(hydroxymethyl)phenyl]-methyl}-3-[(S)-3,5-difluorophenyl)(methylsulfonyl)-methyl]azetidin-3-ol are obtained in the form of a white foam.

The mixture of the 2 B diastereoisomer forms 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)-phenyl]methyl}-3-[(R)-(3,5-difluorophenyl)(methyl-sulfonyl)methyl]azetidine and 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]methyl}-3-[(S)-(3,5-difluorophenyl)methylsulfonyl)methyl]azetidine may be prepared by carrying out the procedure as described in Example 3, starting with 11.2 g of (3,5-difluoro-benzyl)methyl sulfone, 350 cm^3 of tetrahydrofuran, 34 cm^3 of a 1.6 N solution of n-butyllithium in hexane, 11.2 g of 1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)-phenyl]methyl}azetidin-3-one, B isomer form, and 5.5 cm^3 of acetyl chloride. The crude product is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 4 cm, height 40 cm), eluting with a cyclohexane and ethyl acetate (70/30 by volume) mixture and collecting 100-cm^3 fractions. Fractions 10

to 30 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 21 g of a still impure cream-colored foam are obtained, which foam is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 4 cm, height 40 cm), eluting with dichloromethane and collecting 100-cm^3 fractions. Fractions 11 to 30 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 20.0 g of the mixture of the 2 B diastereoisomer forms 3-acetoxy-1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]-methyl}-3-[(R)-(3,5-difluorophenyl)(methylsulfonyl)-methyl]azetidine and 3-acetoxy-{(R*)-(4-chlorophenyl)-[4-(methoxycarbonyl)phenyl]methyl}-3-[(S)-(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine are obtained in the form of a white foam.

1-{(R*)-(4-Chlorophenyl)[4-methoxycarbonyl)-phenyl]methyl}azetidin-3-one, B isomer form, may be prepared by carrying out the procedure as described in Example 3, starting with 8.7 cm^3 of oxalyl chloride, 350 cm^3 of dichloromethane, 14.2 cm^3 of dimethyl sulfoxide, 29.0 g of 1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]methyl}azeditin-3-ol, B isomer form, and 43 cm^3 of triethylamine. The crude product is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 4 cm, height 40 cm), eluting with dichloromethane and collecting 250-cm^3 fractions. Fractions 7 to 25 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 15.5 g of 1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]-

methyl}azetidin-3-one, B isomer form, are obtained in the form of an orange-colored oil.

1-{(R*)-(4-Chlorophenyl)[4-(methoxycarbonyl)-phenyl]methyl}azeditin-3-ol, B isomer form, may be prepared as described in Example 3, starting with 25.5 g of methyl (-)-4-[1-(R*)-amino-1-(4-chlorophenyl)methyl]benzoate, 250 cm^3 of ethanol, 7.9 g of sodium hydrogen carbonate and 7.7 cm^3 of epibromohydrin. 29 g of 1-{(R*)-(4-chlorophenyl)[4-(methoxycarbonyl)phenyl]methyl}azeditin-3-ol, B isomer form, are obtained in the form of a yellow oil.

Methyl (-)-4-[(R*)-amino-(4-chlorophenyl)-methyl]benzoate may be prepared by carrying out two successive recrystallizations of the white crystals (3.4 g) named "A crystals" of Example 3, from 68 cm^3 of ethanol containing 5% of water under reflux. The crystals obtained are filtered, drained and then dried under reduced pressure (2.7 kPa). 2.2 g of methyl (-)-4-[1-(R*)-amino-(4-chlorophenyl)methyl]benzoate D-(-)-tartrate are obtained in the form of white crystals which are dissolved in 50 cm^3 of ethyl acetate. The solution obtained is supplemented with 50 cm^3 of 1 N sodium hydroxide, stirred and then separated after settling. The organic phase is washed with 50 cm^3 of water and then dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). 1.9 g of methyl (-)-4-[(R*)-amino-(4-chlorophenyl)methyl]benzoate are obtained in the form

of a white solid. [a]20°C, 365 nm = -58.1° +/- 1 (c = 0.5%)

Example 5

1-[Bis(thien-2-yl)methyl]-3-[(RS)-(3,5-difluorophenyl)methylsulfonylmethyl]azetidine may be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of 1-[bis(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)methylsulfonyl-methylene]azetidine, 2 cm^3 of methanol, 2 cm^3 of dichloromethane and 25 mg of sodium borohydride, with stirring for 3 hours at 20°C. The crude product is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 7 cm, diameter 1 cm) eluting under an argon pressure of 0.1 bar with dichloromethane and collecting 4-cm^3 fractions. Fractions 2 to 5 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 83 mg of 1-[bis(thien-2-yl)methyl]-3-[(RS)-(3,5-difluorophenyl)methylsulfonylmethyl]-azetidine are obtained in the form of a white solid [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm) : from 2.60 to 2.70 (mt : 1H); 2.66 (s : 3H); 3.31 (mt : 2H); 3.40 (mt : 1H); 3.73 (broad t, J = 7.5 Hz : 1H); 4.27 (d, J = 11 Hz : 1H); 4.92 (s : 1H); 6.83 (tt, J = 9 and 2.5 Hz); from 6.85 to 7.00 (mt : 6H); 7.21 (mt : 2H)].

1-[Bis(thien-2-yl)methyl]-3-[(3,5-difluoro-phenyl)methylsulfonylmethylene]azetidine may be prepared by carrying out the operation according to the procedure described in Example 6, starting with 2.2 g of 1-[bis(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)-

methylsulfonylmethyl-(RS)]azetidin-3-ol, 0.64 cm^3 of methylsulfonyl chloride, 2.3 g of 4-dimethylamino-pyridine and 75 cm^3 of dichloromethane; after purification by chromatography and crystallization from diisopropyl ether, 1.3 g of 1-[bis(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethylene]-azetidine are obtained in the form of white crystals melting at 165°C.

1-[Bis(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl-(RS)]azetidin-3-ol may be prepared by carrying out the procedure in the following manner: 4 cm^3 of 1.6 N n-butyllithium in hexane are added, under argon over 10 minutes, to a solution, cooled to -60°C, of 1.3 g of (3,5-difluoro-benzyl)methyl sulfone in 20 cm^3 of tetrahydrofuran. After stirring for 45 minutes at -70°C, a solution of 1.5 g of 1-[bis(thien-2-yl)methyl]azetidin-3-one in 20 cm^3 of tetrahydrofuran is poured in over 10 minutes. After stirring for 3 hours at -70°C, the reaction mixture is allowed to return to room temperature and then is supplemented with 10 cm^3 of a saturated aqueous ammonium chloride solution. The mixture is separated after settling, the organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up in 20 cm^3 of a mixture of cyclohexane and ethyl acetate (60/40 by volume) the suspension obtained is filtered, the solid is drained and then air-dried. 2.2 g of 1-[bis(thien-2-yl)methyl]-3-[(3,5-difluoro-

phenyl)methylsulfonylmethyl-(RS)]azetidin-3-ol are obtained in the form of white crystals melting at 145°C.

1-[Bis(thien-2-yl)methyl]azetidin-3-one may be prepared by carrying out the procedure as described in Example 1 (method 2) starting with 4 g of 1-[bis(thien-2-yl)methyl]azetidin-3-ol, 2.6 cm^3 of dimethyl sulfoxide, 7.7 cm^3 of triethylamine, 7.7 cm^3 of oxalyl chloride and 100 cm^3 of dichloromethane. The residue obtained is purified by chromatography on a silica gel column (particle size 0.04-0.06 mm, diameter 3 cm, height 30 cm) with, as eluent, a cyclohexane and ethyl acetate (1/1 by volume mixture). The fractions obtained are evaporated to dryness under reduced pressure (2.7 kPa). 3.2 g of 1-[bis(thien-2-yl)methyl]azetidin-3-one are obtained in the form of cream-colored crystals melting at 70°C.

1-[Bis(thien-2-yl)methyl]azetidin-3-ol may be prepared by carrying out the procedure as described in Example 3, starting with 6 g of 1-[bis(thien-2-yl)methyl]amine, 2.5 cm^3 of epibromohydrin, 2.6 g of sodium bicarbonate and 50 cm^3 of ethanol. 4 g of 1-[bis(thien-2-yl)methyl]azetidin-3-ol are obtained in the form of beige crystals melting at 115°C.

1-[Bis(thien-2-yl)methyl]amine may be prepared in the following manner: a solution of 5 cm^3 of 2-thiopheninecarbonitrile in 50 cm^3 of diethyl ether is poured, dropwise, into a solution, cooled under argon to 10°C, of thien-2-ylmagnesium bromide (prepared from

1.29 g of magnesium and 3.22 cm^3 of 2-bromothiophene in 75 cm^3 of diethyl ether). After refluxing for 1 hour and 30 minutes, the reaction medium is cooled to 5°C and then twice 20 cm^3 of methanol are poured in dropwise, the suspension is filtered and the solid is washed with methanol. The filtrate obtained [lacuna] a brown solution. 2.45 g of sodium borohydride are added to this solution in several portions, under argon. The mixture is stirred at room temperature for 16 hours and is then diluted with ethyl acetate and slowly supplemented with water. The organic phase is extracted, washed with water, dried over magnesium sulfate and evaporated to dryness under reduced pressure (2.5 kPa) at 55°C. A brown oil is obtained which is chromatographed on a silica gel column (particle size 0.2-0.063 mm, diameter 8 cm, height 23 cm) and eluted with a cyclohexane and ethyl acetate (90/10 and then 85/15 by volume) mixture. Fractions 21 to 30 are combined and evaporated to dryness under reduced pressure (2.7 kPa). 11 g of 1-[bis(thien-2-yl)methyl]amine are obtained in the form of a crystallized solid.

Example 6

1-[Bis(p-tolyl)methyl]-3-[(RS)methylsulfonyl-phenylmethyl]azetidine may be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of 1-[bis(p-tolyl)methyl]-3-(methylsulfonyl-phenylmethylene)azetidine, 2 cm^3 of methanol, 2 cm^3 of dichloromethane and 25 mg of sodium borohydride. The

crude product is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 7 cm, diameter 1 cm), eluting under an argon pressure of 0.1 bar with dichloromethane and collecting 4-cm^3 fractions. Fractions 5 to 10 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 35 mg of 1-[bis(p-tolyl)methyl]-3-[(RS)methylsulfonylphenylmethyl]azetidine are obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 2.24 (s : 3H); 2.27 (s : 3H); 2.53 (t,J = 7.5 Hz : 1H); 2.58 (s : 3H); 3.19 (mt : 2H); 3.49 (mt : 1H); 3.69 (broad t, J = 7.5 Hz : 1H); 4.22 (s : 1H); 4.28 (d, J = 11.5 Hz : 1H); from 6.95 to 7.45 (mts : 13H)].

1-[Bis(p-tolyl)methyl]-3-(methylsulfonylphenylmethylene)azetidine may be prepared by carrying out the procedure in the following manner: 0.125 cm^3 of methylsulfonyl chloride is added to a solution of 0.48 g of 1-[bis(p-tolyl)methyl]-3-[methylsulfonylphenylmethyl-(RS)]azetidin-3-ol in 25 cm^3 of anhydrous dichloromethane followed in small fractions by 0.465 g of 4-dimethylaminopyridine. After stirring for 20 hours at 20°C, the reaction mixture is washed with twice 80 cm^3 of water, with 80 cm^3 of brine, dried over magnesium sulfate and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 17 cm, diameter 3.2 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (80/20 by volume) and

collecting 40-cm^3 fractions. Fractions 5 to 8 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The residue is stirred with diisopropyl ether, the solid is filtered, drained and then dried under reduced pressure (2.7 kPa). 0.25 g of 1-[bis(p-tolyl)methyl]-3-(methylsulfonylphenyl-methylene)azetidine is obtained in the form of a white solid [NMR spectrum in DMSO-d6, T=300K, δ in ppm (250 MHz) : 2.23 (6H, s, 2Ph-CH_3), 2.98 (3H, s, SCH_3), 3.76 (2H, s, NCH_2), 4.20 (2H, s, NCH_2), 5.55 (1H, s, NCH), 7.10 (4H, d, J=7Hz, 4 CH arom.), 7.32 (4H, d, J=7Hz, 4CH arom.), 7.43 (5H, s, phenyl)].

1-[Bis(p-tolyl)methyl]-3-[(methylsulfonyl)-phenylmethyl-(RS)]azetidin-3-ol may be prepared by carrying out the procedure in the following manner: 0.6 g of 3-[(methylsulfonyl)(phenyl)methyl-(RS)]-azetidin-3-ol hydrochloride is added to a solution of 0.59 g of bromo(bis-p-tolyl)methane in 20 cm^3 of acetonitrile followed by 0.3 g of potassium carbonate. After heating for 1 hour and 15 minutes at the reflux temperature, the reaction mixture is cooled to 20°C and filtered. The filtrate is concentrated to dryness under reduced pressure (2.7 kPa) and the residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 4 cm, height 16 cm), eluting with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 50-cm^3 fractions. Fractions 8 to 13 are concentrated to dryness under reduced pressure (2.7 kPa). 0.48 g of 1-[bis(p-tolyl)methyl]-3-

[(methylsulfonyl)(phenyl)methyl-(RS)]azetidin-3-ol is obtained in the form of a white solid.

Bromo(bis-p-tolyl)methane may be prepared according to the procedure described by BACHMANN W.E., J.Am.Chem.Soc., 2135, (1933).

3-[(Methylsulfonyl)phenylmethyl-(RS)]azeditin-3-ol hydrochloride may be prepared by carrying out the procedure in the following manner: 12.6 cm^3 of a 6.2 N hydrochloric acid solution in dioxane are added to a solution of 2.62 g of 3-[(methylsulfonyl)(phenyl)-methyl-(RS)]-1-(vinyloxycarbonyl)azetidin-3-ol in 12.6 cm^3 of dioxane. After stirring for 20 hours at 20°C, the mixture is concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The residue is taken up in 25 cm^3 of ethanol, heated under reflux for 1 hour and then allowed to return to 20°C and filtered. The solid is rinsed with diethyl ether and then drained and dried under reduced pressure (2.7 kPa). 1.89 g of 3-[(methylsulfonyl)phenylmethyl-(RS)]azeditin-3-ol hydrochloride are obtained in the form of white crystals.

3-[(Methylsulfonyl)(phenyl)methyl-(RS)]-1-(vinyloxycarbonyl)azetidin-3-ol may be prepared by carrying out the procedure in the following manner: a solution of 0.99 cm^3 of vinyl chloroformate in 4 cm^3 of anhydrous dichloromethane is poured dropwise into a mixture, cooled to +5°C, of 3.92 g of 1-benzhydryl-3-[(methylsulfonyl)(phenyl)methyl-(RS)]azetidin-3-ol in 500 cm^3 of anhydrous dichloromethane. After stirring

for 48 hours at 20°C, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 5.6 cm, height 15.5 cm), eluting with a mixture of cyclohexane and ethyl acetate (70/30 by volume) and collecting 50-cm^3 fractions. Fractions 17 to 36 are concentrated to dryness under reduced pressure (2.7 kPa). 0.9 g of 3-[(methylsulfonyl)(phenyl)methyl-(RS)]-1-(vinyloxycarbonyl)azetidin-3-ol is obtained in the form of a white solid.

1-Benzhydryl-3-[(methylsulfonyl)(phenyl)methyl-(RS)]azetidin-3-ol may be prepared by carrying out the procedure as described in Example 1 (method 1), starting with 47 cm^3 of diisopropylamine, 205.6 cm^3 of a 1.6 M solution of n-butyllithium in hexane, 2.2 litres of tetrahydrofuran, 50 g of benzylmethyl sulfone and 69.6 g of 1-benzhydrylazetidin-3-one. 94.3 g of 1-benzhydryl-3-[(methylsulfonyl)(phenyl)methyl-(RS)]azetidin-3-ol are obtained in the form of white crystals.

Example 7

1-[Bis(3-fluorophenyl)methyl]-3-(RS)-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine may be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of 1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methyl-sulfonylmethylene]azetidine, 2 cm^3 of methanol, 2 cm^3 of dichloromethane and 20 mg of sodium borohydride, with

stirring for 48 hours at 20°C. The crude product is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 7 cm, diameter 1 cm), eluting under an argon pressure of 0.1 bar with dichloromethane and collecting 4-cm^3 fractions. Fractions 3 to 7 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 95 mg of 1-[bis(3-fluorophenyl)-methyl]-3-(RS)-[(3,5-difluorophenyl)methylsulfonyl-methyl]azetidine are obtained in the form of white crystals [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 2.57 (t, J = 7.5 Hz : 1H); 2.66 (s : 3H); from 3.15 to 3.30 (mt : 2H); from 3.30 to 3.50 (mt : 1H); 3.66 (broad t, J = 7.5 Hz : 1H); 4.27 (d, J = 11.5 Hz : 1H); 4,28 (s : 1H); from 6.75 to 7.35 (mt : 11H)].

1-[Bis(3-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidine may be prepared by carrying out the procedure as described in Example 6, starting with 1.15 g of 1-[bis(3-fluoro-phenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)-methyl-(RS)]azetidin-3-ol, 30 cm^3 of dichloromethane, 0.264 cm^3 of methylsulfonyl chloride and 0.98 g of 4-dimethylaminopyridine. After chromatography on a silica gel column (particle size 0.06-0.200 mm, diameter 2.8 cm, height 25 cm), under an argon pressure of 1 bar with a mixture of ethyl acetate and cyclohexane (15/85 by volume) as eluent and collecting 60-cm^3 fractions, 0.55 g of 1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine is obtained in the form of a white solid melting at 178°C.

1-[Bis(3-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]azetidin-3-ol may be prepared according to the following procedure: 3.65 cm^3 of a 1.6 M solution of n-butyllithium in hexane are poured over 10 minutes into a mixture, cooled to -60°C, of diisopropylamine and 10 cm^3 of tetrahydrofuran, the mixture is stirred for 10 minutes at -30°C and then cooled to -70°C. A solution of 1.2 g of (3,5-difluorobenzyl)methyl sulfone in 30 cm^3 of tetrahydrofuran is then added over 20 minutes. After stirring for 30 minutes at -70°C, the mixture is supplemented over 30 minutes with a solution of 1.5 g of 1-[bis(3-fluorophenyl)methyl]azetidin-3-one in 10 cm^3 of tetrahydrofuran. After stirring for 2 hours at -70°C, the reaction mixture is brought to room temperature and then supplemented with 20 cm^3 of a saturated aqueous ammonium chloride solution and 100 cm^3 of dichloromethane. The mixture is separated after settling, the organic phase is washed with water and then dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 3.2 cm, height 30 cm), eluting under an argon pressure of 1 bar with a mixture of ethyl acetate and cyclohexane (20/80 by volume) and collecting 60-cm^3 fractions. Fractions 9 to 20 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 1.95 g of 1-[bis(3-fluorophenyl)methyl]-3-

[(3,5-difluorophenyl)(methylsulfonyl)methyl-(RS)]-azetidin-3-ol are obtained in the form of a white solid melting at 170°C (decomposition).

1-[Bis(3-fluorophenyl)methyl]azetidin-3-one may be prepared by carrying out the procedure as described in Example 1 (method 2) starting with 0.7 cm^3 of oxalyl chloride, 16 cm^3 of dichloromethane, 1.12 cm^3 of dimethylsulfoxide, 2 g of 1-[bis(3-fluorophenyl)-methyl]azetidin-3-ol and 3.7 cm^3 of triethylamine. 1.55 g of 1-[bis(3-fluorophenyl)methyl]azetidin-3-one are obtained in the form of an oil which crystallizes at 20°C.

1-[Bis(3-fluorophenyl)methyl]azetidin-3-ol may be prepared by carrying out the procedure as described by KATRITSKY A.R. in J. Heterocycl. Chem, **31**, 271 (1994) starting with 4.9 g of [bis(3-fluorophenyl)-methyl]amine and 1.78 cm^3 of epichlorohydrin.

[Bis(3-fluorophenyl)methyl]amine may be prepared in the following manner: a solution of 5.17 g of 3,3'-difluorobenzophenone oxime in 30 cm^3 of tetrahydrofuran is poured, under an argon atmosphere over 30 minutes, into a suspension of 1.27 g of lithium aluminum hydride in 80 cm^3 of tetrahydrofuran. After stirring for 5 hours under reflux, 1.3 cm^3 of water, 1.3 cm^3 of 4 N sodium hydroxide, 2.6 cm^3 of water and then 50 cm^3 of ethyl acetate are added successively. After drying over magnesium sulfate and concentrating to dryness under reduced pressure (2.7 kPa), 4.9 g of

[bis(3-fluorophenyl)methyl]amine are obtained in the form of a yellow oil.

3,3'-Difluorobenzophenone oxime may be prepared according to the following procedure: a solution of 1.6 g of hydroxylamine hydrochloride in 8 cm^3 of water is poured dropwise into a solution of 5.0 g of 3.3'-difluorobenzophenone in 10 cm^3 of ethanol and then 1.2 g of sodium hydroxide pellets are added in small fractions. The reaction mixture, heated under reflux for 10 minutes, is cooled to 20°C and then acidified with 7.5 cm^3 of 4 N hydrochloric acid. The oily precipitate obtained, once it has been triturated, becomes a white solid which is filtered, washed with water and then dried at 35°C under reduced pressure (2.7 kPa). 5.17 g of 3,3'-difluorobenzophenone oxime are obtained in the form of a white solid.

Example 8

1-[Bis(4-chlorophenyl)methyl]-3-(RS)-{[3-azetidin-1-yl-phenyl]methylsulfonylmethyl}azetidine may be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of 1-[bis(4-chlorophenyl)methyl]-3-[(azetidin-1-yl-phenyl)methylsulfonylmethylene]azetidine, 2 cm^3 of methanol, 2 cm^3 of dichloromethane and 30 mg of sodium borohydride, stirring for 24 hours at 20°C. The crude product is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 7 cm, diameter 1 cm), eluting under an argon pressure of 0.1 bar with dichloromethane and collecting 4-cm^3 fractions. Fractions 5 to 10 are

combined and concentrated to dryness under reduced pressure (2.7 kPa). 20 mg of 1-[bis(4-chlorophenyl)-methyl]-3-(RS)-{[3-azetidin-1-yl-phenyl]methylsulfonyl-methyl}azetidine are obtained in the form of an off-white lacquer [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 2.39 (mt : 2H); from 2.50 to 2.65 (mt : 1H); 2.60 (s : 3H); 3.20 (mt : 2H); 3.47 (mt : 1H); 3.66 (broad t, J = 7 Hz : 1H); 3.89 (broad t, J = 7.5 Hz : 4H); 4.20 (d, J = 11 Hz : 1H); 4.26 (s : 1H); from 6.35 to 6.50 (mt : 2H); 6.67 (broad d, J = 7.5 Hz : 1H); from 7.10 to 7.40 (mt : 9H)].

1-[Bis(4-chlorophenyl)methyl]-3-[(azetidin-1-yl-phenyl)methylsulfonylmethylene]azetidine may be prepared by carrying out the procedure by carrying out the procedure as described in Example 6, starting with 0.83 g of 1-[bis(4-chlorophenyl)methyl]-3-[(azetidin-1-yl-phenyl)methylsulfonylmethyl-(RS)]azetidin-3-ol, 20 cm^3 of dichloromethane, 0.18 cm^3 of methylsulfonyl chloride and 0.75 g of 4-dimethylaminopyridine. 0.40 g of 1-[bis(4-chlorophenyl)methyl]-3-[(azetidin-1-yl-phenyl)methylsulfonylmethylene]azetidine is obtained in the form of a white foam.

1-[Bis(4-chlorophenyl)methyl]-3-[(azetidin-1-yl-phenyl)methylsulfonylmethyl-(RS)]azetidin-3-ol may be prepared by carrying out the procedure as described in Example 5, starting with 1.55 g of 1-(3-methyl-sulfonylmethylphenyl)azetidine, 5.2 cm^3 of a 1.6 M solution of n-butyllithium in hexane, 30 cm^3 of tetrahydrofuran and 2.11 g of 1-[bis(4-chlorophenyl)-

methyl]azetidin-3-one. 0.83 g of 1-[bis(4-chloro-phenyl)methyl]-3-[(azetidin-1-yl-phenyl)methylsulfonyl-methyl-(RS)]azetidin-3-ol is obtained in the form of an ochre-colored solid melting at 172°C.

1-(3-Methylsulfonylmethylphenyl)azetidine may be prepared by carrying out the procedure in the following manner: a solution of 1.9 g of 1-(3-methylsulfanylmethylphenyl)azetidine in 10 cm^3 of ethanol is added to a mixture, cooled to 0°C, of 10 cm^3 of water, 5 cm^3 of acetic acid, 1.5 cm^3 of 36 N sulfuric acid and 6.15 g of oxone. After stirring for 20 hours at 20°C, the reaction mixture is supplemented with 100 cm^3 of water, 100 cm^3 of ethyl acetate and is then neutralized by stirring with sodium hydrogen carbonate. The mixture obtained is separated after settling, the organic phase is dried over magensium sulfate and then filtered and concentrated to dryness under reduced pressure (2.7 kPa). 1.55 g of 1-(3-methylsulfonyl-methylphenyl)azetidine are obtained in the form of a light brown gum.

1-[3-(Methylsulfonylmethyl)phenyl]azetidine may be prepared by carrying out a procedure in the following manner: 2.57 g of potassium tert-butoxide, 0.64 g of 1,1'-bis(diphenylphosphino)ferrocenyl-palladium chloride, 1.49 g of 1,1'-bis(diphenyl-phosphino)ferrocene, 0.12 g of copper iodide and 2.0 g of azetidine are added, under argon, to a solution of 4.6 g of 1-iodo-3-(methylsulfanylmethyl)benzene in 60 cm^3 of tetrahydrofuran. After heating for 3 hours at

the reflux temperature, the reaction mixture is cooled to room temperature and filtered on celite and then washing the latter with 150 cm^3 of ethyl acetate. The combined filtrate and washings is acidified with 120 cm^3 of 1 N hydrochloric acid and then separated after settling. The aqueous phase is supplemented with 60 cm^3 of ethyl acetate and is then alkalinized with sodium hydrogen carbonate and the mixture is separated after settling. The organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 3.5 cm, height 50 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (20/80 by volume) and collecting 100-cm^3 fractions. Fractions 1 to 3 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 1.9 g of 1-[3-(methylsulfonyl-methyl)phenyl]azetidine are obtained in the form of an oil.

1,1'-Bis(diphenylphosphino)ferrocenylpalladium chloride may be prepared by carrying out the procedure according to Hayashi T. et al., in J. Am. Chem. Soc, 106, 158 (1984).

1-Iodo-3-(methylsulfanylmethyl)benzene may be prepared by carrying out the procedure in the following manner: 6.4 g of sodium methylthiolate are added to a solution of 25 g of 3-iodobenzyl bromide in 80 cm^3 of N,N-dimethylformamide. After stirring for 20 hours at

20°C, the reaction mixture is supplemented with 250 cm^3 of water, 200 cm^3 of ethyl acetate and is stirred and then separated after settling. The organic phase is washed with four times 200 cm^3 of water, dried over magnesium sulfate, filtered and then concentrated to dryness at 50°C under reduced pressure (2.7 kPa). 22 g of 1-iodo-3-(methylsulfanylmethyl)benzene are obtained in the form of a gum.

Example 9

The mixture of the 2 A form diastereoisomers 1-(R*)-{4-[(4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl-(R)]-3-imidazolyl-azetidin-1-yl}methyl]benzyl}-1H-imidazole and 1-(R*)-{4(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonyl-methyl-(S))}-3-imidazolyl-azetidin-1-yl}methyl]benzyl]-1H-imidazole may be prepared by carrying out the procedure in the following manner: 13.6 mg of imidazole are added to a solution of 50 mg of 1-{(R*)-[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl}-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidine, A isomer form, in 1 cm^3 of dichloromethane. After stirring for 20 hours at 20°C, the reaction mixture is directly chromatographed on a silica gel column: (particle size 0.063-0.200 mm, height 7 cm, diameter 1 cm), eluting under an argon pressure of 0.1 bar with a mixture of dichloromethane and methanol (98/2 by volume) and collecting 4-cm^3 fractions. Fractions 4 to 9 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 20 mg of the mixture of the

2 A form diastereoisomers 1-(R*)-{4-[(4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl-(R)]-3-imidazolyl-azetidin-1-yl}methyl]benzyl}-1H-imidazole and 1-(R*)-{4-[(4-chlorophenyl)-{3-[3-[(3,5-difluorophenyl)methylsulfonylmethyl-(S)]}-3-imidazolyl-azetidin-1-yl}methyl]benzyl]-1H-imidazole are obtained in the form of a white lacquer [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): a mixture of diastoero-isomers is observed, * 2.64 (s : 3H); 3.42 (d, J = 8 Hz : 1H); 3.50 (d, J = 8 Hz : 1H); 3.75 (mt : 1H); 4.31 (broad d, J = 8 Hz : 1H); 4.40 (s : 1H); 4.54 and 4.55 (2s : 2H in total); 4.72 (s : 1H); 6.84 (mt : 2H); 6.87 (s : 1H); 6.95 (mt : 1H); 7.11 (s : 1H); from 7.20 to 7.40 (mt 12)].

Example 10

(1-Benzhydrylazetidin-3-yl)phenylmethanone O-methyloxime, a mixture of the 2 isomers Z and E, may be prepared by carrying out the procedure in the following manner: 0.286 g of O-methylhydroxylamine and 0.32 g of sodium acetate are added to a suspension of 0.80 g of 1-benzhydryl-3-benzoylazetidine in 30 cm^3 of ethanol. After stirring for 24 hours at reflux temperature, the reaction mixture is allowed to cool at room temperature and filtered. The filtrate is concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The residue is taken up in 100 cm^3 of dichloromethane and the solution is supplemented with 20 cm^3 of water and 1 N hydrochloric acid, stirring until an acidic pH is obtained. The organic phase is

separated after settling, dried over magnesium sulfate and then filtered and concentrated to dryness under reduced pressure (2.7 kPa).

The residue is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 36 cm, diameter 3.8 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (95/5, 92/8 and then 80/20 by volume) and collecting 30-cm^3 fractions. Fractions 8 to 14 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.20 g of (1-benzhydrylazetidin-3-yl)phenyl-methanone O-methyloxime, a mixture of the 2 isomers Z and E, is obtained in the form of a white solid [^{1}H NMR spectrum (250 MHz, $(CD_3)_2SO$ d6, d in ppm). A 65/35 mixture of isomers is observed, * 2.68-3.02 and from 3.25 to 3.90 (mts : 5H in total); 3.76 and 3.80 (2s :3H in total); 4.26 and 4.38 (2s : 1H in total); from 7.10 to 7.50 (mt : 15H)].

1-Benzhydryl-3-benzoylazetidine may be prepared by carrying out the procedure in the following manner: 112 cm^3 of a 1 M solution of phenylmagnesium bromide in tetrahydrofuran are poured dropwise, under argon, into a solution, cooled to 0°C, of 11.5 g of (1-benzhydrylazetidin-3-yl)carboxylic-N-methoxy-N-methylamide acid in 350 cm^3 of tetrahydrofuran, and then the mixture is allowed to return to room temperature. After stirring for 20 hours at 20°C, the reaction mixture is supplemented with 400 cm^3 of a saturated ammonium chloride solution and then with

250 cm^3 of ethyl acetate. After stirring, the mixture is separated after settling, the aqueous phase reextracted with 250 cm^3 of ethyl acetate and the combined two organic phases are washed with twice 250 cm^3 of water, dried over magnesium sulfate, filtered and concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The residue is stirred with 50 cm^3 of diisopropyl ether, the suspension is filtered, the solid is drained and then dried under reduced pressure (2.7 kPa). 1-benzhydryl-3-benzoylazetidine are obtained in the form of a cream-colored solid.

(1-Benzhydrylazetidin-3-yl)carboxylic-N-methoxy-N-methylamide may be prepared by carrying out the procedure in the following manner: 13.35 g of (1-benzhydrylazetidin-3-yl)carboxylic acid and 1.0 g of hydroxybenzotriazole hydrate are added, with stirring, to a suspension of 4.0 g of N,O-dimethylhydroxylamine hydrochloride in 250 cm^3 of dichloromethane. 6.92 g of 1-(3-dimethylaminopropyl)3-ethylcarbodiimide hydrochloride and 8.8 cm^3 of N,N-diisopropylethylamine are added to this mixture, placed under argon and cooled to +5°C. After stirring for 3 hours at +5°C and then for 20 hours at 20°C, the reaction mixture is supplemented with 200 cm^3 of water and then separated after settling. The organic phase is washed with 300 cm^3 of water, dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is stirred with 100 cm^3

of diisopropyl ether, the suspension is filtered and the solid is drained and then dried under reduced pressure (2.7 kPa). 10.76 g of (1-benzhydrylazetidin-3-yl)carboxylic-N-methoxy-N-methylamide are obtained in the form of a cream-colored solid.

(1-Benzhydrylazetidin-3-yl)carboxylic acid may be prepared by carrying out the procedure in the following manner: a solution of 11 g of potassium hydroxide in 9 cm^3 of water is added dropwise to a suspension, cooled to +5°C, of 14 g of (1-benzhydryl-azetidin-3-yl)carbonitrile in 140 cm^3 of 2-ethoxy-ethanol and then the mixture is heated to 95°C. After stirring for 16 hours at this temperature, the reaction mixture is poured slowly, with stirring, over ice and left at 0°C for 68 hours and then concentrated to dryness to dryness at 50°C under reduced pressure (2.7 kPa). The residue is taken up in 400 cm^3 of water, the solution is acidified to pH 4 with 6 N hydrochloric acid and then supplemented with 400 cm^3 of ethyl acetate. The resulting suspension is filtered, the solid is drained and then dried at 50°C under reduced pressure (2.7 kPa). 13.55 g of (1-benzhydrylazetidin-3-yl)carboxylic acid are obtained in the form of a cream-colored solid.

(1-Benzhydrylazetidin-3-yl)carbonitrile may be prepared by carrying out the procedure in the following manner: a solution of 18.54 g of sodium cyanide in 25 cm^3 of water is added dropwise to a solution of 40 g of 1-benzhydrylazetidine-3-yl methylsulfonate in

350 cm^3 of N,N-dimethylformamide. After stirring for 24 hours at 65°C, the reaction mixture, allowed to return to room temperature, is then poured, with stirring, into a mixture of 550 cm^3 of water and 300 g of ice. The suspension obtained is filtered, the solid is washed with three times 110 cm^3 of water and then dissolved in 350 cm^3 of dichloromethane. The solution is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is stirred with 200 cm^3 of diisopropyl ether, the suspension filtered, the solid drained and then dried under reduced pressure (2.7 kPa). 28.4 g of (1-benzhydrylazetidin-3-yl)-carbonitrile are obtained in the form of a pinkish cream-colored solid.

1-Benzhydrylazetidin-3-yl methylsulfonate may be prepared by carrying out the procedure starting with 100 g of 1-benzhydrylazetidin-3-ol, 800 cm^3 of dichloromethane, 31 cm^3 of methylsulfonyl chloride and 35 cm^3 of pyridine. The crude product obtained is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 50 cm, diameter 11 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (80/20, 75/25, and then 70/30 and 60/40 by volume) and collecting 1-litre fractions. Fractions 12 to 31 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 66 g of 1-benzhydrylazetidine-3-yl

methylsulfonate are obtained in the form of a yellowish white solid.

1-Benzhydrylazetidin-3-ol may be prepared by carrying out the procedure as described by Alan R. KATRITZKY et al., in J. Heterocyclic Chem.; 31, 271 (1994).

Example 11

(RS)-1-[3-({1-Bis(4-chlorophenyl)methyl]-azetidin-3-yl}methylsulfonylmethyl)phenyl]pyrrolidine may be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of 1-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethylene)phenyl]pyrrolidine, 1.5 cm^3 of anhydrous methanol, 1.5 cm^3 of anhydrous dichloromethane, and 30 mg of sodium borohydride, stirring for 3 hours at 20°C and then 8 hours at 50°C. The crude product is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 8 cm, diameter 1 cm), eluting under an argon pressure of 0.8 bar with a mixture of cyclohexane and ethyl acetate (80/20 by volume) and collecting 5-cm^3 fractions. Fractions 22 to 28 are combined and concentrated to dryness under reduced pressure (2.7 kPa), the residue is stirred with 5 cm^3 of pentane, the solid is filtered, drained and dried. 18 mg of (RS)-1-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methyl-sulfonylmethyl)phenyl]pyrrolidine are obtained in the form of white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 2.01 (mt : 4H); 2.59 (mt : 1H); 2.61 (s :

3H); from 3.10 to 3.25 (mt : 2H); 3.27 (mt : 4H); from 3.40 to 3.55 (mt : 1H); 3.66 (mt : 1H); 4.20 (d, J = 12 Hz : 1H); 4.25 (s : 1H); from 6.45 to 6.65 (mt : 3H); from 7.10 to 7.35 (mt : 9H)].

1-[3-({1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]pyrrolidine may be prepared by carrying out the procedure as described in Example 6, starting with 0.6 g of 1-[bis(4-chlorophenyl)methyl]-3-[(methylsulfonyl)(3-pyrrolidinylphenyl)methyl-(RS)]azetidin-3-ol, 0.1 cm^3 of methylsulfonyl chloride and 0.5 g of 4-dimethylaminopyridine, the residue obtained is purified by chromatography on a silica gel column (particle size 0.04-0.06 mm, diameter 2 cm, height 30 cm) under an argon pressure of 0.5 bar with a dichloromethane and ethanol mixture as eluent (98.5/1.5 by volume) and collecting 10-cm^3 fractions. Fraction 4 is concentrated to dryness under reduced pressure (2.7 kPa). After recrystallization from 5 cm^3 of diethyl ether, 0.5 g of 1-[3-({1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]-pyrrolidine is obtained in the form of a solid melting at 133°C.

1-[Bis(4-chlorophenyl)methyl]-3-[(methyl-sulfonyl)(3-pyrrolidinylphenyl)methyl-(RS)]azetidin-3-ol may be obtained by carrying out the operation according to the procedure of Example 5, starting with 0.5 g of 1-[3-(methylsulfonylmethyl)phenyl]pyrrolidine, 0.6 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one,

15 cm^3 of tetrahydrofuran and 1.4 cm^3 of a 1.6 N solution of n-butyllithium in hexane. 0.6 g of 1-[bis(4-chlorophenyl)methyl]-3-[(methylsulfonyl)(3-pyrrolidinylphenyl)methyl-(RS)]azetidin-3-ol is obtained in the form of a cream-colored solid.

1-[3-(Methylsulfonylmethyl)phenyl]pyrrolidine may be prepared by carrying out the procedure described in Example 8, starting with 6 cm^3 of water, 6 cm^3 of 100% acetic acid, 3.5 cm^3 of 36 N sulfuric acid, 3.11 g of oxone, 0.96 g of 1-[3-(methylsulfanylmethyl)phenyl]-pyrrolidine and 6 cm^3 of ethanol. 0.478 g of 1-[3-(methylsulfonylmethyl)phenyl]pyrrolidine is obtained in the form of a light brown gum.

1-[3-(Methylsulfanylmethyl)phenyl]pyrrolidine may be prepared by carrying out the procedure as described in Example 8, starting with 4.0 g of 1-iodo-3-(methylsulfanylmethyl)benzene, 120 cm^3 of tetrahydrofuran, 2.2 g of sodium tert-butoxide, 0.556 g of 1,1'-bis(diphenylphosphino)ferrocenylpalladium chloride, 1.26 g of 1,1'-bis(diphenylphosphino)-ferrocene and 2.6 g of pyrrolidine. 1.9 g of 1-[3-(methylsulfanylmethyl)phenyl]pyrrolidine are obtained in the form of an oil.

Example 12

N-(RS)-[3-({1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}methylsulfonylmethyl)phenyl]-N-methyl-carbamic acid tert-butyl ester may be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of N-[3-({1-[bis(4-chlorophenyl)-

methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]-N-methylcarbamic acid tert-butyl ester, 1.5 cm^3 of anhydrous methanol, 1.5 cm^3 of anhydrous dichloromethane and 30 mg of sodium borohydride, with stirring for 3 hours at 20°C. The crude product is stirred with 10 cm^3 of diisopropyl ether, the solid is filtered, drained and then dried under reduced pressure (2.7 kPa). 94 mg of N-(RS)-[3-({1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}methylsulfonylmethyl)phenyl]-N-methylcarbamic acid tert-butyl ester are obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 1.36 (s : 9H); 2.46 (t, J = 7.5 Hz : 1H); 2.75 (s : 3H); from 3.00 to 3.55 (mt : 4H); 3.17 (s : 3H); 4.45 (s : 1H); 4.78 (d, J = 11 Hz : 1H); from 7.20 to 7.50 (mt : 12H)].

N-[3-({1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]-N-methylcarbamic acid tert-butyl ester may be prepared by carrying out the procedure as described in Example 6, starting with 5.6 g of 1-[bis(4-chlorophenyl)methyl]-3-{[3-(N-tert-butyloxycarbonyl-N-methylamino)phenyl]methylsulfonyl-methyl-(RS)}azetidin-3-ol, 100 cm^3 of dichloromethane, 1.59 g of methylsulfonyl chloride and 4.5 g of 4-dimethylaminopyridine. The crude product obtained is purified by chromatography on a silica gel column (particle size 0.04-0.06 mm, diameter 4 cm and weight of silica 250 g), eluting under a nitrogen pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (30/70 by volume) and collecting 100-cm^3 fractions.

Fractions 12 to 18 are combined, concentrated to dryness under reduced pressure (2.7 kPa). 3.2 g of N-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]-N-methylcarbamic acid tert-butyl ester are obtained in the form of a white foam.

1-[Bis(4-chlorophenyl)methyl]-3-{[3-(N-tert-butyloxycarbonyl-N-methylamino)phenyl]methylsulfonyl-methyl-(RS)}azetidin-3-ol, may be prepared by carrying out the procedure as described in Example 5, starting with 3.8 g of N-[3-(methylsulfonylmethyl)phenyl]-N-methylcarbamic acid tert-butyl ester, 50 cm^3 of tetrahydrofuran, 9.5 cm^3 of a 1.6 N solution of n-butyllithium in hexane, and 3.82 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one. The crude product is purified by chromotography on a silica gel column (particle size 0.04-0.06 mm, diameter 4 cm, weight of silica 250 g), eluting under a nitrogen pressure of 0.5 bar with dichloromethane and then with a dichloromethane and ethanol (99/1 by volume) mixture and collecting 500-cm^3 fractions. Fractions 10 to 16 are combined, concentrated to dryness under reduced pressure (2.7 kPa). 5.6 g of 1-[bis(4-chlorophenyl)-methyl]-3-{[3-(N-tert-butyloxycarbonyl-N-methylamino)-phenyl]methylsulfonylmethyl-(RS)}azetidin-3-ol are obtained in the form of a foam.

N-[3-(Methylsulfonylmethyl)phenyl]-N-methylcarbamic acid tert-butyl ester may be prepared by carrying out the procedure in the following manner:

3.7 g of di-tert-butyl dicarbonate are added to a solution of 3 g of N-[3-(methylsulfonylmethyl)phenyl]N-methylamine in 80 cm^3 of dichloromethane. After stirring for 20 hours at 20°C, the reaction mixture is supplemented with 100 cm^3 of water and then separated after settling. The organic phase is dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 4 cm and weight of silica 300 g), eluting under a nitrogen pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (45/55 by volume) and collecting 100-cm^3 fractions. Fractions 11 to 16 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 3.8 g of N-[3-(methylsulfonylmethyl)phenyl]-N-methylcarbamic acid tert-butyl ester are obtained in the form of a gum which crystallizes.

N-[3-(Methylsulfonylmethyl)phenyl]N-methylamine may be obtained by carrying out the procedure in the following manner: a mixture of 9.65 cm^3 of formic acid and 19.63 cm^3 of acetic anhydride is heated at 50°C for 3 hours under argon, and then the solution obtained is allowed to return to room temperature. 40 cm^3 of tetrahydrofuran are poured in and the medium is cooled to -20°C. After stirring for 2 hours at -20°C, a solution of 14.8 g of 3-(methylsulfonylmethyl)phenylamine is poured in while the temperature is maintained. After stirring for 2 hours at -20°C, and then for

48 hours at 20°C, the mixture is filtered, the solid is drained and then washed with three times 50 cm^3 of diisopropyl ether and dried under reduced pressure (2.7 kPa). A solid A is obtained. The filtrate is concentrated to half the volume, the resulting suspension is filtered, the solid is drained, washed with diisopropyl ether and dried. A solid B is obtained. The two solids A and B are combined and taken up in 375 cm^3 of tetrahydrofuran and the mixture, cooled to 0°C, is supplemented, over 20 minutes, with 80 cm^3 of a 2 M solution of borane-dimethyl sulfide complex in tetrahydrofuran and then heated at reflux temperature for 3 hours. The reaction mixture, cooled to +5°C, is supplemented over 20 minutes with 60 cm^3 of methanol, stirred for 1 hour at room temperature and then supplemented with gaseous hydrochloric acid to a pH of 1. The mixture is heated under reflux for one hour and then supplemented with 300 cm^3 of water and with a 3 N solution of sodium hydroxide to pH 8. The resulting mixture is extracted with 500 cm^3 of ethyl acetate, the organic phase is washed successively with a saturated aqueous sodium hydrogen carbonate solution, and with brine, and is then dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up in 100 cm^3 of 4 N sulfuric acid, the solution obtained is washed with 100 cm^3 of ethyl acetate, then alkalinized to pH 8 with 3 N sodium hydroxide and with a saturated aqueous sodium carbonate solution and is then extracted with

twice 75 cm^3 of ethyl acetate. The combined extracts are dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). 8.98 g of N-[3-(methylsulfonylmethyl)phenyl]N-methylamine are obtained in the form of a pink solid.

3-(Methylsulfonylmethyl)phenylamine may be prepared by carrying out the procedure in the following manner: a suspension of 23.7 g of 1-(methylsulfonyl-methyl)-3-nitrobenzene in 150 cm^3 of methanol and 65 cm^3 of 36% hydrochloric acid is heated to reflux temperature and then 18.5 g of iron are carefully added over 10 minutes, in small fractions. After heating under reflux for 4 hours and then stirring at room temperature for 20 hours, the reaction mixture is supplemented with 5 g of iron and then again heated under reflux for one hour and then at room temperature for 20 hours. The mixture is then alkalinized to pH 9 with aqueous ammonia and with sodium hydrogen carbonate, and then extracted with 3 times 250 cm^3 of ethyl acetate, dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). 14.9 g of 3-(methylsulfonylmethyl)phenyl-amine are obtained in the form of a beige powder.

1-(Methylsulfonylmethyl)-3-nitrobenzene may be prepared by heating under reflux 23.8 g of 3-nitro-benzyl chloride, 20 g of sodium methyl sulfinate and 250 cm^3 of absolute ethanol. 23.74 g of 1-(methyl-sulfonylmethyl)-3-nitrobenzene are obtained in the form of a white powder.

Example 13

(RS)-N-[3-({1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}methylsulfonylmethyl)phenyl]-N-methylamine may be prepared by carrying out the procedure as described in Example 3 starting with 0.10 g of N-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]-N-methylamine, 1.5 cm^3 of anhydrous methanol, 1.5 cm^3 of anhydrous dichloromethane and 45 mg of sodium borohydride, with stirring for 20 hours at 20°C and then for 5 hours at 50°C. The crude product is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 10 cm, diameter 1 cm), eluting under an argon pressure of 0.8 bar with a mixture of cyclohexane and ethyl acetate (80/20, and then 60/40 by volume) and collecting 5-cm^3 fractions. Fractions 20 to 26 are combined and concentrated to dryness under reduced pressure (2.7 kPa), the residue is stirred with 5 cm^3 of pentane, the solid is filtered, drained and dried. 20 mg of (RS)-N-[3-({1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}methylsulfonylmethyl)phenyl]-N-methylamine are obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : from 2.50 to 2.65 (mt : 1H); 2.60 (s : 3H); 2.82 (d, J = 5 Hz : 3H); 3.18 (mt : 2H); from 3.35 to 3.50 (mt : 1H); 3.64 (broad t, J = 7.5 Hz : 1H); 3.80 (mt : 1H); 4.18 (d, J = 11.5 Hz : 1H); 4.24 (s : 1H); from 6.50 to 6.70 (mt : 3H); from 7.10 to 7.35 (mt : 9H].

N-[3-({1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]-N-methylamine may be prepared by carrying out the procedure in the following manner: 2.7 g of 1-[bis(4-chlorophenyl)methyl]-3-{[3-(N-tertbutyloxycarbonyl-N-methylamino)phenyl]methylsulfonylmethylene}azetidine in 30 cm^3 of dioxane and 30 cm^3 of a 4.7 N solution of hydrochloric dioxane are stirred for 20 hours. The reaction medium is evaporated to dryness under reduced pressure (2.7 kPa), taken up in 50 cm^3 of water and 50 cm^3 of ethyl acetate, stirred and cautiously neutralized with a saturated aqueous sodium bicarbonate solution. The organic phase is separated, dried over magnesium sulfate, treated with animal charcoal and then concentrated under reduced pressure (2.7 kPa) to a volume of about 25 cm^3, then filtered and concentrated to dryness under reduced pressure. 1.3 g of N-[3-({1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]-N-methylamine are obtained in the form of white crystals melting at 228°C.

Example 14

(RS)-1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-bis-trifluoromethylphenyl)methylsulfonylmethyl]azetidine may be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bis-trifluoro-methylphenyl)methylsulfonylmethylene]azetidine, 1.5 cm^3 of anhydrous methanol, 1.5 cm^3 of anhydrous dichloromethane and 15 mg of sodium borohydride, with

stirring for 3 hours at 20°C. The crude product is stirred with 5 cm^3 of pentane, the solid is filtered, drained and dried. 82 mg of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bis-trifluoromethylphenyl)-methylsulfonylmethyl]azetidine are obtained in the form of a white powder [^1H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 2.84 (s : 3H); 3.08 (mt : 2H); from 3.25 to 3.40 (mt : 1H); from 3.45 to 3.65 (mt : 2H); 4.45 (s : 1H); 5.13 (d, J = 10.5 Hz : 1H); from 7.25 to 7.50 (mt : 8H); 8.11 (broad s : 2H); 8.15 (broad s : 1H)].

1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-bis-trifluoromethylphenyl)methylsulfonylmethylene]azetidine may be prepared by carrying out the procedure in the following manner: 0.96 g of crushed sodium hydroxide is added in fractions to a solution of 3.16 g of 3-acetoxy-1-[bis(4-chlorophenyl)methyl]-3-{[3,5-bis(trifluoromethyl)phenyl]methylsulfonylmethyl-(RS)}-azetidine in 40 cm^3 of dioxane. After stirring for 1 hour at room temperature, the reaction mixture is supplemented with 200 cm^3 of ethyl acetate, 200 cm^3 of water and is then separated after settling. The organic phase is washed with twice 80 cm^3 of water, then with 80 cm^3 of brine, dried over magnesium sulfate, then filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 14.5 cm, diameter 4.8 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and

ethyl acetate (85/15 by volume) and collecting 40-cm^3 fractions. Fractions 8 to 15 are combined and concentrated to dryness under reduced pressure (2.7 kPa), 1.49 g of 1-[bis(4-chlorophenyl)methyl]-3-{[(3,5-bis-trifluoromethylphenyl]methylsulfonyl-methylene}azetidine are obtained in the form of a white foam.

3-Acetoxy-1-[bis(4-chlorophenyl)methyl]-3-{[3,5-bis(trifluoromethyl)phenyl]methylsulfonylmethyl-(RS)}-azetidine may be prepared by carrying out the procedure in the following manner: 4.1 cm^3 of a 1.6 N solution of n-butyllithium in hexane are poured dropwise, under argon, into a solution, cooled to -78°C, of 2.0 g of [3,5-bis(trifluoromethyl)benzyl]-methyl sulfone in 35 cm^3 of tetrahydrofuran. After stirring for one hour at -70°C, a solution of 2.0 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one in 35 cm^3 of tetrahydrofuran is added dropwise. After stirring for 2 hours at -78°C, a solution of 0.7 cm^3 of acetyl chloride in 5 cm^3 of anhydrous diethyl ether is poured in and then the mixture is allowed to return to room temperature. After stirring for 2 hours and 30 minutes, the reaction mixture is supplemented with 100 cm^3 of water and separated after settling. The organic phase is washed with 100 cm^3 of water, then with 100 cm^3 of brine and is then dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter

5.6 cm, height 16 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (10/90 and then 40/60 by volume) and collecting 100-cm^3 fractions. Fractions 37 to 52 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 3.56 g of 3-acetoxy-1-[bis(4-chlorophenyl)methyl]-3-{[3,5-bis(trifluoromethyl)-phenyl]methylsulfonylmethyl-(RS)}-azetidine are obtained in the form of a white foam.

[3,5-Bis(trifluoromethyl)benzyl]methyl sulfone may be prepared by heating under reflux 1.8 g of 3,5-bis(trifluoromethyl)benzyl chloride, 50 cm^3 of absolute ethanol and 1.22 g of sodium methyl sulfinate. 1.86 g of [3,5-bis(trifluoromethyl)benzyl]methyl sulfone are obtained in the form of a white solid.

Example 15

N-[4-((4-Chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl-(RS)]azetidin-1-yl}methyl-(RS))benzyl]-N,N-dimethylamine, a mixture of two diastereoisomers, may be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of N-[4-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}methyl-(RS)-benzyl]-N,N-dimethylamine, 1.5 cm^3 of anhydrous methanol, 1.5 cm^3 of anhydrous dichloromethane and 45 mg of sodium borohydride, with stirring for 16 hours at 20°C and then for 16 hours at 50°C. The crude product is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 22 cm,

diameter 1 cm), eluting under an argon pressure of 0.8 bar with a mixture of ethyl acetate and methanol (97/3 by volume) and collecting 20-cm^3 fractions. Fractions 17 to 25 are combined and concentrated to dryness under reduced pressure (2.7 kPa), the residue is stirred with 5 cm^3 of pentane, the solid is filtered, drained and dried. 6 mg of N-[4-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonyl-methyl-(RS)]azetidin-1-yl}methyl-(RS))benzyl]-N,N-dimethylamine, a mixture of two diastereoisomers, are obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 2.20 (s : 6H); 2.53 (t, J = 7 Hz : 1H); 2.65 (s : 3H); from 3.10 to 3.25 (mt : 2H); from 3.30 to 3.45 (mt : 1H); 3.35 (broad s : 2H); 3.63 (broad t, J = 7 Hz : 1H); 4.24 (s : 1H); 4.25 (d, J = 11 Hz : 1H); 6.82 (tt, J = 9 and 2 Hz : 1H); 6.94 (mt : 2H); from 7.15 to 7.35 (mt : 8H)].

N-[4-((4-Chlorophenyl)-{3-[(3,5-difluoro-phenyl)methylsulfonylmethylene]azetidin-1-yl}methyl-(RS))benzyl]-N,N-dimethylamine may be prepared by carrying out the procedure in the following manner: 1.0 g of (RS)-4-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)benzaldehyde is added, under argon, to a solution of 0.93 cm^3 of a 2 M solution of dimethylamine in methanol in 30 cm^3 of anhydrous 1,2-dichloroethane. After stirring for 30 minutes at room temperature, 0.9 g of sodium triacetoxyborohydride is added in small fractions. After stirring for 48 hours, the reaction

mixture is supplemented with 2.65 cm^3 of 1 N sodium hydroxide, 100 cm^3 of water and 100 cm^3 of dichloromethane and is then separated after settling. The organic phase is washed with twice 80 cm^3 of water and with 80 cm^3 of brine and is then dried over magnesium sulfate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 4 cm, height 17.5 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (30/70 by volume) and collecting 40-cm^3 fractions. Fractions 48 to 53 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.46 g of N-[4-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]-azetidin-1-yl}methyl-(RS))benzyl]-N,N-dimethylamine is obtained in the form of a white solid.

(RS)-4-((4-Chlorophenyl)-{3-[(3,5-difluoro-phenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)-benzaldehyde may be prepared by carrying out the procedure in the following manner: 75.6 cm^3 of 5 N hydrochloric acid are added to a solution of 18.9 g of 1-[(4-chlorophenyl)-(4-[1,3]dioxolan-2-ylphenyl)-methyl]-(RS)-3-[(3,5-difluorophenyl)methylsulfonyl-methylene]azetidine in 80 cm^3 of tetrahydrofuran. After 3 hours at room temperature, the mixture is taken up in dichloromethane and distilled water and then brought to pH 14 by addition of 30% sodium hydroxide and separated after settling. The organic phase is washed twice with

100 m^3 of water and then 100 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). 16 g of (RS)-4-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]-azetidin-1-yl}methyl)benzaldehyde are obtained in the form of a white foam.

1-[(4-Chlorophenyl)-(4-[1,3]dioxolan-2-ylphenyl)methyl]-(RS)-3-[(3,5-difluorophenyl)methyl-sulfonylmethylene]azetidine may be prepared according to the following method: 13.0 cm^3 of 1,8-diazabicyclo-[5-4-0]undec-7-ene are added dropwise to a solution of 34.45 g of the mixture of the two diastereoisomers of 1-[(4-chlorophenyl)-(4-[1,3]dioxolan-2-ylphenyl)methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonylmethyl-(RS)]azetidin-3-yl acetate in 400 cm^3 of tetrahydrofuran under argon at 0°C, and after the usual treatment, the product is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 10.2 cm, height 23 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (20/80 by volume) and collecting 250-cm^3 fractions; 16.6 g of 1-[(4-chlorophenyl)-(4-[1,3]dioxolan-2-ylphenyl)methyl]-(RS)-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidine are obtained in the form of a white solid.

The mixture of the two diastereoisomers 1-[(4-chlorophenyl)-(4-[1,3]dioxolan-2-ylphenyl)methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonylmethyl-

(RS)]azetidin-3-yl acetate diastereoisomers may be obtained in the following manner: by carrying out the procedure according to Example 1 (method 2), starting with 11.6 g of (3,5-difluorobenzyl)methyl sulfone, 35.1 cm^3 of a 1.6 N solution of n-butyllithium in hexane, 19.3 g of 1-{(4-chlorophenyl)[4-([1,3]dioxolan-2-yl)phenyl]methyl-(RS)}azetidin-3-one and 8.8 cm^3 of acetyl chloride in 500 cm^3 of tetrahydrofuran, 37.8 g of the mixture of the two 1-[(4-chlorophenyl)-(4-[1,3]dioxolan-2-ylphenyl)methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonylmethyl-(RS)]azetidin-3-yl acetate diastereoisomers are obtained in the form of a white foam.

1-{(4-Chlorophenyl)[4-([1,3]dioxolan-2-yl)-phenyl]methyl-(RS)}azetidin-3-one may be prepared in the following manner: 46 cm^3 of triethylamine are added, at room temperature, to a solution of 28.32 g of 1-{(4-chlorophenyl)[4-([1,3]dioxolan-2-yl)phenyl]-methyl-(RS)}azetidin-3-ol in 200 cm^3 of dimethyl sulfoxide, followed by the dropwise addition of a solution of 34 g of sulfur trioxide-pyridine complex in 100 cm^3 of dimethyl sulfoxide. After 0.25 hour at room temperature, the reaction mixture is poured over ice, extracted with ethyl acetate, washed with 3 times 400 cm^3 of water and then with 400 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is chromatographed on a silica gel column (particle size

0.04-0.06 mm, diameter 9.2 cm, height 21 cm) under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (20/80 by volume) as eluent and collecting 250-cm^3 fractions. Fractions 9 to 18 are combined and then concentrated to dryness under reduced pressure (2.7 kPa). 20.4 g of 1-{(4-chlorophenyl)[4-([1,3]dioxolan-2-yl)phenyl]methyl-(RS)}azetidin-3-one are obtained in the form of a yellow oil.

1-{(4-Chlorophenyl)[4-([1,3]dioxolan-2-yl)phenyl]methyl-(RS)}azetidin-3-ol may be prepared as described in Example 3, starting with 35.0 g of {(4-chlorophenyl)[4-(1,3-dioxolan-2-yl)phenyl]methyl}amine, 8.3 g of epibromohydrin, 5.1 g of sodium hydrogen carbonate and 400 cm^3 of ethanol. 30.3 g of 1-{(4-chlorophenyl)[4-([1,3]dioxolan-2-yl)phenyl]methyl-(RS)}azetidin-3-ol are isolated.

{(4-Chlorophenyl)[4-([1,3]-dioxolan-2-yl)phenyl]methyl-(RS)}amine hydrochloride may be prepared according to the method described by GRISAR M. et al., J. Med Chem., 885 (1973) starting with 67.2 g of 4-([1,3]-dioxolan-2-yl)benzonitrile, 88.2 g of 1-bromo-4-chlorobenzene, 11 g of magnesium and 600 cm^3 of ethyl ether. 42.3 g of {(4-chlorophenyl)[4-([1,3]-dioxolan-2-yl)phenyl]methyl-(RS)}amine are obtained in the form of a yellow oil.

Example 16

1-[(4-Chlorophenyl)(thien-2-yl)methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonylmethyl-(RS)]azetidine, a mixture of two diastereoisomers, may

be prepared by carrying out the procedure as described in Example 3, starting with 0.10 g of 1-[(4-chlorophenyl)(thien-2-yl)methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidine, 1.5 cm^3 of anhydrous methanol, 1.5 cm^3 of anhydrous dichloromethane and 45 mg of sodium borohydride, with stirring for 16 hours at 20°C and then for 16 hours at 50°C. The crude product is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 25 cm, diameter 1 cm), eluting under an argon pressure of 1 bar with a mixture of cyclohexane and ethyl acetate (90/10 by volume), and collecting 20-cm^3 fractions. Fractions 37 to 42 are combined and concentrated to dryness under reduced pressure (2.7 kPa), the residue is stirred with 5 cm^3 of pentane, the solid is filtered, drained and dried. 8 mg of 1-[(4-chlorophenyl)(thien-2-yl)methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonylmethyl-(RS)]azetidine, a mixture of two diastereoisomers, are obtained in the form of a white powder [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm). A mixture of diastereoisomers is observed, from 2.50 to 2.70 (mt : 1H); 2.66 and 2.68 (2s : 3H in total); from 3.15 to 3.80 (mt : 4H); from 4.20 to 4.30 (mt : 1H); 4.31 and 4.57 (2s : 1H in total); from 6.80 to 7.00 and from 7.10 to 7.40 (mts : 10H in total)].

1-[(4-Chlorophenyl)(thien-2-yl)methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidine may be prepared by carrying out the procedure as described in Example 6, starting with 0.52 g of a

mixture of the two 1-[(4-chlorophenyl)(thien-2-yl)-methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonyl-methyl-(RS)]azetidin-3-ol diastereoisomers, 0.14 cm^3 of methylsulfonyl chloride and 0.49 g of 4-dimethylamino-pyridine. After chromatography on a silica gel column (particle size 0.06-0.200 mm, diameter 2.4 cm, height 20 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (20/80 by volume) and collecting 30-cm^3 fractions, 0.32 g of (RS)-1-[(4-chlorophenyl(thien-2-yl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidine is obtained in the form of a white solid melting at 176°C.

The mixture of the two 1-[(4-chlorophenyl)-(thien-2-yl)methyl-(RS)]-3-[(3,5-difluorophenyl)methyl-sulfonylmethyl-(RS)]azetidin-3-ol diastereoisomers may be prepared by carrying out the procedure as described in Example O, starting with 1.60 cm^3 of 1.6 N n-butyllithium in solution in hexane, 0.83 g of (3,5-difluorobenzyl)methyl sulfone and 1.06 g of 1-[(4-chlorophenyl)(thien-2-yl)methyl-(RS)]azetidin-3-one. After purification on a silica gel column (particle size 0.06-0.200 mm, diameter 2.8 cm, height 30 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (25/75 by volume) and collecting 40-cm^3 fractions, 0.55 g of the mixture of the 1-[(4-chlorophenyl)(thien-2-yl)methyl-(RS)]-3-[(3,5-difluorophenyl)methylsulfonylmethyl-(RS)]azetidin-3-ol diastereoisomers is obtained in the form of an off-white solid.

1-[(4-Chlorophenyl)(thien-2-yl)methyl-(RS)]azetidin-3-one may be prepared by carrying out the procedure as described in Example 1 (method 2), starting with 1.83 cm^3 of oxalyl chloride, 20 cm^3 of dichloromethane, 3.04 cm^3 of dimethyl sulfoxide, 5.2 g of 1-[(4-chlorophenyl)(thien-2-yl)methyl-(RS)]azetidin-3-ol, 80 cm^3 of dichloromethane and 9.12 cm^3 of triethylamine. 3.3 g of 1-[(4-chlorophenyl)(thien-2-yl)methyl-(RS)]azetidin-3-one are obtained in the form of a yellow oil which crystallizes at room temperature.

1-[(4-Chlorophenyl)(thien-2-yl)methyl-(RS)]azetidin-3-ol may be prepared by carrying out a procedure in the following manner: 4.12 g of sodium bicarbonate are added to a solution of 11.0 g of [(4-chlorophenyl)(thien-2-yl)methyl-(RS)]amine in 80 cm^3 of ethanol. The mixture, heated to 65°C, is supplemented with 4.03 cm^3 of epibromohydrin. After stirring for 20 hours at 65°C, the crude mixture is filtered and the filtrate concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 3.6 cm, height 32 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (25/75 by volume) and collecting 60-cm^3 fractions. 6.3 g of 1-[(4-chlorophenyl)(thien-2-yl)methyl-(RS)]azetidin-3-ol are obtained in the form of a pale yellow oil.

[(4-Chlorophenyl)(thien-2-yl)methyl-(RS)]amine may be prepared in the following manner: a solution of

10.92 g of 2-thiophenecarbonitrile in 80 cm^3 of diethyl ether is poured slowly into a suspension, cooled to 10°C of 4-chlorophenylmagnesium bromide (prepared from 19.15 g of 4-bromochlorobenzene and 2.43 g of magnesium) in 120 cm^3 of anhydrous ethyl ether. After refluxing for one hour, the mixture is cooled to 10°C, supplemented slowly with 40 cm^3 of methanol and then filtered on supercel. 4.54 g of sodium borohydride are added under argon and in small fractions over 15 minutes and then the reaction medium is stirred for 20 hours at 20°C. The mixture obtained is diluted with ethyl acetate and then washed with water. The organic phase is dried over magnesium sulfate, concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 5 cm, height 42 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (4/6 by volume) and collecting 100-cm^3 fractions. Fractions 6 to 12, concentrated to dryness, correspond to 13 g of imine in the form of a yellow oil which is taken up in 100 cm^3 of methanol. The solution obtained is supplemented with 2.4 g of sodium borohydride and stirred for one hour at 5°C. The mixture obtained is diluted with ethyl acetate and then washed with water. The organic phase is dried over magnesium sulfate, concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter

3.2 cm, height 40 cm), eluting under an argon pressure of 0.5 bar with a mixture of ethyl acetate and cyclohexane (4/6 by volume) and collecting 60-cm^3 fractions. 11.0 g of [(4-chlorophenyl)(thien-2-yl)methyl-(RS)]amine are obtained in the form of a yellow oil.

Example 17

(RS)-[3-({1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}methylsulfonylmethyl)phenyl]methanol may be prepared by carrying out the procedure as described in Example 3, starting with 0.050 g of [3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonyl-methylene)phenyl]methanol, 1.0 cm^3 of anhydrous methanol, 1.0 cm^3 of anhydrous dichloromethane and 20 mg of sodium borohydride, with stirring for 3 hours at 20°C. The crude product is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 20 cm, diameter 1 cm), eluting under an argon pressure of 0.8 bar with a mixture of cyclohexane and ethyl acetate (90/10 by volume) and collecting 10-cm^3 fractions. Fractions 30 to 38 are combined and concentrated to dryness under reduced pressure (2.7 kPa), the residue is stirred with 5 cm^3 of pentane, the solid is filtered, drained and dried. 13 mg of (RS)-[3-({1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}methylsulfonylmethyl)phenyl]methanol are obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 1.75 (t, J = 6 Hz : 1H); 2.52 (t, J = 7.5 Hz : 1H); 2.59 (s : 3H); 3.17 (broad

t, J = 7.5 Hz : 2H); 3.48 (mt : 1H); 3.65 (mt : 1H); 4.23 (s : 1H); 4.28 (d, J = 11.5 Hz : 1H); 4.70 (d, J = 6 Hz : 2H); from 7.15 to 7.40 (mt : 12H)].

[3-({1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethylene)phenyl]methanol may be prepared by carrying out the procedure in the following manner: 17 cm^3 of a 1 M solution of tetrabutylammonium fluoride in tetrahydrofuran are poured into a solution, cooled to +5°C, of 5.1 g of 1-[bis(4-chlorophenyl)-methyl]-3-{[3-(tertbutyldimethylsilyloxymethyl)phenyl]-methylsulfonyl-methylene}azetidine in 51 cm^3 of tetrahydrofuran. After stirring for 20 minutes at cooled temperature and then for 3 hours at 20°C, the reaction mixture is poured into a mixture of 200 cm^3 of water and 100 cm^3 of ethyl acetate and then separated after settling. The organic phase is washed with water, dried over magnesium sulfate and then filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is purified by chromatography on a silica gel column (particle size 0.04-0.06 mm, diameter 2 cm, height 30 cm), eluting under a nitrogen pressure of 0.5 bar with a dichloromethane and ethanol (97/3 by volume) mixture and collecting 100-cm^3 fractions. Fractions 10 to 14 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The yellow solid obtained is taken up in 2 cm^3 of dichloromethane and 10 cm^3 of ethyl acetate and then filtered on sintered glass and washed with 2 cm^3 of ethyl acetate. 1.6 g of [3-({1-[bis(4-

chlorophenyl)methyl]azetidin-3-yl}methylsulfonyl-methylene)phenyl]methanol are obtained in the form of a white solid melting at 214°C.

1-[Bis(4-chlorophenyl)methyl]-3-{[3-(tert-butyldimethylsilyloxymethyl)phenyl]methylsulfonyl-methylene}azetidine may be prepared by carrying out the operation according to the procedure of Example 1, starting with 10.8 g of 1-[bis(4-chlorophenyl)methyl]-3-{[3-(tert-butyldimethylsilyloxymethyl)phenyl]-methylsulfonylmethyl-(RS)}azetidin-3-ol, 2 cm^3 of methylsulfonyl chloride and 8.5 g of 4-dimethylamino-pyridine, the residue obtained is purified by chromotography on a silica gel column (particle size 0.04-0.06 mm, diameter 4 cm, height 40 cm) under a nitrogen pressure of 0.5 bar with dichloromethane as eluent and collecting 100-cm^3 fractions. Fractions 12 to 29 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 5.2 g of 1-[bis(4-chloro-phenyl)methyl]-3-{[3-(tert-butyldimethylsilyloxy-methyl)phenyl]methylsulfonyl-methylene}azetidine are obtained in the form of a gum.

1-[Bis(4-chlorophenyl)methyl]-3-{[3-(tert-butyldimethylsilyloxymethyl)phenyl]methylsulfonyl-methyl-(RS)}azetidin-3-ol may be prepared by carrying out the operation according to the procedure of Example 5, starting with 5.8 g of tert-butyl-(3-methylsulfonyl-methylbenzyloxy)dimethylsilane and 5.6 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one, 10.8 g of 1-[bis(4-chlorophenyl)methyl]-3-{[3-(tert-butyldimethylsilyloxy-

methyl)phenyl]methylsulfonylmethyl-(RS)}azetidin-3-ol are obtained in the form of a gum.

tert-Butyl-(3-methylsulfonylmethylbenzyloxy)-dimethylsilane may be prepared by carrying out the procedure in the following manner: 4.87 g of imidazole are added to a solution of 5.73 g of (3-methylsulfonylmethylphenyl)methanol in 50 cm^3 of N,N-dimethylformamide, followed by 10.3 cm^3 of tert-butylchlorodimethylsilane. After stirring for 20 hours at room temperature, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.06-0.200 mm, diameter 3.5 cm, weight of silica 100 g), eluting under a nitrogen pressure of 0.5 bar with dichloromethane, and collecting 100-cm^3 fractions. Fractions 2 to 7 are combined, concentrated to dryness under reduced pressure (2.7 kPa). 5.8 g of an oil are obtained, which oil crystallizes at room temperature (m.p. = 75°C.)

(3-Methylsulfonylmethylphenyl)methanol may be prepared by carrying out the procedure in the following manner: a mixture of 26 g of 3-(methylsulfonylmethyl)-benzoic acid and 4.6 g of lithium aluminum hydride in 600 cm^3 of tetrahydrofuran is stirred for 18 hours at a temperature close to 20°C. The solution is cooled to 0°C and then 15 cm^3 of ethyl acetate, 30 cm^3 of water, 5 cm^3 of a 15% aqueous solution of sodium hydroxide and finally 30 cm^3 of water are added successively. The mixture is filtered on celite and the filtrate taken up

in 600 cm^3 of ethyl acetate. The organic phase is taken up in 500 cm^3 of water and then 200 cm^3 of a saturated aqueous sodium chloride solution, separated after settling, dried over anhydrous magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). 10.4 g of (3-methylsulfonyl-methylphenyl)methanol are obtained in the form of a gum.

3-(Methylsulfonylmethyl)benzoic acid may be prepared in the following manner: by carrying out the operation according to the procedure of Example 14, starting with 23.3 g of 3-chloromethylbenzoic acid. 23.3 g of sodium methane sulfinate,26 g of 3-(methylsulfonylmethyl) benzoic acid are obtained in the form of a white solid melting at 210°C.

Example 18

1-[Bis(4-chlorophenyl)methyl]-3-(phenylsulfonylmethyl)azetidine may be prepared by carrying out the procedure in the following manner: 13 mg of sodium borohydride are added, under argon, to a solution of 0.15 g of 1-[bis(4-chlorophenyl)methyl)]-3-(phenylsulfonylmethylene)azetidine in 3 cm^3 of anhydrous ethanol and 3.5 cm^3 of anhydrous dichloromethane. After stirring for 1 hour and 45 minutes, 14 mg of sodium borohydride are again added and then the mixture is kept stirring for 20 hours at 20°C. The reaction mixture is then heated to 50°C, supplemented with 9.5 mg of sodium borohydride and kept stirred for 2 hours and 30 minutes at 50°C and then

cooled to room temperature. 0.5 cm^3 of water, 10 cm^3 of dichloromethane and then 50 mg of magnesium sulfate are then added to the mixture, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 15 cm, diameter 1 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (80/20 by volume) and collecting 5-cm^3 fractions. Fractions 12 to 19 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 29 mg of 1-[bis(4-chlorophenyl)methyl]-3-(phenylsulfonylmethyl)azetidine are obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : from 2.75 to 8.90 (mt : 3H); 3.32 (mt : 2H); 3.37 (d, J = 7 Hz : 2H); 4.22 (s : 1H); from 7.20 to 7.30 (mt : 8H); 7.57 (broad t, J = 7.5 Hz : 2H); 7.67 (tt, J = 7.5 and 1.5 Hz : 1H); 7.88 (broad d, J = 7.5 Hz : 2H)].

Example 19

1-[Bis(4-chlorophenyl)methyl]-3-(phenylsulfonylmethylene)azetidine may be prepared by carrying out the procedure in the following manner: 12 cm^3 of a 1.6 M solution of n-butyllithium in hexane are poured, over 5 minutes, into a solution, cooled to -70°C, under argon, of 4.34 g of (phenylsulfonylmethyl)trimethylsilane in 40 cm^3 of dimethyl ether. After stirring the mixture for 30 minutes at -60°C, a solution of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one in 30 cm^3 of dimethyl ether [produced in the form of a

base prepared by treating 7.35 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one hydrobromide dissolved in 30 cm^3 of water, with 25 cm^3 of 1 N sodium hydroxide and extracting the base obtained with 30 cm^3 of diethyl ether, then drying and concentrating to dryness under reduced pressure (2.7 kPa)] is poured in over 10 minutes. After stirring for 45 minutes at -70°C and then for 2 hours at 20°C, the reaction mixture is supplemented with 12 cm^3 of a saturated aqueous ammonium chloride solution, 20 cm^3 of water and then extracted with 12 40 cm^3 of ethyl acetate. The combined organic phases are [lacuna] with 40 cm^3 of water, dried over magnesium sulfate and then concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 40 cm, diameter 5 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (90/10 and then 85/15 by volume) and collecting 100-cm^3 fractions. Fractions 10 to 16 are combined and concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained is triturated in 10 cm^3 of diethyl ether, the suspension filtered and the solid dried. 1.17 g of 1-[bis(4-chlorophenyl)methyl)]-3-(phenylsulfonylmethylene)-azetidine are obtained in the form of a white solid [^1H NMR spectrum (300 MHz, $CDCl_3$ d in ppm) : 3.88 (mt : 2H); 4.29 (mt : 2H); 4.50 (s : 1H); 6.17 (mt : 1H); from 7.20 to 7.40 (mt : 8H); 7.56 (broad t,

J = 7.5 Hz : 2H); 7.64 (tt, J = 7.5 and 1.5 Hz : 1H); 7.87 (broad d, J = 7.5 Hz : 2H)].

(Phenylsulfonylmethyl)trimethylsilane may be prepared by carrying out the procedure in the following manner: 13 cm^3 of a 1.6 M solution of n-butyllithium in hexane are poured, with stirring under argon over 20 minutes, into a solution, cooled to -70°C, of 3 g of methyl phenyl sulfone in 40 cm^3 of anhydrous tetrahydrofuran. After stirring for 30 minutes at -70°C, 2.66 cm^3 of trimethylchlorosilane are added to the mixture, and the heating is stopped. After stirring for 4 hours at room temperature, the reaction mixture is supplemented with 30 cm^3 of water and extracted with 30 cm^3 of ethyl acetate. The organic phase is washed with 30 cm^3 of water, dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). 4.34 g of (phenylsulfonylmethyl)-trimethylsilane are obtained in the form of a yellow liquid.

Example 20

2-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-ylmethylsulfonyl}pyridine may be prepared by carrying out the procedure in the following manner: 0.125 g of sodium borohydride is added to a solution of 0.25 g of 2-{1-[bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}pyridine in 20 cm^3 of a 50/50 mixture of dichloromethane and ethanol. After stirring for 1 hour at 50°C, the reaction mixture is cooled to 20°C, supplemented with 20 cm^3 of dichloromethane, 1 cm^3

of water and 0.1 g of magnesium sulfate. The mixture is filtered and the filtrate is concentrated at 50°C under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.040-0.063 mm, height 15 cm, diameter 1 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (40/60 by volume) and collecting 10-cm^3 fractions. Fractions 5 to 10 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.18 g of 2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylmethylsulfonyl}-pyridine is obtained in the form of a white powder (^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : from 2.80 to 3.00 (mt : 3H); 3.34 (mt : 2H); 3.70 (d, J = 7 Hz : 2H); 4.25 (s : 1H); from 7.20 to 7.40 (mt : 8H); 7.57 (ddd, J = 8-5 and 1 Hz : 1H); 7.97 (split t, J = 8 and 1.5 Hz : 1H); 8.07 (broad d, J = 8 Hz : 1H); 8.75 (broad d, J = 5 Hz : 1H)].

2-{1-[Bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}pyridine may be prepared by carrying out the procedure in the following manner: 0.25 cm^3 of methylsulfonyl chloride is added to a solution of 0.9 g of 1-[bis(4-chlorophenyl)methyl)]-3-(pyrid-2-ylsulfonylmethyl)azetidin-3-ol in 50 cm^3 of dichloromethane, the mixture is stirred for 15 minutes and 0.9 g of 4-dimethylaminopyridine is added. After stirring for 3 hours at 20°C, 30 cm^3 of water and 30 cm^3 of dichloromethane are added to the mixture and then the organic phase is separated after settling, dried

over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.063 mm, height 25 cm, diameter 2 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (40/60 by volume) and collecting 20-cm^3 fractions. Fractions 4 to 8 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.50 g of 2-{1-[bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}-pyridine is obtained in the form of a yellow powder.

1-[Bis(4-chlorophenyl)methyl)]-3-(pyrid-2-ylsulfonylmethyl)azetidin-3-ol may be prepared by carrying out the procedure in the following manner: 2.13 g of potassium tert-butoxide are added to a solution, cooled to -78°C under argon, of 2.92 g of 1-[bis(4-chlorophenyl)methyl)]azetidin-3-one and 3 g of 2-methylsulfonylpyridine in 50 cm^3 of tetrahydrofuran. After stirring for 3 hours at -78°C, the reaction mixture is allowed to return to 0°C and then 50 cm^3 of diethyl ether, 10 cm^3 of water and 10 cm^3 of a saturated aqueous ammonium chloride solution are added. The organic phase is separated after settling, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.063-0.200 mm, height 30 cm, diameter 3 cm), eluting under an argon pressure of 0.5 bar, first with dichloromethane and then with a mixture of

dichloromethane and methanol (97/3 by volume) and collecting 20-cm^3 fractions. Fractions 8 to 15 are combined and concentrated to dryness under reduced pressure (2.7 kPa). A still impure brown oil is obtained which is chromatographed on a silica gel column (particle size 0.04-0.063 mm, height 20 cm, diameter 2 cm), eluting under an argon pressure of 0.5 bar, first with dichloromethane and then with a mixture of dichloromethane and methanol (97/3 by volume) and collecting 20-cm^3 fractions. Fractions 5 to 25 are combined and concentrated to dryness and the residue obtained is again chromatographed on the same column and under the same conditions but eluting with dichloromethane. Fractions 12 to 20 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.3 g of 1-[bis(4-chlorophenyl)methyl)]-3-(pyrid-2-ylsulfonylmethyl)azetidin-3-ol is obtained in the form of a white foam.

2-Methylsulfonylpyridine may be prepared by carrying out the procedure in the following manner: 0.25 cm^3 of 100% acetic acid is added, with stirring under argon, to a solution of 20 g of sodium tungstate dihydrate in 10 cm^3 of water, followed by 7.0 g of 2-methylsulfanylpyridine. This mixture is heated to 65°C, 10 cm^3 of 30% hydrogen peroxide are slowly poured in over 15 minutes, then the mixture is stirred at 85°C for 30 minutes and then cooled to +10°C. 1.0 cm^3 of 32% aqueous ammonia and 5.0 cm^3 of a 37.5% aqueous solution of sodium hydrogen sulfite are added to the medium,

followed by 10 cm^3 of water and 50 cm^3 of dichloromethane. The mixture is separated after settling, the organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The colorless oil obtained is disintegrated with 50 cm^3 of petroleum ether and the insoluble gum is filtered and taken up in 30 cm^3 of dichloromethane. The solution obtained is concentrated to dryness at 50°C under reduced pressure (2.7 kPa). 3.5 g of 2-methylsulfonylpyridine are obtained in the form of a colorless oil.

2-Methylsulfanylpyridine may be prepared by carrying out the procedure in the following manner: 6.2 cm^3 of methyl iodide are slowly added to a solution of 11.0 g of 2-mercaptopyridine in 105 cm^3 of 1 N sodium hydroxide. The reaction mixture, whose temperature has risen to 30°C, is cooled to room temperature. After stirring for 2 hours, the mixture is extracted with 100 cm^3 of dichloromethane, the organic phase is dried over magnesium sulfate and concentrated to dryness at 50°C under reduced pressure (2.7 kPa). The oil obtained is purified by distillation under reduced pressure. 9.0 g of 2-methylsulfanylpyridine are obtained in the form of a colorless liquid, b.p. = 84°C/45 mmHg.

Example 21

3-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-ylmethylsulfonyl}pyridine may be prepared by carrying out the procedure as described in Example 20, starting

with 0.15 g of 3-{1-[bis(4-chlorophenyl)methyl)]-azetidin-3-ylidenemethylsulfonyl}pyridine, 20 cm^3 of a 50/50 mixture of dichloromethane and ethanol, and 80 mg of sodium borohydride. 0.11 g of 3-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylmethylsulfonyl}pyridine is obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : from 2.75 to 2.95 (mt : 3H); 3.35 (mt : 2H); 3.43 (d, J = 6.5 Hz ; 2H); 4.25 (s : 1H); from 7.20 to 7.40 (mt : 8H); 7.54 (ddd, J = 8-5 and 1 Hz : 1H); 8.18 (ddd, J = 8-2.5 and 1.5 Hz : 1H); 8.90 (dd, J = 5 and 1.5 Hz : 1H); 9.11 (dd, J = 2.5 and 1 Hz : 1H)].

3-{1-[Bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}pyridine may be prepared by carrying out the procedure as described in Example 20, starting with 0.8 g of 1-[bis(4-chlorophenyl)methyl)]-3-(pyrid-3-ylsulfonylmethyl)azetidin-3-ol, 50 cm^3 of dichloromethane, 0.22 cm^3 of methylsulfonyl chloride and 0.8 g of 4-dimethylaminopyridine. 0.50 g of 3-{1-[bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}pyridine is obtained in the form of a cream-colored powder.

1-[Bis(4-chlorophenyl)methyl)]-3-(pyrid-3-ylsulfonylmethyl)azetidin-3-ol may be prepared by carrying out the procedure as described in Example 20, starting with 3.3 g of 1-[bis(4-chlorophenyl)methyl)]-azetidin-3-one, 50 cm^3 of tetrahydrofuran, 3.5 g of 3-methylsulfonylpyridine and 2.4 g of potassium tert-butoxide. 1.4 g of 1-[bis(4-chlorophenyl)methyl)]-3-

(pyrid-3-ylsulfonylmethyl)azetidin-3-ol are obtained in the form of a white powder.

3-Methylsulfonylpyridine may be prepared by carrying out the procedure as described in Example 20, starting with 33 g of sodium tungstate, 10 cm^3 of water, 0.25 cm^3 of 100% acetic acid, 9.5 g of 3-methylsulfanylpyridine, 15 cm^3 of 30% hydrogen peroxide and then 2 cm^3 of 32% aqueous ammonia and 2 cm^3 of a 37.5% aqueous solution of sodium hydrogen sulfite. The crude oil obtained is crystallized with 20 cm^3 of diisopropyl ether, the crystals are filtered, drained and dried under reduced pressure (2.7 kPa). 4.5 g of 3-methylsulfonylpyridine are obtained in the form of white crystals (m.p. = 58°C.)

3-Methylsulfanylpyridine may be prepared by carrying out the procedure in the following manner: 20 cm^3 of isoamyl nitrite are added to a mixture, heated to 80°C under argon, of 9.4 g of 3-aminopyridine and 100 cm^3 of dimethyl disulfide. After stirring for 2 hours at 90°C, the reaction mixture is cooled to 20°C and then purified by fractional distillation under reduced pressure. 8.4 g of 3-methylsulfanylpyridine are obtained in the form of a pale yellow liquid, b.p. = 90°C/30 mm of mercury.

Example 22

4-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-ylmethylsulfonyl}pyridine may be prepared by carrying out the procedure as described in Example 20, starting with 0.15 g of 4-{1-[bis(4-chlorophenyl)methyl)]-

azetidin-3-ylidenemethylsulfonyl}pyridine, 20 cm^3 of a 50/50 mixture of dichloromethane and ethanol, and 80 mg of sodium borohydride. 0.13 g of 4-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylmethylsulfonyl}pyridine is obtained in the form of a white powder [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : from 2.75 to 2.90 (mt : 1H); 2.88 (t, J = 7 Hz : 2H); 3.36 (t, J = 7 Hz : 2H); 3.42 (d, J = 7 Hz : 2H); 4.25 (s : 1H); from 7.20 to 7.35 (mt : 8H); 7.75 (broad d, J = 6 Hz : 2H); 8.93 (broad d, J = 6 Hz : 2H)].

4-{1-[Bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}pyridine may be prepared by carrying out the procedure as described in Example 20, starting with 0.8 g of 1-[bis(4-chlorophenyl)methyl)]-3-(pyrid-4-ylsulfonylmethyl)azetidin-3-ol, 50 cm^3 of dichloromethane, 0.22 cm^3 of methylsulfonyl chloride and 0.8 g of 4-dimethylaminopyridine. The crude product is purified by chromatography on a silica gel column (particle size 0.04-0.063 mm, height 20 cm, diameter 2 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (40/60 by volume) and collecting 20-cm^3 fractions. Fractions 5 to 10 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.42 g of 4-{1-[bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}-pyridine is obtained in the form of a white crystalline powder.

1-[Bis(4-chlorophenyl)methyl)]-3-(pyrid-4-ylsulfonylmethyl)azetidin-3-ol may be prepared by

3-Methylsulfonylpyridine may be prepared by carrying out the procedure as described in Example 20, starting with 33 g of sodium tungstate, 10 cm^3 of water, 0.25 cm^3 of 100% acetic acid, 9.5 g of 3-methylsulfanylpyridine, 15 cm^3 of 30% hydrogen peroxide and then 2 cm^3 of 32% aqueous ammonia and 2 cm^3 of a 37.5% aqueous solution of sodium hydrogen sulfite. The crude oil obtained is crystallized with 20 cm^3 of diisopropyl ether, the crystals are filtered, drained and dried under reduced pressure (2.7 kPa). 4.5 g of 3-methylsulfonylpyridine are obtained in the form of white crystals (m.p. = 58°C.)

3-Methylsulfanylpyridine may be prepared by carrying out the procedure in the following manner: 20 cm^3 of isoamyl nitrite are added to a mixture, heated to 80°C under argon, of 9.4 g of 3-aminopyridine and 100 cm^3 of dimethyl disulfide. After stirring for 2 hours at 90°C, the reaction mixture is cooled to 20°C and then purified by fractional distillation under reduced pressure. 8.4 g of 3-methylsulfanylpyridine are obtained in the form of a pale yellow liquid, b.p. = 90°C/30 mm of mercury.

Example 22

4-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-ylmethylsulfonyl}pyridine may be prepared by carrying out the procedure as described in Example 20, starting with 0.15 g of 4-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-ylidenemethylsulfonyl}pyridine, 20 cm^3 of a 50/50 mixture of dichloromethane and ethanol, and 80 mg

of sodium borohydride. 0.13 g of 4-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylmethylsulfonyl}pyridine is obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : from 2.75 to 2.90 (mt : 1H); 2.88 (t, J = 7 Hz : 2H); 3.36 (t, J = 7 Hz : 2H); 3.42 (d, J = 7 Hz : 2H); 4.25 (s : 1H); from 7.20 to 7.35 (mt : 8H); 7.75 (broad d, J = 6 Hz : 2H); 8.93 (broad d, J = 6 Hz : 2H)].

4-{1-[Bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}pyridine may be prepared by carrying out the procedure as described in Example 20, starting with 0.8 g of 1-[bis(4-chlorophenyl)methyl)]-3-(pyrid-4-ylsulfonylmethyl)azetidin-3-ol, 50 cm^3 of dichloromethane, 0.22 cm^3 of methylsulfonyl chloride and 0.8 g of 4-dimethylaminopyridine. The crude product is purified by chromatography on a silica gel column (particle size 0.04-0.063 mm, height 20 cm, diameter 2 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (40/60 by volume) and collecting 20-cm^3 fractions. Fractions 5 to 10 are combined and concentrated to dryness under reduced pressure (2.7 kPa). 0.42 g of 4-{1-[bis(4-chlorophenyl)methyl)]azetidin-3-ylidenemethylsulfonyl}-pyridine is obtained in the form of a white crystalline powder.

1-[Bis(4-chlorophenyl)methyl)]-3-(pyrid-4-ylsulfonylmethyl)azetidin-3-ol may be prepared by carrying out the procedure as described in Example 20, starting with 2.5 g of 1-[bis(4-chlorophenyl)methyl)]-

azetidin-3-one, 50 cm^3 of tetrahydrofuran, 2.6 g of 4-methylsulfonylpyridine and 1.8 g of potassium tert-butoxide. The crude product obtained is purified by chromatography on a silica gel column (particle size 0.04-0.063 mm, height 30 cm, diameter 3 cm), eluting under an argon pressure of 0.5 bar with dichloromethane and then with a mixture of dichloromethane and methanol (98/2 by volume) and collecting 20-cm^3 fractions. Fractions 8 to 27 are combined and concentrated to dryness under reduced pressure (2.7 kPa). A cream-colored powder is obtained which is recrystallized from 5 cm^3 of acetonitrile. The crystals are filtered, drained and dried under reduced pressure (2.7 kPa). 1.4 g of 1-[bis(4-chlorophenyl)methyl]-3-(pyrid-4-ylsulfonylmethyl)azetidin-3-ol are obtained in the form of white crystals, m.p. = 130°C.

4-Methylsulfonylpyridine may be prepared by carrying out the procedure as described in Example 20, starting with 14 g of sodium tungstate, 4 cm^3 of water, 0.05 cm^3 of 100% acetic acid, 3.3 g of 4-methylsulfanylpyridine, 6.5 cm^3 of 30% hydrogen peroxide and then 0.25 cm^3 of 32% aqueous ammonia and 1 cm^3 of 37.5% aqueous solution of sodium hydrogen sulfite. The crude oil obtained is crystallized with 10 cm^3 of diisopropyl ether, the crystals are filtered, drained and dried under reduced pressure (2.7 kPa). 2.6 g of 4-methylsulfonylpyridine are obtained in the form of white crystals.

4-Methylsulfanylpyridine may be prepared by carrying out the procedure as described in Example 20, starting with 11.0 g of 4-mercaptopyridine, 105 cm^3 of 1 N sodium hydroxide and 6.2 cm^3 of methyl iodide. The crude oil obtained is purified by distillation under reduced pressure. 4.0 g of 4-methylsulfanylpyridine are obtained in the form of a white paste, b.p. = 120°C/45 mm of mercury.

Example 23

1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)sulfonylmethyl]azetidine may be prepared by carrying out the procedure in the following manner: 78 mg of sodium borohydride are added, under argon, to a solution of 0.50 g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)sulfonylmethylene]azetidine dissolved in 25 cm^3 of anhydrous methanol and 25 cm^3 of anhydrous dichloromethane. After stirring for 24 hours, 80 cm^3 of water and 50 cm^3 of dichloromethane are added, the mixture is separated after settling, washed with 80 cm^3 of water and then 80 cm^3 of a saturated aqueous sodium chloride solution. The organic phase is dried with magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.02-0.04 mm, height 20 cm, diameter 14 cm), eluting under an argon pressure of 0.7 bar with a mixture of cyclohexane and ethyl acetate (90/10 by volume) and collecting 5-cm^3 fractions. Fractions 60 to 82 are combined and concentrated to dryness under

reduced pressure (2.7 kPa). 0.29 g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)sulfonyl-methyl]azetidine is obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : from 2.75 to 2.95 (mt : 1H); 2.88 (t, J = 7 Hz : 2H); 3.36 (t, J = Hz : 2H); 3.41 (d, J = 7 Hz : 2H); 4.26 (s : 1H); 7.13 (tt, J = 9 and 2.5 Hz : 1H); from 7.20 to 7.35 (mt : 8H); 7.44 (mt : 2H)].

Example 24

1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)sulfonylmethylene]azetidine may be prepared by carrying out the procedure in the following manner: 4.3 cm^3 of methylsulfonyl chloride are added to 18.8 g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)sulfonylmethyl]azetidin-3-ol dissolved in 800 cm^3 of dichloromethane at room temperature, followed, in small portions, by 16 g of 4-dimethylamino pyridine. After 22 hours, the reaction mixture is washed with 3 times 700 cm^3 of water and then 700 cm^3 of a saturated aqueous sodium chloride solution. The organic phase is dried with magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). The residue (25 g) is chromatographed on a silica gel column (particle size 0.02-0.04 mm, height 36 cm, diameter 8.5 cm) eluting under an argon pressure of 0.7 bar with a mixture of cyclohexane and ethyl acetate (90/10 by volume) and collecting 250-cm^3 fractions. Fractions 2 to 148 are combined and concentrated to dryness under reduced pressure (2.7

kPa). 2.79 g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)sulfonylmethylene]azetidine are obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 3.91 (mt : 2H); 4.28 (mt : 2H); 4.51 (s : 1H); 6.15 (mt : 1H); 7.08 (tt, J = 9 and 2.5 Hz : 1H); from 7.25 to 7.40 (mt : 8H); 7.40 (mt : 2H)].

1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)sulfonylmethyl]azetidin-3-ol may be prepared by carrying out the procedure in the following manner:

42.9 cm^3 of 1.6 M butyllithium in hexane are added dropwise to a solution of 13.2 g of (3,5-difluorophenyl)methyl sulfone in 800 cm^3 of tetrahydrofuran. After 0.5 hour at -70°C and 0.5 hour at -30°C, 14 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one dissolved in 150 cm^3 of tetrahydrofuran are added dropwise at -70°C. After 3 hours at -70°C, the reaction mixture is poured into a saturated ammonium chloride solution and extracted with ethyl acetate. The organic phase is washed twice with 400 cm^3 of water and then 400 cm^3 of a saturated aqueous sodium chloride solution, dried with magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). The residue (25.14 g) is chromatographed on a silica gel column (particle size 0.06-0.04 mm, height 31 cm, diameter 7.5 cm), eluting under an argon pressure of 0.5 bar with a mixture of cyclohexane and ethyl acetate (85/15 by volume) and collecting 200-cm^3 fractions. Fractions 13 to 16 are combined and concentrated to dryness under reduced pressure (2.7 kPa). After crystallization from

ethyl ether, filtration and drying, 4.5 g of 1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)sulfonylmethyl]azetidin-3-ol are obtained in the form of a white solid.

(3,5-Difluorophenyl)methyl sulfone may be prepared by carrying out the procedure in the following manner: 225 cm^3 of water and, in small quantities at 5°C, 56.3 g of oxone® are added to a solution of 13.3 g of (3,5-difluorophenyl)methylsulfide dissolved in 450 cm^3 of methanol. After 20 hours at room temperature, the reaction mixture is diluted with dichloromethane and water and separated after settling. The organic phase is washed twice with 700 cm^3 of water and then 700 cm^3 of a saturated aqueous sodium chloride solution, dried with magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). 13.2 g of (3,5-difluorophenyl)methyl sulfone are obtained in the form of a white solid.

(3,5-Difluorophenyl)methylsulfide may be prepared by carrying out the procedure in the following manner: 64 cm^3 of 1.6 M n-butyllithium in hexane are added dropwise at -70°C to 11.8 cm^3 of 1-bromo-3,5-difluorobenzene diluted in 200 cm^3 of ethyl ether. After 0.5 hour at -70°C, 14.2 g of S-methyl methylthiosulfonate dissolved in 60 cm^3 of tetrahydrofuran are added dropwise at -70°C. After 3 hours at -70°C and then 18 hours at room temperature, the reaction mixture is poured into a saturated ammonium chloride solution and extracted with ethyl

acetate. The organic phase is washed twice with 200 cm^3 of water and then 300 cm^3 of a saturated aqueous sodium chloride solution, dried with magnesium sulfate, filtered and then evaporated to dryness under reduced pressure (2.7 kPa). 13.3 g of (3,5-difluorophenyl)-methylsulfide are obtained in the form of a yellow oil.

Example 25

0.25 g of meta-chloroperbenzoic acid is added at room temperature to a solution of 0.40 g of 1-[bis(4-chlorophenyl)methyl]-3-(phenylsulfanyl)azetidine in 20 cm^3 of dichloromethane. After stirring for 3 hours at room temperature, the reaction mixture is washed with 30 cm^3 of a saturated sodium hydrogen carbonate solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). After chromatography on a silica gel column (particle size 0.06-0.200 mm, height 25 cm, diameter 2 cm), eluting under an argon pressure of 0.8 bar with an ethyl acetate/cyclohexane 20/80 by volume mixture and collecting 60-cm^3 fractions, fractions 9 to 16 are combined and concentrated to dryness under reduced pressure (2.7 kPa), taken up in heptane in order to isolate 100 mg of 1-[bis(4-chloro-phenyl)methyl]-3-[(RS)-phenylsulfinyl]azetidine in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 3.01 (broad t, J = 7.5 Hz : 1H); 3.32 (broad t, J = 7.5 Hz : 1H); 3.45 (broad t, J = 7.5 Hz : 2H); 3.59 (mt : 1H); 4.45 (broad s, : 1H); from 7.15 to 7.65 (mts : 13H)].

Example 26

1.2 g of oxone^{R} are added in several portions to a solution of 0.80 g of 1-[bis(4-chlorophenyl)methyl]-3-(phenylsulfanyl)azetidine in 3.4 cm^3 of water, 3.4 cm^3 of acetic acid, 3.4 cm^3 of ethanol and 1.7 cm^3 of sulfuric acid. After stirring for 20 hours at room temperature, the reaction mixture is diluted with 100 cm^3 of dichloromethane, washed with 3 times 100 cm^3 of water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). After chromatography on a silica gel column (particle size 0.06-0.200 mm, height 40 cm, diameter 2 cm), eluting under an argon pressure of 0.8 bar with an ethyl acetate/cyclohexane (20/80 by volume) mixture and collecting 60-cm^3 fractions, fractions 9 to 15 are combined and concentrated to dryness under reduced pressure (2.7 kPa), taken up in heptane, the solid filtered and dried in order to isolate 0.23 g of 1-[bis(4-chlorophenyl)methyl]-3-(phenylsulfonyl)azetidine in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : from 3.35 to 3.50 (mt : 4H); 3.96 (mt : 1H); 4.44 (s : 1H); from 7.20 to 7.35 (mt : 8H); 7.57 (broad t, J = 7.5 Hz : 2H); 7.68 (tt, J = 7.5 and 1.5 Hz : 1H); 7.88 (broad d, J = 7.5 Hz : 2H)].

Example 27

43.5 mg of sodium borohydride are added to a solution of 0.6 g of methyl 5-({1-[bis(4-chlorophenyl)-methyl]azetidin-3-ylidene}methylsulfonylmethyl)thien-2-

ylcarboxylate in 70 cm^3 of methanol cooled to around 0°C. The reaction medium is stirred for 15 minutes at this temperature, and then for 5 hours at 20°C before again being cooled to around 0°C and supplemented with 8.7 mg of sodium borohydride. After 18 hours at room temperature, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is supplemented with 100 cm^3 of dichloromethane and 20 cm^3 of distilled water. The mixture is separated after settling, the organic phase washed with twice 20 cm^3 of distilled water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is purified by flash chromatography on silica gel [eluent: cyclohexane/ethyl acetate (70/30 by volume)]. 0.18 g of methyl (RS)-5-({1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}methylsulfonylmethyl)thien-2-ylcarboxylate is obtained in the form of a white powder [^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm) : 2.60 (t, J = 7.5 Hz : 1H); 2.86 (s : 3H); 3.14 (mt : 2H); from 3.20 to 3.35 (mt : 1H); 3.45 (broad t, J = 7.5 Hz : 1H); 3.82 (s : 3H); 4.47 (s : 1H); 5.27 (d, J = 11 Hz : 1H); 7.28 (d, J = 4 Hz : 1H); from 7.30 to 7.50 (mt : 8H); 7.72 (d, J = 4 Hz : 1H)].

Methyl 5-({1-[bis(4-chlorophenyl)methyl]-azetidin-3-ylidene}methylsulfonylmethyl)thien-2-yl-carboxylate may be obtained in the following manner: 5.15 g of methyl 5-(methylsulfonylmethyl)thien-2-ylcarboxylate are added, at room temperature under an argon atmosphere, to a solution of 6.12 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one in 200 cm^3 of tetrahydrofuran and then the suspension obtained is cooled to -70°C. There are successively added 2.47 g of potassium *tert*-butoxide, and then after 1 hour 30 min at this temperature a solution of 1.7 cm^3 of methylsulfonylchloride in 8 cm^3 of ethyl ether over 2 minutes. The reaction medium is maintained for 1 hour at -70°C and then the temperature is allowed to rise to around 20°C before pouring in 80 cm^3 of distilled water. The tetrahydrofuran is expelled under reduced pressure and the aqueous residue obtained is extracted with 500 cm^3 of dichloromethane. The mixture is separated after settling, the organic phase is washed with 3 times 80 cm^3 of distilled water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is purified by flash chromatography on silica gel [eluent: cyclohexane/ethyl acetate (70/30 by volume)]. 1.6 g of methyl 5-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}methylsulfonylmethyl)thien-2-ylcarboxylate are obtained in the form of a cream-colored foam.

Methyl 5-(methylsulfonylmethyl)thien-2-ylcarboxylate may be obtained in the following manner: 31.7 g of sodium methyl sulfinate are added to a solution of 73 g of methyl 5-(bromomethyl)thien-2-ylcarboxylate in 150 cm^3 of ethanol and the suspension obtained is heated under reflux for 7 hours. The reaction medium is then concentrated to dryness under reduced pressure (2.7 kPa). The residue is extracted with four times 500 cm^3 of ethyl acetate, the combined organic phases are washed successively with 250 cm^3 of distilled water and 250 cm^3 of a saturated sodium chloride solution, dried over magnesium sulfate, filtered and incompletely concentrated under reduced pressure. The solid which appears is isolated by filtration, rinsed with three times 25 cm^3 of ice-cold ethyl acetate and provides 21.4 g of methyl 5-(methylsulfonylmethyl)thien-2-ylcarboxylate in the form of a cream-colored powder.

Methyl 5-(bromomethyl)thien-2-ylcarboxylate may be prepared according to the method described by Wityak J. et al., Bioorg. Med. Chem. Lett. (1995), 5(18), 2097-100.

Example 28

(RS)-1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylcyclopropylamine may be prepared in the following manner: 2.52 cm^3 of cyclopropylamine are added to a solution of 3 g of 1-[bis(4-chlorophenyl)methyl)]-3-

[(3,5-difluorophenyl)(methylsulfonyl)methylene]-azetidine in 30 cm^3 of dichloromethane, at a temperature in the region of 24°C, under an inert argon atmosphere. After 39 hours at a temperature in the region of 24°C, the reaction medium is concentrated under reduced pressure (3 mbar) at a temperature in the region of 40°C. 3.26 g of a pale yellow foam are thus obtained, which foam is taken up in 30 cm^3 of dichloromethane and 2.52 cm^3 of cyclopropylamine. The solution obtained is stirred at a temperature in the region of 21°C, under an inert argon atmosphere, for 87 hours and then concentrated under 3 mbar at a temperature in the region of 40°C. 3.64 g of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-3-ylcyclopropylamine are thus obtained in the form of a pale yellow foam. [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm) : 0.29 (mt : 1H); from 0.40 to 0.75 (mt : 3H); 2.50 (mt : 1H); 2.73 (s : 3H); 2.90 (unresolved complex : 1H); from 3.45 to 3.70 (mt : 3H); 4.36 (broad s : 1H); from 4.60 to 4.80 (broad unresolved complex : 1H); 6.87 (tt, J = 9 and 2.5 Hz : 1H); from 7.20 to 7.40 (mt : 10H)].

Example 29

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}-(2-pyrrolidin-1-ylethyl)amine may be prepared in the following manner: 0.076 cm^3 of 1-(2-aminoethyl)-pyrrolidine is added to a solution of 50 mg of 1-

[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)-(methylsulfonyl)methylene]azetidine in 0.5 cm^3 of dichloromethane, at a temperature in the region of 21°C, under an inert argon atmosphere. The solution obtained is stirred at a temperature in the region of 21°C, under an argon atmosphere, for 22 hours, concentrated under an air stream at a temperature in the region of 42°C and then the crude residue obtained is dried under reduced pressure (about 3 mbar) at a temperature in the region of 40°C. (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methyl-sulfonylmethyl]azetidin-3-yl}-(2-pyrrolidin-1-yl-ethyl)amine is obtained in the form of an ochre-colored foam. [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm); from 1.75 to 1.95 (mt : 4H); from 2.55 to 2.85 (mt : 6H); 2.79 (s : 3H); 2.91 (t, J = 6.5 Hz : 2H); 3.06 (d, J = 8.5 Hz : 1H); 3.17 (d, J = 8.5 Hz : 1H); 3.32 (d, J = 8.5 Hz : 1H); 3.41 (d, J = 8.5 Hz : 1H); 4.31 (s : 1H); 4.56 (s : 1H); 6.88 (tt, J = 8.5 and 2.5 Hz : 1H); 7.22 (s : 4H); 7.25 (s : 4H; 7.34 (mt : 2H)].

Example 30

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methanesulfonylmethyl]azetidin-3-yl}methylamine may be prepared according to Example 29, starting with 50 mg of 1-[bis(4-chorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]-azetidine, 0.5 cm^3 of dichloromethane and 0.3 cm^3 of a solution of methylamine in tetrahydrofuran (2 M

solution). (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}methylamine is obtained in the form of a yellow gum. [^{1}H NMR spectrum (400 MHz, $CDCl_3$ δ in ppm) : from 2.00 to 2.20 (broad unresolved complex : 1H); 2.62 (s : 3H); 2.76 (s : 3H); 3.04 (d, J = 9 Hz : 1H); 3.18 (d, J = 9 Hz : 1H); 3.37 (AB, J = 9 Hz : 2H); 4.31 (s : 1H); 4.55 (s : 1H); 6.89 (tt, J = 9 and 2.5 Hz : 1H); 7.22 (s : 4H); 7.24 (s : 4H); 7.32 (mt : 2H)].

Example 31

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}isobutylamine may be prepared according to Example 29, starting with 50 mg of 1-[bis(4-chlorophenyl)-methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)-methylene]azetidine, 0.5 cm^3 of dichloromethane and 0.0596 cm^3 of isobutylamine. (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonyl-methyl]azetidin-3-yl}isobutylamine is obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$ δ in ppm) : 1.01 (2d, J = 7 Hz : 6 H); from 1.70 to 2.15 (broad unresolved complex : 1H); 1.76 (mt : 1H); 2.51 (dd, J = 10.5 and 7 Hz : 1H); 2.76 (s : 3H); 2.80 (dd, J = 10.5 and 6 Hz : 1H); 3.01 (d, J = 8.5 Hz : 1H); 3.14 (d, J = 8.5 Hz : 1H); 3.32 (d, J = 8.5 Hz : 1H); 3.44 (d, J = 8.5 Hz : 1H); 4.31 (s : 1H); 4.58 (s : 1H); 6.88 (tt, J = 8.5 and 2.5 Hz : 1H); from 7.15 to 7.30 (mt : 8H); 7.35 (mt : 2H)].

Example 32

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}ethylamine may be prepared according to Example 29 starting with 50 mg of 1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]-azetidine, 0.5 cm^3 of dichloromethane and 0.3 cm^3 of a solution of ethylamine in tetrahydrofuran (2 M solution). (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}ethylamine is obtained in the form of a yellow gum [^{1}H NMR spectrum(300 MHz, $CDCl_3$ δ in ppm) : 1.22 (t, J = 7 Hz : 3 H); from 2.70 to 2.85 (mt : 2H); 2.77 (s : 3H); from 2.95 to 3.10 (unresolved complex : 1H); 3.05 (d, J = 8.5 Hz : 1H); 3.17 (d, J = 8.5 Hz : 1H); 3.33 (d, J = 8.5 Hz : 1H); 3.40 (d, J = 8.5 Hz : 1H); 4.30 (s : 1H); 4.54 (s : 1H); 6.89 (tt, J = 9 and 2.5 Hz : 1H); from 7.15 to 7.30 (mt : 8H); 7.34 (mt : 2H)].

Example 33

(RS)-N-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}-N',N'-dimethylethane-1,2-diamine may be prepared according to Example 29, starting with 50 mg of 1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)-(methylsulfonyl)methylene]azetidine, 0.5 cm^3 of dichloromethane and 0.0659 cm^3 of N,N-dimethylethylene-diamine. (RS)-N-{1-bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}-

N',N'-dimethylethane-1,2-diamine is obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$ δ in ppm) : 2.32 (s : 6H); 2.53 (t, J = 6 Hz : 2H); 2.79 (s : 3H); 2.94 (t, J = 6 Hz : 2H); 3.06 (d, J = 8.5 Hz : 1H); 3.16 (d, J = 8.5 Hz : 1H); 3.30 (d, J = 8.5 Hz : 1H); 3.41 (d, J = 8.5 Hz : 1H); 4.30 (s : 1H); 4.55 (s : 1H); 6.88 (tt, J = 9 and 2.5 Hz : 1H); 7.21 (s : 4H); 7.24 (s : 4H); 7.34 (mt : 2H)].

Example 34

(RS)-1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methanesulfonylmethyl]-3-methylazetidine may be prepared in the following manner: a few drops of pure methyl iodide are added, under an argon atmosphere at a temperature in the region of 24°C, to a suspension of 400 mg of magnesium turnings in 2.5 cm^3 of anhydrous diethyl ether, followed by 1 cm^3 of methyl iodide in solution in 22.5 cm^3 of diethyl ether. The suspension obtained is stirred for 30 minutes at a temperature in the region of 24°C and then cooled to a temperature in the region of 0°C with an ice + water mixture. 1.65 g of CuBr.Me_2S complex, are added, at a temperature in the region of 0°C, and then the reaction mixture is stirred for 15 minutes at a temperature in the region of 0°C. The yellow suspension obtained is added, at a temperature in the region of 0°C, to a solution of 0.5 g of 1-[Bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]-azetidine in a mixture of 1 cm^3 of tetrahydrofuran and

1 cm^3 of diethyl ether. The suspension obtained is stirred for 4 hours at a temperature in the region of 0°C and then at a temperature in the region of 25°C for 16 hours. The black suspension obtained is diluted with 100 cm^3 of ethyl acetate and 15 cm^3 of saturated aqueous ammonium chloride solution. The reaction mixture is filtered on sintered glass covered with Celite, the solid residue is rinsed with ethyl acetate and then with water. After decantation of the filtrate, the organic phase is separated, washed with 10 cm^3 of water, 10 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered on sintered glass and concentrated under reduced pressure (20 mbar) at a temperature in the region of 43°C. 550 mg of an orange-colored foam are thus obtained, which foam is purified by preparative thin-layer chromatography on silica [14 preparative Merck Kieselgel 60F254 plates; 20×20 cm; thickness 0.5 mm; deposition in solution in dichloromethane], eluting with a methanol-dichloromethane mixture (0.5-99.5 by volume). After elution of the zone corresponding to the desired product with a methanol-dichloromethane (15-85 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 290 mg of a white foam are obtained, which foam is dissolved in 15 cm^3 of anhydrous dichloromethane and reacted with 500 mg of thiophenol resin (supplier Argonaut, 1.45 mMol/g) and

1 g of ethylenediamine resin (0.8 mMol/g) for 38 hours at a temperature in the region of 20°C. The suspension is filtered on sintered glass, the resins are rinsed with dichloromethane and the filtrate is concentrated under reduced pressure (5 mbar) at a temperature in the region of 43°C. 272.8 mg of a white foam are obtained, which foam is dissolved in 2 cm^3 of dichloromethane and reacted with 1 cm^3 of ethylenediamine for 72 hours at a temperature in the region of 24°C. The crude residue obtained is taken up in 50 cm^3 of ethyl acetate and 10 cm^3 of water. After decantation, the organic phase is washed with 10 cm^3 of a 1 N aqueous hydrochloric acid solution, 10 cm^3 of a saturated aqueous sodium hydrogen carbonate solution, 10 cm^3 of water, 10 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered on sintered glass and concentrated under reduced pressure (8 mbar) at a temperature in the region of 42°C. 263.4 mg of a pale yellow foam are obtained, which foam is purified by preparative thin-layer chromatography on silica [7 preparative Merck Kieselgel 60F254 plates; 20×20 cm; thickness 0.5 mm; deposition in solution in dichloromethane], eluting with a methanol-dichloromethane mixture (0.5-99.5 by volume). After elution of the zone corresponding to the desired product with a methanol-dichloromethane (15-85 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a

temperature in the region of 40°C, 191.4 mg of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[([3,5-difluorophenyl)methylsulfonylmethyl]-3-methylazetidine are obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.75 (s : 3H); 2.67 (s : 3H); 2.74 (broad d, J = 7.5 Hz : 1H); 2.93 (d, J = 7.5 Hz : 1H); 3.21 (broad d, J = 7.5 Hz : 1H); 3.46 (d, J = 7.5 Hz : 1H); 4.33 (broad s : 2H); 6.87 (tt, J = 9 and 2.5 Hz : 1H); 7.12 (mt : 2H) from 7.15 to 7.35 (mt : 8H].

Example 35

(RS)-1-(2-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylsulfanyl}ethyl)-4-methylpiperazine may be prepared in the following manner: 128 mg of 1-(ethanethiol-2-yl)-4-methylpiperazine are added to a solution of 99 mg of 1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)-(methylsulfonyl)methylene]-azetidine in 2 cm^3 of dichloromethane, at a temperature in the region of 20°C. After stirring overnight at a temperature in the region of 20°C, 706 mg of Merrifield resin (1.7 mMol/g) are added. After stirring overnight at a temperature in the region of 20°C, the suspension is filtered and the resin is rinsed with twice 1 cm^3 of dichloromethane. The filtrate is concentrated under reduced pressure. 125 mg of a white oil are thus obtained, which oil is purified by chromatography on silica (13 cm^3 of 0.06-0.2 mm silica), eluting with a methanol-dichloromethane (0-100

and then 5-95 by volume) mixture. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure. 62 mg of (RS)-1-(2-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylsulfanyl}ethyl)-4-methylpiperazine are thus obtained in the form of white crystals [^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$ d6, δ in ppm): 2.15 (s : 3H); 2.30 and 2.41 (2mfs : 8H); 2.55 (mt : 2H); 2.85 (s : 3H); 3.02 (mt : 2H); 3.09 (d, J = 8.5 Hz : 1H); 3.38 (d, J = 8.5 Hz : 1H); 3.42 (d, J = 8.5 Hz : 1H); 3.79 (d, J = 8.5 Hz : 1H); 4.68 (s : 1H); 5.37 (s : 1H); from 7.30 to 7.50 (mt : 11H)].

Example 36

(RS)-(2-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylsulfanyl}ethyl)dimethylamine may be prepared by carrying out the procedure as in Example 35, starting with 99 mg of 1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]-azetidine, 2 cm^3 of dichloromethane, 84 mg of 2-(dimethylamino)ethanethiol and 706 mg of Merrifield resin (1.7 mMol/g). 36 mg of (RS)-(2-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-3-ylsulfanyl}ethyl)-dimethylamine are thus obtained in the form of an off-white powder.

Example 37

(RS)-{1-[[4-(Chloromethyl)phenyl]-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}ethylamine may be prepared in the following manner: A solution of 40 mg of (RS)-{1-[[4-(chloromethyl)phenyl]-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidine in 0.1125 cm^3 of ethylamine (2 M solution in tetrahydrofuran), containing a grain of sodium iodide, is stirred at a temperature in the region of 20°C for 2 hours and then diluted with 20 cm^3 of ethyl acetate and 5 cm^3 of a saturated aqueous sodium hydrogen carbonate solution. The separated organic phase is washed with 5 cm^3 of water, 5 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered on sintered glass and concentrated under reduced pressure (15 mbar) at a temperature in the region of 40°C. The yellow oil obtained is purified by preparative thin-layer chromatography on silica [2 preparative Merck Kieselgel 60F254 plates; 20×20 cm; thickness 0.5 mm; deposition in solution in dichloromethane], eluting with a methanol-dichloromethane mixture (3-97 by volume). After elution of the zone corresponding to the desired product with a methanol-dichloromethane (15-85 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 17 mg of (RS)-{1-[[4-

(chloromethyl)phenyl]-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}ethylamine are obtained in the form of a white solid [^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm): 1.11 (t, J = 7 Hz : 3H); from 2.10 to 3.55 (mt : 8H); 2.95 (s : 3H); 4.44 (s : 1H); 5.09 (s : 1H); from 7.10 to 7.55 (mt : 11H)].

(RS)-{1-[[4-(Chloromethyl)phenyl]-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin may be prepared in the following manner: 0.525 cm^3 of N,N-diisopropylethylamine is added, at a temperature in the region of 21°C, to a solution of 590 mg of (RS)-[4-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)phenyl]methanol in 5 cm^3 of anhydrous dichloromethane, followed by 0.19 cm^3 of methanesulfonyl chloride. After 1 hour at a temperature in the region of 21°C, 2 cm^3 of a methanol/dichloromethane (2.5/97.5 by volume) mixture are added and then after 5 minutes the reaction mixture is concentrated under reduced pressure (20 mbar) at a temperature in the region of 40°C. The yellow foam obtained is purified by chromatography on silica (50 g of 0.06-0.2 mm silica contained in a column 3 cm in diameter), eluting with a methanol/dichloromethane (0/100 and then 1/99 by volume) mixture, collecting 10-cm^3 fractions. The fractions containing only the desired product are combined and concentrated to dryness under reduced

pressure. 421.2 mg of (RS)-{1-[[4-(chloromethyl)-phenyl]-(4-chlorophenyl)methyl]-3-[(3,5-difluoro-phenyl)methylsulfonylmethylene]azetidine are thus obtained in the form of a yellow foam.

(RS)-[4-((4-Chlorophenyl)-{3-[(3,5-difluoro-phenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)-phenyl]methanol may be prepared in the following manner: 49 mg of sodium tetraborohydride are added portionwise to a solution of 420 mg of (RS)-[4-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methyl-sulfonylmethylene]azetidin-1-yl}methyl)benzaldehyde in 7 cm^3 of methanol, cooled to a temperature in the region of 0°C (ice + water). After 2 hours at a temperature in the region of 0°C, the reaction medium is concentrated under reduced pressure (15 mbar) at a temperature in the region of 35°C. The residue obtained is purified by chromatography on silica (40 g of 0.06-0.2 mm silica contained in a column 3 cm in diameter), eluting with a methanol/dichloromethane (1/99 and then 2.5/97.5 by volume) mixture, collecting 10-cm^3 fractions. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure. 418 mg of (RS)-[4-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethylene]azetidin-1-yl}methyl)phenyl]methanol are thus obtained in the form of a white foam.

Example 38

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-bistrifluoromethylphenyl)methylsulfonylmethyl]azetidin-3-yl}isobutylamine may be prepared according to Example 29 starting with 50 mg of 1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-bistrifluoromethylphenyl)(methylsulfonyl-methylene]azetidine, 0.5 cm^3 of dichloromethane and 0.05 cm^3 of isobutylamine. 57 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bistrifluoromethylphenyl)methylsulfonylmethyl]azetidin-3-yl}isobutylamine are obtained in the form of a pale yellow foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.01 (d, J = 7.5 Hz : 6H); 1.76 (mt : 1H); 2.47 (dd, J = 10.5 and 7.5 Hz : 1H); from 2.75 to 2.85 (mt : 1H); 2.79 (s : 3H); 2.82 (dd, J = 10.5 and 5.5 Hz : 1H); 3.00 (d, J = 9 Hz : 1H); 3.10 (d, J = 9 Hz : 1H); 3.31 (d, J = 9 Hz : 1H); 3.40 (d, J = 9 Hz : 1H); 4.30 (s : 1H); 4.74 (s : 1H); 7.13 (d, J = 8.5 Hz : 2H); from 7.15 to 7.25 (mt : 6H); 7.96 (broad s : 1H); 8.31 (broad s : 2H)].

Example 39

(RS)-1-[Bis(4-chlorophenyl)methyl]-3-cyano-3-[(3,5-difluorophenylmethylsulfonylmethyl]azetidine may be prepared in the following manner: 17 mg of potassium cyanide are added to a solution of 99 mg of 1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methyl-sulfonyl)methylene]azetidine in 2.5 cm^3 of dimethyl

sulfoxide, at a temperature in the region of 20°C. The yellow and then brown solution obtained is heated for 15 minutes at a temperature in the region of 40°C and then cooled to a temperature in the region of 20°C. The reaction medium is concentrated under reduced pressure and then taken up in 10 cm^3 of dichloromethane, washed with three times 5 cm^3 of water. The organic phase obtained is dried over magnesium sulfate, filtered and concentrated under reduced pressure. 100 mg of a yellow paste are thus obtained, which paste is purified by chromatography on silica (10 cm^3 of 0.06-0.2 mm silica contained in a column 1 cm in diameter), eluting with dichloromethane. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure. 60 mg of (RS)-1-[bis(4-chlorophenyl)methyl]-3-cyano-3-[(3,5-difluorophenyl-methylsulfonylmethyl]azetidine are thus obtained in the form of a yellow paste [^{1}H NMR spectrum (300 MHz, $(CD_3)_2SO$, d6, δ in ppm): 2.94 (s : 3H); 3.07 (d, J = 7.5 Hz : 1H); from 3.20 to 3.40 (mt : 1H); 3.61 (broad d, J = 7.5 Hz : 1H); 3.68 (broad d, J = 7.5 Hz : 1H); 4.64 (s : 1H); 5.51 (s : 1H); from 7.25 to 7.50 (mt : 11H)].

Example 40

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}-(1-cyclopropylethyl)amine may be prepared in the following manner: 0.03 cm^3 of cyclopropyl methyl

ketone, 0.006 cm^3 of acetic acid and then 32 mg of sodium triacetoxyborohydride are successively added to a solution of 53 mg of (RS)-C-{1-[bis(4-chlorophenyl)-methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-azetidin-3-yl}methylamine in 2 cm^3 of 1,2-dichloroethane at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for 18 hours and then 2 cm^3 of a saturated aqueous sodium hydrogen carbonate solution are added. After decantation, the organic phase is concentrated under reduced pressure. 60 mg of a viscous yellow oil are thus obtained, which oil is triturated with isopropyl ether and petroleum ether. After drying under 0.1 mbar, 55 mg of a residue are obtained which is purified by chromatography on silica (4 cm^3 of 0.06-0.2 mm silica contained in a column 1.2 cm in diameter), eluting with a methanol/dichloromethane (0/100 and then 5/95 by volume) mixture. The fractions containing only the desired product are combined, concentrated to dryness under reduced pressure and repurified by chromatography on silica (4 cm^3 of 0.04-0.063 mm silica contained in a column 1.2 cm in diameter), eluting with a methanol/dichloromethane (0/100 and then 1/99 by volume) mixture. The fractions containing only the desired product are combined and concentrated to dryness. 20 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}-(1-cyclopropylethyl)amine are thus obtained

[^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): a mixture of diastereoisomers is observed, from 0.00 to 0.30 and from 0.40 to 0.80 (mts : 5H); 1.09 and 1.17 (2d, J = 6.5 Hz : 3H in total); 1.87 (mt : 1H); from 2.55 to 2.75-from 2.75 to 2.95 and from 3.25 to 3.55 (mts : 4H); 2.68 (s : 3H); 3.12 (d, J = 8.5 Hz : 1H); from 3.80 to 3.90 (mt : 1H); 4.42 and 4.43 (2s : 1H in total); 4.79 and 4.84 (2s : 1H in total); 6.89 (tt, J = 9 and 2.5 Hz : 1H); 7.16 (mt : 2H); from 7.15 to 7.35 (mt : 8H]).

(RS)-C-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}methylamine may be prepared in the following manner: 1.27 cm^3 of a 1.5 M solution of diisobutylaluminum hydride in tetrahydrofuran are added dropwise to a solution of 250 mg of (RS)-1-[bis(4-chlorophenyl)-methyl]-3-cyano-3-[(3,5-difluorophenyl)methylsulfonyl-methyl]azetidine in 10 cm^3 of anhydrous tetrahydrofuran, cooled to a temperature in the region of 0°C. After 30 minutes at a temperature in the region of 0°C and then 4 hours at a temperature in the region of 20°C, the solution is again cooled to a temperature of 0°C. 6.35 cm^3 of water and then 1.06 cm^3 of aqueous hydrochloric acid (12 N) are added successively. After decantation, the aqueous phase is extracted with three times 10 cm^3 of ethyl acetate. The organic phases are combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. 0.42 g of a dark

yellow oil is thus obtained which is purified by chromatography on silica (40 cm^3 of 0.063-0.2 mm silica contained in a column 2.7 cm in diameter), eluting with a methanol/dichloromethane (0/100 and then 5/95 by volume) mixture. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure. 110 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}methylamine are thus obtained.

Example 41

(RS)-N-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}isobutyramide may be prepared in the following manner: 0.0187 cm^3 of isobutyric acid, 0.032 cm^3 of 1,3-diisopropylcarbodiimide and 2.5 mg of 4-dimethylaminopyridine are successively added to a solution of 53 mg of (RS)-C-{1-[bis(4-chlorophenyl)-methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-azetidin-3-yl}methylamine in 2 cm^3 of anhydrous dichloromethane at a temperature in the region of 20°C. After stirring for 72 hours at a temperature in the region of 20°C, 2 cm^3 of water are added, the mixture is separated after settling and then the organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The crude residue obtained is purified by preparative thin-layer chromatography on silica [1 preparative Merck Kieselgel

60F254 plate; 20×20 cm; thickness 1 mm], eluting with an ethyl acetate-dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product, filtration on sintered glass and then evaporation of the solvent under reduced pressure at a temperature in the region of 40°C, 16 mg of (RS)-N-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-3-ylmethyl}isobutyramide are obtained in the form of a pale yellow powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.22 (d, J = 7 Hz : 6H); 2.46 (mt : 1H); 2.69 (s : 3H); 2.99 (d, J = 8.5 Hz : 1H); 3.23 (AB, J = 8.5 Hz : 2H); 3.40 (d, J = 8.5 Hz : 1H); 3.57 (dd, J = 14 and 4.5 Hz : 1H); 4.09 (dd, J = 14 and 7.5 Hz : 1H); 4.34 (s : 1H); 4.35 (s : 1H); 6.71 (dd, J = 7.5 and 4.5 Hz : 1H); 6.95 (tt, J = 9 and 2.5 Hz : 1H); from 7.10 to 7.35 (mt : 10H)].

Example 42

(RS)-N-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}cyclopropanecarboxamide may be prepared in a manner similar to Example 39, starting with 53 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluoro-phenyl)methanesulfonylmethyl]azetidin-3-yl}methylamine, 2 cm^3 of anhydrous dichloromethane, 0.0167 cm^3 of cyclopropanecarboxylic acid, 0.032 cm^3 of 1,3-diisopropylcarbodiimide and 2.5 mg of 4-dimethylaminopyridine. 28 mg of (RS)-N-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-

methylsulfonylmethyl]azetidin-3-ylmethyl}-cyclopropanecarboxamide are obtained in the form of a beige powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.81 (mt : 2H); 1.01 (mt : 2H); from 1.35 to 1.55 (mt : 1H); 2.70 (s : 3H); 3.02 (d, J = 8.5 Hz : 1H); 3.21 (limiting AB, J = 8 Hz : 2H); 3.45 (d, J = 8.5 Hz : 1H); 3.62 (dd, J = 14 and 4.5 Hz : 1H); 4.10 (dd, J = 14 and 7.5 Hz); 4.31 (s : 1H); 4.36 (s : 1H); 6.75 (dd, J = 7.5 and 4.5 Hz : 1H); 6.95 (tt, J = 9 and 2 Hz : 1H); from 7.15 to 7.35 (mt : 10H)].

Example 43

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}diethylamine may be prepared in a manner similar to Example 40, starting with 53 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}methylamine, 2 cm^3 of 1,2-dichloroethane, 0.017 cm^3 of acetaldehyde, 0.006 cm^3 of acetic acid and 32 mg of sodium triacetoxyborohydride. 12 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}diethylamine are thus obtained in the form of an off-white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.00 (t, J = 7 Hz : 6H); 2.49 (q, J = 7 Hz : 4H); 2.54 (d, J = 13.5 Hz : 1H); 2.69 (s : 3H); 2.76 (broad d, J = 7.5 Hz : 1H); 3.07 (broad d, J = 7.5 Hz : 1H); 3.15 (d, J = 13.5 Hz : 1H); 3.24 (broad d, J = 7.5 Hz : 1H); 4.06 (broad d,

J = 7.5 Hz : 1H): 4.35 (s : 1H); 5.02 (s : 1H); 6.91 (mt : 1H); from 7.15 to 7.40 (mt : 10H)].

Example 44

(RS)-N-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}methanesulfonamide may be prepared in the following manner: 150 mg of anhydrous IRA-68 resin are added to a solution of 53 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-3-yl}methylamine in 2 cm^3 of ethyl acetate, at a temperature in the region of 20°C, followed by 0.012 cm^3 of methylsulfonyl chloride. After stirring overnight at a temperature in the region of 20°C, 0.001 cm^3 of water and then 150 mg of anhydrous IRA-68 resin are added. After stirring for 1 hour at a temperature in the region of 20°C, the reaction mixture is filtered and the filtrate is concentrated under reduced pressure. 81 mg of a yellow paste are thus obtained, which paste is purified by preparative thin-layer chromatography on silica [1 preparative Merck Kieselgel 60F254 plate; 20×20 cm; thickness 1 mm], eluting with an ethyl acetate-dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product, filtration on sintered glass and evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 25 mg of (RS)-N-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-

ylmethyl}methanesulfonamide are obtained in the form of a pale yellow powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.70 (s : 3H); from 2.95 to 3.10 (mt : 2H); 3.05 (s : 3H); 3.22 (broad d, J = 8 Hz : 1H); 3.52 (d, J = 8 Hz : 1H); 3.74 (dd, J = 13.5 and 8 Hz : 1H); 3.90 (dd, J = 13.5 and 5.5 Hz : 1H); 4.23 (s : 1H); 4.46 (s : 1H); 5.54 (mt : 1H); 7.00 (tt, J = 9 and 2 Hz : 1H); from 7.05 to 7.35 (mt : 10H)].

Example 45

(RS)-1-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}-3-isopropylurea may be prepared in the following manner: 0.0197 cm^3 of isopropyl isocyanate is added to a solution of 53 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}methylamine in 2 cm^3 of dichloromethane, at a temperature in the region of 20°C. After stirring overnight at a temperature in the region of 20°C, 0.05 cm^3 of water is added and then after stirring for 15 minutes at a temperature in the region of 20°C, the reaction mixture is dried over magnesium sulfate, filtered and concentrated under reduced pressure. The residue obtained (75 mg) is purified by preparative thin-layer chromatography on silica [1 preparative Merck Kieselgel 60F254 plate; 20×20 cm; thickness 1 mm], eluting with an ethyl acetate-dichloromethane (5-95 by volume) mixture. After elution of the zone

corresponding to the desired product, filtration on sintered glass and then evaporation of the solvent under reduced pressure at a temperature in the region of 40°C, 16 mg of (RS)-1-{1-[bis(4-chlorophenyl)-methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-azetidin-3-ylmethyl}-3-isopropylurea are obtained in the form of a pale yellow powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.17 (d, J = 7 Hz : 6H); 2.68 (s : 3H); 3.00 (broad d, J = 8.5 Hz : 1H); 3.11 (d, J = 8.5 Hz : 1H); 3.17 (d, J = 8.5 Hz : 1H); 3.46 (broad d, J = 8.5 Hz : 1H); 3.64 (dd, J = 14 and 5 Hz : 1H); 3.86 (mt : 1H); 3.96 (dd, J = 14 and 7.5 Hz : 1H); 4.15 (d, J = 8 Hz : 1H); 4.29 (s : 1H); 4.43 (s : 1H); 5.11 (mt : 1H); 6.94 (tt, J = 9 and 2 Hz : 1H); from 7.10 to 7.30 (mt : 10H)].

Example 46

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}carbamic acid isobutyl ester may be prepared in the following manner: 0.016 cm^3 of isobutyl chloroformate is added to a solution of 53 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluoro-phenylmethylsulfonylmethyl]azetidin-3-yl}methylamine in 2 cm^3 of pyridine, at a temperature in the region of 20°C. After stirring overnight at a temperature in the region of 20°C, the reaction mixture is concentrated under reduced pressure. 68 mg of a yellow paste are obtained, which paste is purified by preparative thin-

layer chromatography on silica gel [1 preparative Merck Kieselgel 60F254 plate; 20x20 cm; thickness 1 mm], eluting with an ethyl acetate-dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 14 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}carbamic acid isobutyl ester are obtained in the form of an off-white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.96 (d, J = 7 Hz : 6H); 1.95 (mt : 1H); 2.68 (s : 3H); 3.04 (d, J = 8.5 Hz : 1H); 3.19 (s : 2H); 3.51 (d, J = 8 Hz : 1H); 3.75 (dd, J = 14 and 5 Hz : 1H); from 3.80 to 4.00 (mt : 3H); 4.30 (s : 1H); 4.34 (s : 1H); 5.63 (unresolved complex: 1H); 6.95 (tt, J = 9 and 2 Hz : 1H); from 7.10 to 7.30 (mt : 10H)].

Example 47

(RS)-{1-[Bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-ylmethyl}dimethylamine may be prepared in the following manner: 138 mg of potassium carbonate are added, at a temperature in the region of 20°C, to a solution of 52 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-3-yl}methylamine in 2 cm^3 of acetonitrile, followed by 0.0075 cm^3 of methyl iodide. After stirring overnight at

temperature in the region of 20°C, the reaction medium is filtered on sintered glass, the solid is rinsed with dichloromethane and the filtrate is concentrated under reduced pressure. The crude residue obtained (90 mg) is purified by preparative thin-layer chromatography on silica [1 preparative Merck Kieselgel 60F254 plate; 20×20 cm; thickness 1 mm], eluting with an ethyl acetate-dichloromethane (5-95 by volume) mixture. After elution of the zone corresponding to the desired product, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 11 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-3-ylmethyl}dimethylamine are obtained [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.18 (s : 6H); 2.30 (d, J = 13 Hz : 1H); from 4.65 to 4.78 (mt : 1H); 2.70 (s : 3H); 2.98 (d, J = 13 Hz : 1H); 3.09 (d, J = 8 Hz : 1H); 3.32 (d, J = 7.5 Hz : 1H); 4.11 (d, J = 8 Hz : 1H); 4.35 (s : 1H); 4.94 (s : 1H); 6.92 (mt : 1H); from 7.10 to 7.40 (mt : 10H)].

Example 48

(RS)-1-[Bis(4-chlorophenyl)methyl]-3-[(4-methoxyphenyl)methylsulfonylmethyl]azetidine may be prepared in the following manner: 25.5 mg of sodium tetraborohydride are added to a solution of 400 mg of 1-[bis(4-chlorophenyl)methyl]-3-[(4-methoxyphenyl)-methylsulfonylmethylene]azetidine in 4.5 cm^3 of ethanol,

under an argon atmosphere, at a temperature in the region of 20°C. After stirring for 16 hours at a temperature in the region of 20°C, 26 mg of sodium tetraborohydride are added. The reaction medium is stirred at a temperature in the region of 20°C for 4.5 hours and then at a temperature in the region of 50°C for 3 hours. After cooling to a temperature in the region of 20°C, the reaction medium is concentrated under reduced pressure. The white deposit obtained is taken up in 2 cm^3 of water and 2 cm^3 of dichloromethane. After decantation, the organic phase is concentrated under reduced pressure and the yellow foam obtained is purified by preparative thin-layer chromatography on silica [2 preparative Merck Kieselgel 60F254 plates, 20×20 cm; thickness 0.5 mm], eluting with a methanol-dichloromethane (1-99 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol-dichloromethane (10-90 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 14 mg of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[(4-methoxyphenyl)methylsulfonylmethyl]azetidine are obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.56 (mt : 1H); 2.58 (s : 3H); 3.20 (mt : 2H); from 3.35 to 3.55 (mt : 1H); 3.66 (broad t, J = 7.5 Hz : 1H); 3.81 (s : 3H); 4.21 (d, J = 4.5 Hz : 1H); 4.26 (broad s :

1H); 6.90 (d, J = 8.5 Hz : 2H); from 7.15 to 7.40 (mt : 10H)].

1-[Bis(4-chlorophenyl)methyl]-3-[(4-methoxyphenyl)methylsulfonylmethylene]azetidine may be prepared by carrying out the procedure as described in Example 1, starting with 1 g of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[methylsulfonyl-(4-methoxyphenyl)methyl]azetidin-3-ol, 20 cm^3 of dichloromethane, 0.229 cm^3 of methylsulfonyl chloride and 722 mg of 4-dimethylaminopyridine. After purification by chromatography on silica at atmospheric pressure (100 g of silica, particle size 0.063-0.2 mm contained in a column 3 cm in diameter), eluting with dichloromethane), the fractions containing only the desired product are combined and concentrated to dryness under reduced pressure. 650 mg of 1-[bis(4-chlorophenyl)methyl]-3-[(4-methoxyphenyl)methyl-sulfonylmethylene]azetidine are thus obtained in the form of a yellow gum.

(RS)-1-[Bis(4-chlorophenyl)methyl]-3-[methylsulfonyl-(4-methoxyphenyl)methyl]azetidin-3-ol may be prepared by carrying out the procedure as described in Example 1, starting with 19.6 cm^3 of 1.6 N n-butyllithium in solution in hexane, 5.7 g of 4-methoxybenzyl methyl sulfone and 8.71 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one in 450 cm^3 of tetrahydrofuran. 8.3 g of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[methylsulfonyl-(4-methoxyphenyl)-

methyl]azetidin-3-ol are thus obtained in the form of a beige solid.

4-Methoxybenzyl methyl sulfone may be prepared by carrying out the procedure as described in Example 27, starting with 13.6 cm^3 of 4-methoxybenzyl chloride, 30 mg of sodium iodide, 14.4 g of sodium methyl sulfinate in 125 cm^3 of ethanol. 5.75 g of 4-methoxybenzyl methyl sulfone are thus obtained in the form of a white powder.

Example 49

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetyl-morpholine may be prepared in the following manner: 252 mg of supported EDCI (2.3 equivalents, the supported EDCI reagent is commercially available, and may also be prepared according to the following reference: M. Desai, L. Stramiello, Tetrahedron Letters, 34, 48, 7685-7688 (1993)), 2 cm^3 of anhydrous dichloromethane, 0.006 cm^3 or morpholine and then 0.010 cm^3 of triethylamine are successively added, at a temperature in the region of 20°C, to 37 mg of (RS-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride. After stirring for 12 hours at a temperature in the region of 20°C, the reaction mixture is filtered on sintered glass. The filtrate is washed with 2 cm^3 of water, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at a

temperature in the region of 20°C. 15 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetylmorpholine are thus obtained in the form of a beige foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 2.60 to 3.80 (mt : 13H); 3.93 (d, J = 10 Hz : 1H); 4.27 (s : 1H) from 6.65 to 6.85 (mt : 3H) from 7.20 to 7.40 (mt : 8H)].

Example 50

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexyl-acetamide may be prepared in the following manner: 0.070 cm^3 of cyclohexylamine, 144 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.141 cm^3 of triethylamine and then 4 mg of hydroxybenzotriazole hydrate are successively added to a solution of 250 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 10 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (25 cm^3) filled with 12 g of fine silica (0.040-0.063 mm), conditioned and then eluted with a dichloromethane-petroleum ether (80-20 by volume) mixture with the aid of a Duramat pump, collecting 1.5-cm^3 fractions. Fractions 11 to 17 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 169 mg of (RS)-2-{1-[bis(4-

chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylacetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 0.90 to 1.45 (mt : 6H); from 1.50 to 1.90 (mt : 4H); 2.66 (mt : 1H); 2.90 (mt : 1H) from 3.00 to 3.15 (mt : 2H); 3.42 (broad t, J = 7.5 Hz : 1H); 3.52 (d, J = 10.5 Hz : 1H); from 3.60 to 3.80 (mt : 1H); 4.27 (s : 1H); 5.25 (broad d, J = 8 Hz : 1H); 6.90 (tt, J = 9 and 2.5 Hz : 1H); 6.82 (mt : 2H); from 7.20 to 7.35 (mt : 8H].

Example 51

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetylpiperidine may be prepared in the following manner: 0.012 cm^3 of piperidine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), eluting with dichloromethane with the aid of a Duramat pump. The fractions between 8 and 15 cm^3 are combined and concentrated to dryness under reduced pressure

(2.7 kPa) at 40°C. 14 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetylpiperidine are thus obtained in the form of a white crystalline powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 0.95 to 1.15 and from 1.30 to 1.50 (2mts : 6H in total); 2.74 (mt : 2H); from 3.00 to 3.15 (mt : 2H) from 3.30 to 3.45 (mt : 4H); from 3.55 to 3.70 (mt : 1H); 3.95 (d, J = 10 Hz : 1H); 4.26 (s : 1H); 6.68 (tt, J = 9 and 2.5 Hz : 1H); 6.80 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 52

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetyl-pyrrolidine may be prepared in the following manner: 0.010 cm^3 of pyrrolidine and 0.023 cm^3 of diisopropylcarbodiimide, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), eluting with dichloromethane with the aid of a Duramat pump. The fractions between 11 and 19 cm^3 are combined and concentrated to dryness under reduced pressure

(2.7 kPa) at 40°C. 29 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetylpyrrolidine are thus obtained in the form of a white foam [^{1}HNMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 1.75 to 2.00 (mt : 4H); 2.74 (mt : 2H); from 3.00 to 3.30 (mt : 3H); from 3.35 to 3.60 (mt : 4H); 3.80 (d, J = 10.5 Hz : 1H); 4.25 (s : 1H); 6.68 (tt, J = 9 and 2.5 Hz : 1H); 6.84 (mt : 2H); from 7.20 to 7.40 (mt : 8H)].

Example 53

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropyl-acetamide may be prepared in the following manner: 0.009 cm^3 of cyclopropylamine, 29 mg of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned and then eluted with dichloromethane with the aid of a Duramat pump, collecting 2-cm^3 fractions. Fractions 2 to 6 are combined and concentrated to dryness under reduced

pressure (2.7 kPa) at 40°C. 29 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylacetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.40 (mt : 2H); 0.74 (mt : 2H); 2.64 (mt : 2H); 2.89 (dd, J = 7.5 and 5 Hz : 1H); 3.08 (mt : 2H); 3.42 (broad t, J = 7.5 Hz : 1H); 3.51 (d, J = 10.5 Hz : 1H); 4.25 (s : 1H); 5.50 (unresolved complex : 1H); 6.70 (tt, J = 9 and 2.5 Hz : 1H); 6.81 (mt : 2H) from 7.15 to 7.35 (mt : 8H)].

Example 54

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexyl-N-methylacetamide may be prepared in the following manner: 0.016 cm^3 of N-methylcyclohexylamine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned and eluted with dichloromethane with the aid of a Duramat pump, collecting 2-cm^3 fractions. Fractions 4 to 6 are

combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 17 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexyl-N-methylacetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (250 MHz, $(CD_3)_2SO$ d6, at a temperature of 373K, δ in ppm): from 0.98 to 1.85 (mt : 10H); from 2.60 to 3.05 (mt : 8H); (broad t, J = 7.5 Hz : 1H); 4.25 (broad d, J = 9 Hz : 1H); 4.45 (s : 1H); 7.00 (mt : 3H); from 7.25 to 7.45 (mt : 8H)].

Example 55

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(tetrahydrofuran-2-ylmethyl)acetamide may be prepared in the following manner: 0.013 cm^3 of tetrahydrofurylamine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-bis(4-chlorophenyl)-methyl]azetidin-3-yl]-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned and then eluted with dichloromethane with the aid of a Duramat pump, collecting 2-cm^3 fractions. Fractions 3 to 8 are

combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 27 mg of 2(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(tetrahydrofuran-2-ylmethyl)acetamide are thus obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 1.65 to 1.95 (mt : 4H); 2.64 (mt : 1H); 2.89 (dd, J = 7.5 and 5.5 Hz : 1H); from 3.00 to 3.20 (mt : 3H); from 3.30 to 3.60 (mt : 2H); 3.58 (d, J = 10.5 Hz : 1H); from 3.65 to 3.95 (mt : 3H); 4.25 (s : 1H); 5.81 (mt : 1H); 6.68 (tt, J = 9 and 2.5 Hz : 1H); 6.82 (mt : 2H); from 7.15 to 7.35 (mt : 8H)].

Example 56

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(2-morpholin-4-ylethyl)acetamide may be prepared in the following manner: 0.016 cm^3 of aminoethylmorpholine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned with

dichloromethane with the aid of a Duramat pump, eluted successively with a dichloromethane-ethyl acetate (70-30 by volume) mixture, collecting 2-cm^3 fractions for fractions 1 to 12, and then with a dichloromethane-methanol (98-2 by volume) mixture, collecting 2-cm^3 fractions for fractions 12 to 27. Fractions 13 to 27 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 34 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(2-morpholin-4-ylethyl)acetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.33 (broad t, J = 5 Hz : 4H); 2.38 (t, J = 7 Hz : 2H); 2.65 (mt : 1H); from 2.85 to 3.20 (mt : 3H); 3.25 (broad q, J = 7 Hz : 2H); 3.43 (mt : 1H); 3.57 (t, J = 5 Hz : 4H); 3.61 (d, J = 10.5 Hz : 1H); 4.26 (s : 1H); 5.98 (unresolved complex: 1H); 6.70 (tt, J = 9 and 2.5 Hz : 1H); 6.83 (mt : 2H); from 7.15 to 7.35 (mt : 8H)].

Example 57

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(1-ethyl-pyrrolidin-2-ylmethyl)acetamide may be prepared in the following manner: 0.018 cm^3 of aminomethylethyl-pyrrolidine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-

(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (of 12 mm in diameter) filled with 4 cm^3 of silica (0.060-0.200 mm), conditioned with dichloromethane with the aid of a vacuum apparatus, eluting with dichloromethane between 0 and 6 cm^3 and then with a dichloromethane-methanol (95-5 by volume) mixture. The fractions containing the desired product are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C for 2 hours. The yellow paste thus obtained is taken up in 2 cm^3 of ethyl acetate and then with 2 cm^3 of distilled water. After stirring, the mixture is frozen, the organic phase is concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. The residue obtained is taken up in 2 cm^3 of diisopropyl ether and is then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 38 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(1-ethylpyrrolidin-2-ylmethyl)acetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$ with addition of a few drops of CD_3COOD d4, δ in ppm): 0.96 and 1.17 (2t, J = 7.5 Hz : 3H in total); from 1.60 to 2.00 (mt : 4H); from 2.50 to 2.95-from 3.10 to 3.85 (mts : 11H); from 3.95 to 4.10 (mt : 1H); 4.10 and 4.14

(2d, J = 10.5 Hz : 1H in total); 5.18 and 5.25 (2 broad s : 1H in total); 6.66 (mt : 1H); from 6.80 to 7.00 (mt : 2H); from 7.15 to 7.45 (mt : 8H)].

Example 58

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isobutyl-acetamide may be prepared in the following manner: 0.012 cm^3 of isobutylamine, 29 mg of 1-(3-dimethyl-aminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chloro-phenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (of 12 mm in diameter) filled with 5 cm^3 of silica (0.060-0.200 mm), conditioned in dichloromethane with the aid of a vacuum apparatus, eluting with dichloromethane between 0 and 6 cm^3 and then with a dichloromethane-ethyl acetate (95-5 by volume) mixture. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 40 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isobutylacetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum

(300 MHz, $(CD_3)_2SO$ d6 δ in ppm): 0.75 (d, J = 7.5 Hz : 6H); 1.62 (mt : 1H); 2.61 (mt : 1H); from 2.70 to 2.95 (mt : 3H); 3.03 (mt : 2H); 3.22 (broad t, J = 7 Hz : 1H); 3.83 (d, J = 10.5 Hz : 1H); 4.45 (s : 1H); 7.00 (mt : 2H); 7.08 (tt, J = 9 and 2.5 Hz : 1H); from 7.25 to 7.45 (mt : 8H); 8.11 (t, J = 6 Hz : 1H)].

Example 59

(RS)-2-{1-[Bis(4-chlorophenyl)-methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N,N-dimethylacetamide may be prepared in the following manner: 0.06 cm^3 of dimethylamine in 2 M solution in tetrahydrofuran, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (of 12 mm in diameter) filled with 4.4 cm^3 of silica (0.060-0.200 mm), conditioned in dichloromethane with the aid of a vacuum apparatus, eluting with dichloromethane between 0 and 6 cm^3 and then with a dichloromethane-ethyl acetate (95-5 by volume) mixture. The fractions containing only the desired product are combined and concentrated to dryness under reduced

pressure (2.7 kPa) at 40°C. 13 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N,N-dimethylacetamide are thus obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 2.70 to 2.80 (mt : 2H); 2.92 (s : 3H); 2.95 (s : 3H); from 3.00 to 3.15 (mt : 2H); 3.38 (broad t, J = 7.5 Hz : 1H); 3.96 (d, J = 10 Hz : 1H); 4.26 (s : 1H); 6.69 (tt, J = 9 and 2.5 Hz : 1H); 6.81 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 60

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-benzylacetamide may be prepared in the following manner: 0.013 cm^3 of benzylamine, 29 mg of 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction mixture is deposited on a Varian cartridge (of 12 mm in diameter) filled with 4.4 cm^3 of silica (0.060-0.200 mm) conditioned in dichloromethane with the aid of a vacuum apparatus, eluting with dichloromethane between 0 and 6 cm^3 and then with a dichloromethane-ethyl acetate (95-5 by volume) mixture.

The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 37 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-benzylacetamide are thus obtained in the form of white crystals [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.67 (mt : 1H); 2.93 (mt : 1H) : 3.11 (mt : 2H); 3.43 (broad t, J = 7.5 Hz : 1H); 3.62 (d, J = 10.5 Hz : 1H); 4.26 (s : 1H); 4.38 (mt : 2H); 5.71 (mt : 1H); 6.71 (broad t, J = 9 Hz : 1H); 6.83 (mt : 2H); from 7.10 to 7.40 (mt : 13H)].

Example 61

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylmethylacetamide may be prepared in the following manner: 0.016 cm^3 of aminomethylcyclohexane, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of {1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned and then eluted with dichloromethane with the aid of a Duramat

pump, collecting 2-cm^3 fractions. Fractions 2 to 3 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 49 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylmethylacetamide are thus obtained in the form of a white foam [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 0.75 to 1.75 (mt : 11H); 2.65 (mt : 1H); from 2.85 to 3.15 (mt : 5H); 3.42 (broad t, J = 7.5 Hz : 1H); 3.57 (d, J = 10.5 Hz : 1H); 4.27 (s : 1H); 5.40 (mt : 1H); 6.71 (broad t, J = 9 Hz : 1H); 6.83 (mt : 2H); from 7.15 to 7.40 (mt : 8H)].

Example 62

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-[3-(2-oxopyrrolidin-1-yl)propyl]acetamide may be prepared in the following manner: 0.017 cm^3 of aminopropyl-pyrrolidinone, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned and then eluted with dichloromethane with

the aid of a Duramat pump, collecting 2-cm^3 fractions. Fractions 4 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 35 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-[3-(2-oxopyrrolidin-1-yl)propyl]acetamide are thus obtained in the form of a white foam [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 1.50 to 1.65 (mt : 2H); 2.04 (mt : 2H); 2.43 (t, J = 8 Hz : 2H); 2.64 (mt : 1H); 2.88 (dd, J = 7.5 and 5.5 Hz : 1H); from 3.00 to 3.30 (mt : 6H); from 3.30 to 3.45 (mt : 3H); 3.64 (d, J = 10.5 Hz : 1H); 4.27 (s : 1H); 6.67 (tt, J = 9 and 2.5 Hz : 1H); 6.90 (mt : 2H); 7.15 (t, J = 6 Hz : 1H); from 7.20 to 7.35 (mt : 8H)].

Example 63

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetyl(4-methylpiperazine) may be prepared in the following manner: 0.013 cm^3 of N-methylpiperazine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g

of fine silica (0.040-0.063 mm), conditioned with dichloromethane with the aid of a Duramat pump, eluted with a dichloromethane-ethanol (98-02 by volume) mixture, collecting 2-cm^3 fractions. Fractions 10 to 24 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 39 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetyl(4-methylpiperazine) are thus obtained in the form of a white foam [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.83 (mt : 1H); from 2.10 to 2.45 (mt : 3H); 2.21 (s : 3H); 2.74 (mt : 2H); from 2.95 to 3.15 (mt : 2H); from 3.30 to 3.55 (mt : 4H); 3.73 (mt : 1H); 3.93 (d, J = 10 Hz : 1H); 4.25 (s : 1H); 6.69 (tt, J = 9 and 2.5 Hz : 1H); 6.78 (mt : 2H); from 7.15 to 7.35 (mt : 8H)].

Example 64

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(2,2-dimethyl-propyl)acetamide may be prepared in the following manner: 0.014 cm^3 of neopentylamine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of

20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned with dichloromethane with the aid of a Duramat pump, eluted with a dichloromethane-petroleum ether (80-20 by volume) mixture, collecting 1.5-cm^3 fractions. Fractions 4 to 8 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 40 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(2,2-dimethylpropyl)acetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.81 (s : 9H); 2.66 (mt : 1H); from 2.90 to 3.20 (mt : 5H); 3.44 (broad t, J = 7.5 Hz : 1H); 3.61 (d, J = 10.5 Hz : 1H) : 4.28 (s : 1H); 5.40 (mt : 1H); 6.72 (tt, J = 9 and 2.5 Hz : 1H); 6.85 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 65

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(2-pyrrolidin-1-ylethyl)acetamide may be prepared in the following manner: 0.015 cm^3 of aminoethylpyrrolidine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution

obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned with dichloromethane with the aid of a Duramat pump, eluted with a dichloromethane-ethanol (98-04 by volume) mixture, collecting 1.5-cm^3 fractions. Fractions 13 to 20 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 33 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(2-pyrrolidin-1-ylethyl)acetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.78 (mt : 4H); from 2.50 to 2.70 (mt : 3H); 2.54 (mt : 4H); 2.91 (dd, J = 7.5 and 5 Hz : 1H); 3.10 (mt : 2H); from 3.20 to 3.45 (mt : 3H); 3.64 (d, J = 10.5 Hz : 1H); 4.27 (s : 1H); 6.67 (tt, J = 9 and 2.5 Hz : 1H); 6.86 (mt : 2H); from 7.15 to 7.35 (mt : 8H)].

Example 66

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylmethylacetamide may be prepared in the following manner: 0.011 cm^3 of cyclopropanemethylamine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-

(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned and then eluted with a dichloromethane-petroleum ether (80-20 by volume) mixture with the aid of a Duramat pump, collecting 1.5-cm^3 fractions. Fractions 3 to 8 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 37 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylmethylacetamide are thus obtained in the form of a white foam [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.13 (mt : 2H) : 0.45 (mt : 2H); 0.86 (mt : 1H); 2.65 (mt : 1H); 2.91 (dd, J = 7.5 and 5 Hz : 1H); from 3.00 to 3.15 (mt : 4H); 3.41 (broad t, J = 7.5 Hz : 1H); 3.57 (d, J = 10.5 Hz : 1H); 4.25 (s : 1H); 5.50 (mt : 1H); 6.70 (tt, J = 9 and 2.5 Hz : 1H); 6.84 (mt : 2H); from 7.15 to 7.35 (mt : 8H)].

Example 67

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-propylacetamide may be prepared in the following manner: 0.015 cm^3 of propylamine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole

hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm), conditioned and eluted with dichloromethane with the aid of a Duramat pump. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 21 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-propylacetamide are thus obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.84 (t, J = 7.5 Hz : 3H); 1.45 (mt : 2H); 2.65 (mt : 1H); 2.92 (dd, J = 7.5 and 5.5 Hz : 1H); from 3.00 to 3.20 (mt : 2H); 3.15 (q, J = 7 Hz : 2H); 4.43 (broad t, J = 7.5 Hz : 1H); 3.56 (d, J = 10.5 Hz : 1H); 4.26 (s : 1H); 5.39 (mt : 1H); 6.70 (tt, J = 9 and 2.5 Hz : 1H); 6.83 (mt : 2H); from 7.15 to 7.35 (mt : 8H].

Example 68

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-propylacetamide may be prepared in the following manner: 0.050 cm^3 of a 2 M solution of methylamine in tetrahydrofuran, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide

hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm) conditioned and eluted with dichloromethane with the aid of a Duramat pump. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 19 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-methylacetamide are thus obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.66 (mt : 1H); 2.76 (d, J = 5 Hz : 3H); 2.93 (mt : 1H); 3.10 (mt : 2H); 3.44 (broad t, J = 7.5 Hz : 1H); 3.59 (d, J = 10.5 Hz : 1H); 4.28 (s : 1H); 5.41 (unresolved complex : 1H); 6.71 (tt, J = 9 and 2.5 Hz : 1H); 6.83 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 69

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isopropylacetamide may be prepared in the following manner: 0.011 cm^3 of isopropylamine, 29 mg of

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm) conditioned and then eluted with dichloromethane with the aid of a Duramat pump, collecting 1.5-cm^3 fractions. Fractions 6 to 14 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 21 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isopropylacetamide are thus obtained in the form of a white foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.05 (d, J = 7 Hz : 3H); 1.10 (d, J = 7 Hz : 3H); 2.65 (mt : 1H); 2.90 (dd, J = 7.5 and 5.5 Hz : 1H); from 3.00 to 3.15 (mt : 2H); 3.42 (broad t, J = 7.5 Hz : 1H); 3.51 (d, J = 10.5 Hz : 1H); 4.00 (mt : 1H); 4.26 (s : 1H); 5.19 (broad d, J = 7.5 Hz : 1H); 6.70 (tt, J = 9 and 2.5 Hz : 1H); 6.82 (mt : 2H) : from 7.20 to 7.40 (mt : 8H)].

Example 70

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-piperidin-1-

ylacetamide may be prepared in the following manner: 0.013 cm^3 of aminopiperidine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm) conditioned with dichloromethane with the aid of a Duramat pump, eluted with a dichloromethane-ethanol (98-02 by volume) mixture, collecting 2-cm^3 fractions. Fractions 7 to 12 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 33 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-piperidin-1-ylacetamide are thus obtained in the form of a white solid [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 0.95 to 1.85-2.05 and 2.29 (mts : 10H); from 2.60 to 2.80 (mt : 2H); from 3.00 to 3.20 (mt : 2H); 3.39 (broad t, J = 7.5 Hz : 1H); 4.26 (s : 1H); 4.32 (d, J = 10.5 Hz : 1H); 6.00 (s : 1H); 6.65 (tt, J = 9 and 2.5 Hz : 1H); 6.85 (mt : 2H); from 7.15 to 7.35 (mt : 8H)].

Example 71

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cycloheptylacetamide may be prepared in the following manner: 0.015 cm^3 of cycloheptylamine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm) conditioned and then eluted with dichloromethane with the aid of a Duramat pump, collecting 2-cm^3 fractions. Fractions 3 to 6 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 24 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cycloheptylacetamide are thus obtained in the form of a white foam [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): from 1.20 to 1.95 (mt : 12H); 2.65 (mt : 1H); 2.90 (dd, J = 7.5 and 5.5 Hz : 1H); from 3.00 to 3.15 (mt : 2H); 3.42 (broad t, J = 7.5 Hz : 1H); 3.52 (d, J = 10.5 Hz : 1H); 3.86 (mt : 1H); 4.26 (s : 1H); 5.31 (broad d, J = 7.5 Hz : 1H);

6.70 (tt, J = 9 and 2.5 Hz : 1H); 6.82 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 72

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)acetamide may be prepared in the following manner: 60 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride and 3 mg of hydroxybenzotriazol hydrate are successively added to a solution of 98 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 4 cm^3 of anhydrous dichloroethane, at a temperature in the region of 20°C, ammonia is bubbled through for 2 hours, with stirring at a temperature in the region of 20°C. The reaction medium is washed with water and is then deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm) conditioned and eluted with a dichloromethane-ethyl acetate (9-1 by volume) mixture with the aid of a Duramat pump. The fractions between 36 and 80 ml are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 32 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)acetamide are thus obtained in the form of an amorphous powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.66 (mt : 1H); 2.95 (dd, J = 7 and 5 Hz : 1H); from 2.95 to 3.15 (mt : 2H); 3.45 (broad t, J = 7 Hz : 1H); 3.67 (d, J = 10.5 Hz : 1H); 4.27 (s : 1H); from 5.20 to 5.40 (unresolved complex :

2H); 6.72 (tt, J = 9 and 2.5 Hz : 1H); 6.84 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 73

Methyl (RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetylamino acetate may be prepared in the following manner: 100 mg of glycine methyl ester hydrochloride, 115 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, and 6 mg of hydroxybenzotriazol hydrate are successively added to a solution of 200 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 8 cm^3 of dichloroethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is washed with water, dried, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. The residue thus obtained is taken up in 1 cm^3 of dichloromethane and then deposited on an IST FlashPack cartridge with the reference SIL-020-005 conditioned and eluted with a dichloromethane-ethyl acetate (95-05 by volume) mixture with the aid of a Duramat pump. The fractions between 18 and 42 ml are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 68 mg of methyl (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-acetylamino acetate are thus obtained in the form of white cottony crystals [^1H NMR

spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.67 (mt : 1H); 2.93 (broad dd, J = 7.5 and 5 Hz : 1H); from 3.00 to 3.15 (mt : 2H); 3.41 (broad t, J = 7.5 Hz : 1H); 3.68 (d, J = 10.5 Hz : 1H); 3.74 (s : 3H); 3.93 (dd, J = 18 and 5 Hz : 1H); 4.03 (dd, J = 18 and 5 Hz : 1H); 4.27 (s : 1H); 5.96 (mt : 1H); 6.71 (tt, J = 9 and 2 Hz : 1H); 6.85 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 74

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(3-dimethylaminopropyl)acetamide may be prepared in the following manner: 0.015 cm^3 of N,N-dimethylpropane-1,3-diamine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a Varian cartridge (of 12 mm in diameter) filled with 4 cm^3 of silica (0.060-0.200 mm) conditioned with dichloromethane with the aid of a vacuum apparatus, eluting with dichloromethane between 0 and 6 cm^3 and then with a dichloromethane-methanol (95-5 by volume) mixture. The fractions containing only the desired product are combined and concentrated to

dryness under reduced pressure (2.7 kPa) at 40°C. 33 mg [lacuna] (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(3-dimethylamino-propyl)acetamide are thus obtained in the form of white crystals [^{1}H NMR spectrum (300 MHz, $CDCl_3$, with addition of a few drops of CD_3COOD d4, δ in ppm): 1.91 (mt : 2H); 2.71 (s : 6H); 2.95 (mt : 2H); from 3.15 to 3.40 (mt : 2H); from 3.40 to 3.60 (mt : 1H); from 3.60 to 3.80 (mt : 2H); 4.00 (mt : 2H); 4.28 (d, J = 10.5 Hz : 1H); 5.22 (s : 1H); 6,68 (tt, J = 9 and 2.5 Hz : 1H); 6.90 (mt : 2H); 7.33 (mt : 4H); 7.46 (d, J = 8 Hz : 4H)].

Example 75

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(2-hydroxyethyl)acetamide may be prepared in the following manner: 0.024 cm^3 of ethanolamine, 29 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.028 cm^3 of triethylamine and 1.5 mg of hydroxybenzotriazole hydrate are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C. The reaction medium is washed with 2 cm^3 of a saturated sodium bicarbonate solution, dried over magnesium sulfate and is then deposited on an IST FlashPack cartridge with the reference SIL-016-002

conditioned with dichloromethane and eluted with a dichloromethane-ethyl acetate (95-05 by volume) mixture with the aid of a Duramat pump. The fractions between 25 and 60 cm^3 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. The residue obtained is again chromatographed on an IST FlashPack cartridge with the reference SIL-016-002 conditioned with dichloromethane and eluted with a dichloromethane-ethyl acetate (95-05 by volume) mixture with the aid of a Duramat pump. The fractions between 25 and 35 cm^3 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 14 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-(2-hydroxyethyl)acetamide are thus obtained in the form of a white solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.65 (mt : 1H); 2.91 (mt : 1H); from 3.00 to 3.15 (mt : 2H); from 3.30 to 3.50 (mt : 3H); 3.60 (d, J = 10.5 Hz : 1H); 3.66 (t, J = 5.5 Hz : 2H); 4.26 (s : 1H); 5.88 (mt : 1H); 6.71 (tt, J = 9 and 2 Hz : 1H); 6.84 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 76

(RS)-1-[{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)methyl]-3-propylurea may be prepared in the following manner: 0.056 cm^3 of triethylamine and 0.064 cm^3 of diphenylphosphonoazide are successively added to a solution of 50 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-

(3,5-difluorophenyl)acetic acid hydrochloride in 3 cm^3 of anhydrous toluene, under an inert argon atmosphere, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 50°C for about 1 hour. 0.016 cm^3 of propylamine is added, the stirring is maintained at a temperature in the region of 20°C for about 12 hours. The reaction medium is concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. The residue is taken up in 1 cm^3 of dichloromethane and then deposited on a Varian cartridge (6 cm^3) filled with 3 g of fine silica (0.040-0.063 mm) conditioned and eluted with a dichloromethane-ethyl acetate (95-5 by volume) mixture with the aid of a Duramat pump. The fractions between 12 and 16 cm^3 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 13 mg of (RS)-1-[{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2(3,5-difluorophenyl)methyl]-3-propylurea are thus obtained in the form of a beige solid [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 0.92 (t, J = 7.5 Hz : 3H); 1.53 (mt : 2H); from 2.55 to 2.75 (mt : 1H); from 2.80 to 3.25 (mt : 6H); 4.26 (t, J = 5.5 Hz : 1H); 4.29 (s : 1H); 4.92 (t, J = 7 Hz : 1H); 5.31 (d, J = 5.5 Hz : 1H); 6.66 (tt, J = 9 and 2.5 Hz : 1H); 6.79 (mt : 2H); from 7.15 to 7.40 (mt : 8H)].

Example 77

(RS)-{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride may be prepared in the following manner: 3 cm^3 of 6 N hydrochloric acid are added to a solution of 0.44 g of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid ethyl ester in 7 cm^3 of dioxane. The solution obtained is stirred under reflux for about 2 hours and then left at a temperature in the region of 20°C for about 12 hours. The precipitate formed is filtered on No. 3 sintered glass, washed with 10 cm^3 of diisopropyl ether and then dried under reduced pressure (0.27 kPa) at a temperature in the region of 40°C. 0.185 g of (RS)-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride is thus obtained in the form of a white powder [^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, at a temperature of 363K, δ in ppm): 2.87 (dd, J = 14 and 4 Hz : 1H); 2.95 (mt : 1H); 3.18 (mt : 1H); 3.96 (d, J = 10.5 Hz : 1H); 4.18 (t, J = 9 Hz : 1H); 4.72 (t, J = 9 Hz : 1H); 5.26 (unresolved complex : 1H); 7.00 (mt : 2H); 7.06 (tt, J = 9.5 and 2.5 Hz : 1H); from 7.30 to 7.60 (mt : 8H)].

Example 78

(RS){1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid ethyl ester may be prepared in the following manner: 121 mg of sodium borohydride are added, at a temperature in the region

of 0°C, to a suspension of 0.78 g of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene]-(3,5-difluorophenyl)acetic acid ethyl ester in 20 cm^3 of ethanol. The suspension obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is poured into 200 cm^3 of distilled water and then extracted with three times 40 cm^3 of ethyl acetate. The organic phase is successively washed with 3 times 40 cm^3 of distilled water and then with 40 cm^3 of a saturated sodium chloride solution. After decantation, the organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. The residue obtained is chromatographed on a column filled with 75 cm^3 of fine silica (0.040-0.063 mm) under a pressure of 0.7 bar with a dichloromethane-ethyl acetate mixture (the percentage of ethyl acetate varying from 0 to 10%), collecting 15-cm^3 fractions. Fractions 4 to 11 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 0.46 g of (RS)-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid ethyl ester is thus obtained in the form of a yellow lacquer [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.19 (t, J = 7 Hz : 3H); 2.62 (broad t, J = 6 Hz : 1H); 2.87 (dd, J = 7.5 and 6 Hz : 1H); from 2.95 to 3.15 (mt : 2H); 3.39 (broad t, J = 7.5 Hz : 1H); 3.78 (d, J = 10.5 Hz : 1H); 4.10

(mt : 2H); 4.25 (s : 1H); 6.69 (tt, J = 9 and 2.5 Hz : 1H); 6.80 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Fractions 16 to 26 from the preceding chromatography are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 0.24 g of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethanol is thus obtained in the form of a yellow foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.98 (unresolved complex : 1H); 2.69 (mt : 1H); from 2.70 to 2.85 (mt : 1H); from 2.90 to 3.10 (mt : 2H); 3.18 (mt : 1H); 3.44 (mt : 1H); from 3.65 to 3.85 (mt : 2H); 4.28 (s : 1H); from 6.60 to 6.80 (mt : 3H); from 7.20 to 7.35 (mt : 8H)].

{1-[Bis(4-chlorophenyl)methyl]azetidin-3-ylidene}-(3,5-difluorophenyl)acetic acid ethyl ester may be prepared in the following manner: 6.6 g of 4-dimethylaminopyridine and 2.1 cm^3 of methylsulfonyl chloride are added to a solution of 9.1 g of {1-[bis-4-chlorophenyl)methyl]-3-hydroxyazetidin-3-yl}-(3,5-difluorophenyl)acetic acid ethyl ester in 200 cm^3 of dichloromethane. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction mixture is washed three times with 250 cm^3 of distilled water and then dried with magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. The residue obtained is taken up hot with 50 cm^3 of isopropyl ether and then left at a

temperature in the region of 20°C for about 12 hours. The white suspension obtained is filtered on sintered glass, washed with 20 cm^3 of petroleum ether and then dried under vacuum under reduced pressure (0.27 kPa) at a temperature in the region of 40°C for 2 hours. 7.9 g of {1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}-(3,5-difluorophenyl)acetic acid ethyl ester are thus obtained in the form of a cream-colored powder [^1H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.25 (t, J = 7 Hz : 3H); 3.85 (mt : 2H); 4.12 (AB, J = 7.5 Hz : 2H); 4.23 (mt : 2H); 4.51 (s : 1H); from 6.65 to 6.80 (mt : 3H); from 7.20 to 7.40 (mt : 8H)].

{1-[Bis(4-chlorophenyl)methyl]-3-hydroxyazetidin-3-yl}-(3,5-difluorophenyl)acetic acid ethyl ester may be prepared in the following manner: 34.54 cm^3 of a 1.6 M butyllithium solution in hexane are added dropwise over 15 minutes to a solution of 7.73 cm^3 of diisopropylamine in 125 cm^3 of anhydrous tetrahydrofuran under an inert nitrogen atmosphere at a temperature in the region of -70°C, the stirring is maintained at this temperature for 45 minutes, a solution of 11.01 g of ethyl 3,5-difluorophenylacetate in 85 cm^3 of anhydrous tetrahydrofuran are added over 15 minutes, the stirring is continued for 1 hour at -78°C, 16.84 g of 1-[bis(4-chlorophenyl)methyl]-azetidin-3-one in 90 cm^3 of anhydrous tetrahydrofuran are added, the stirring is continued for 1 hour at -70°C, 300 cm^3 of a saturated ammonium chloride solution

are added over 30 minutes at 0°C with vigorous stirring, the reaction mixture is separated after settling after 12 hours, the organic phase is washed 3 times with a saturated sodium bicarbonate solution, dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is chromatographed on a column 70 mn in diameter filled with 2000 cm^3 of fine silica (0.040-0.063 mm) under a pressure of 0.7 bar with a dichloromethane-ethyl acetate (99-01 by volume) mixture. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C for 2 hours. 9.1 g of {1-[bis(4-chlorophenyl)methyl]-3-hydroxyazetidin-3-yl}-(3,5-difluorophenyl)acetic acid ethyl ester are thus obtained in the form of a cream-colored solid [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.25 (t, J = 7 Hz : 3H); 2.87 (d, J = 8 Hz : 1H); 3.07 (d, J = 8 Hz : 1H); (broad d, J = 8 Hz : 1H); 3.28 (broad d, J = 8 Hz : 1H); 4.12 (s : 2H); 4.21 (mt : 2H); 4.36 (s : 1H); 6.78 (tt, J = 9 and 2.5 Hz : 1H); 6.98 (mt : 2H); from 7.20 to 7.40 (mt : 8H)].

Ethyl 3,5-difluorophenylacetate may be prepared in the following manner: 20.4 cm^3 of triethylamine and then 27.6 g of 3,5-difluorophenylacetic acid chloride in solution in 60 cm^3 of dichloromethane are successively added to a solution of 12 cm^3 of ethanol in 300 cm^3 of anhydrous

dichloromethane at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction mixture is successively washed with twice 150 cm^3 of a decinormal solution of hydrochloric acid and then with twice 150 cm^3 of a saturated sodium bicarbonate solution. The organic phase is dried with magnesium sulfate, filtered and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 29 g of ethyl 3,5-difluorophenyl acetate are thus obtained in the form of a yellow oil.

3,5-Difluorophenylacetic acid chloride may be prepared in the following manner: 19.3 cm^3 of oxalyl chloride and then a few drops of dimethylformamide are successively added to a solution of 25 g of 3,5-difluorophenylacetic acid in 350 cm^3 of 1,2-dichloroethane at a temperature in the region of 20°C, after stirring for 3 hours at a temperature in the region of 20°C, 30 cm^3 of oxalyl chloride and a then few drops of dimethylformamide are again successively added. The reaction medium is concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 27.6 g of 3,5-difluorophenylacetic acid chloride are thus obtained in the form of a yellow oil.

Example 79

(RS)-1-[Bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluorophenyl)-1-methylsulfonylethyl]azetidine is

obtained in the following manner: 0.5 cm^3 of a 2 M solution of lithium diisopropylamide is added to a solution of 0.5 g of (RS)-1-[bis(4-chlorophenyl)-methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)-methyl]azetidine in 10 cm^3 of tetrahydrofuran cooled to -78°C and maintained under an inert atmosphere. The temperature is allowed to rise to -20°C and then 0.06 cm^3 of iodomethane is added. The temperature is allowed to rise to 0°C over a period of 2 hours and then 20 cm^3 of a saturated aqueous ammonium chloride solution are added. The reaction medium is separated after settling and the aqueous phases are extracted with twice 20 cm^3 of ethyl acetate. The organic extracts are combined, dried over magnesium sulfate and evaporated to dryness at 40°C under 2.7 kPa, providing 550 mg of cream-colored residue. The residue is chromatographed on a silica column (Dynamax, reference 83-121-C, size 21.4 mm × 250 mm, precolumn 21.4 mm × 50 mm, reference R00083121G, 8 µ silica, porosity 60 Angstroem; Rainin Instrument Co. Inc., Mac Road, Woburn, MA 01801, USA), eluting with a heptane: isopropanol (99:1 by volume) mixture at 15 cm^3 per minute (detection 254 nm, 10-cm^3 fractions). The fractions containing the compound with an Rf=32/77 (cyclohexane:ethyl acetate 70:30, 254 nm, silica plates reference 1.05719, Merck KGaA, 64271 Darmstadt, Germany) are combined and evaporated at 40°C under 2.7 kPa, providing 80 mg of 1-[bis(4-chlorophenyl)-

methyl]-3-[1-(3,5-difluorophenyl)-1-methylsulfonyl-ethyl]azetidine in the form of a white amorphous powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.05 (s : 3H); 2.54 (s : 3H); 2.63 (t, J = 7.5 Hz : 1H); 3.17 (broad t, J = 8 Hz : 1H); 3.32 (mt : 1H); 3.44 (broad t, J = 8 Hz : 1H); 3.71 (mt : 1H); 4.27 (s : 1H); 6.83 (tt, J = 9 and 2.5 Hz : 1H); 7.15 (mt : 2H); from 7.20 to 7.40 (mt : 8H)].

Example 80

(RS)-1-[Bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine may be prepared in the following manner: a few granules of potassium iodide are added to a suspension of 0.191 cm^3 of bis(4-fluorophenyl)chloromethane, 300 mg of (RS)-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-azetidine and 167 mg of potassium carbonate in 5 cm^3 of acetonitrile, at a temperature in the region of 20°C. After 48 hours at a temperature in the region of 20°C, the reaction medium is filtered on sintered glass, the solid is rinsed with acetonitrile and the filtrate is purified by preparative thin-layer chromatography on silica [3 preparative Merck Kieselgel 60F254 plates, 20×20 cm; thickness 1 mm], eluting with a methanol-dichloromethane (1-99 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol-dichloromethane (10-90 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in

the region of 40°C, 39 mg of (RS)-1-[bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine are obtained in the form of a yellow foam [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.54 (broad t, J = 7 Hz : 1H); 2.66 (s : 3H); 3.18 (mt : 2H); from 3.20 to 3.45 (mt : 1H); 3.63 (broad t, J = 7 Hz : 1H); 4.27 (s : 1H); 4.28 (d, J = 11 Hz : 1H); 6.83 (tt, J = 9 and 2 Hz : 1H); from 6.90 to 7.05 (mt : 6H); from 7.25 to 7.40 (mt : 4H)].

(RS)-3-[(3,5-Difluorophenyl)methylsulfonylmethyl]azetidine hydrochloride may be prepared may be prepared in the following manner: a suspension of 8.5 g of 1-benzhydryl-3-[(3,5-difluorophenyl)(methylsulfonyl methylene]azetidine and 1.3 g of palladium hydroxide (20% by weight of palladium), in 600 cm^3 of methanol, 20 cm^3 of 1 N hydrochloric acid and 4 cm^3 of acetic acid, is stirred at a temperature in the region of 20°C under a hydrogen atmosphere (1.5 bar) until complete absorption of a volume of 2.1 liters of hydrogen is obtained. The reaction medium is then filtered on sintered glass covered with charcoal. The filtrate is concentrated to dryness under reduced pressure and then the residue obtained is taken up in ethanol. The crystallized white product is filtered and dried. 5.4 g of (RS)-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine hydrochloride are thus obtained in the form of white crystals.

1-Benzhydryl-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine may be prepared may be prepared in the following manner: a mixture of 18.8 g of 3-acetoxy-1-benzhydryl-3-[(3,5-difluorophenyl)-(methylsulfonyl)methyl]azetidine and 3.9 g of lithium hydroxide monohydrate in 120 cm^3 of acetonitrile is heated at a temperature in the region of 70°C for 3 hours. After cooling to a temperature in the region of 2°C, 120 cm^3 of tert-butyl and methyl ether and 80 cm^3 of distilled water are successively added followed, slowly, by 5 cm^3 of acetic acid. After decantation, the organic phase is washed with 80 cm^3 of a saturated aqueous sodium hydrogen carbonate solution, 80 cm^3 of distilled water, 80 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The residue obtained is taken up in ethanol. After leaving overnight at a temperature in the region of 20°C, the mixture obtained is filtered on sintered glass, the white crystals obtained are rinsed with ethanol, diisopropyl ether and dried under reduced pressure at a temperature in the region of 45°C. 14.6 g of 1-benzhydryl-3-[(3,5-difluorophenyl)(methylsulfonyl)methylene]azetidine are thus obtained in the form of white crystals.

3-Acetoxy-1-benzhydryl-3-[(3,5-difluorophenyl)methylsulfonyl)methyl]azetidine may be prepared may be prepared in the following manner: 47.1 cm^3 of

1.6 N n-butyllithium in solution in hexane are added dropwise over approximately 25 minutes to a suspension of 12.37 g of 3,5-difluorobenzyl methyl sulfone in 200 cm^3 of tetrahydrofuran, under an inert nitrogen atmosphere at a temperature in the region of -30°C. The cloudy yellow solution is stirred at a temperature in the region of -30°C for 2 hours and then a solution of 11.87 g of 1-benzhydrylazetidin-3-one in 75 cm^3 of dichloromethane is added dropwise. The reaction mixture is stirred for 1.5 hours at a temperature in the region of -30°C and then 6.07 cm^3 of acetyl chloride are added and the temperature of the medium is allowed to return to a temperature in the region of -10°C over about 30 minutes. 200 cm^3 of water and 100 cm^3 of dichloromethane are added. After stirring vigorously for 30 minutes and decantation, the organic phase is washed with 3 times 150 cm^3 of a saturated aqueous sodium hydrogen carbonate solution, 150 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure. The crystalline residue obtained is taken up in 50 cm^3 of boiling ethanol. The white suspension obtained is allowed to stand overnight at a temperature in the region of 20°C and then the solid obtained is drained over sintered glass, rinsed with diisopropyl ether and dried under reduced pressure at a temperature in the region of 50°C. 19.5 g of 3-acetoxy-1-benzhydryl-3-[(3,5-difluorophenyl)(methyl-

sulfonyl)methyl]azetidine are thus obtained in the form of white crystals.

1-Benzhydrylazetidin-3-one may be prepared according to the procedure described by KATRITZKY A.R. et al. in J. Heterocycl. Chem., 271 (1994).

3,5-Difluorobenzyl methyl sulfone may be prepared may be prepared in the following manner: a mixture of 66.69 cm^3 of 3,5-difluorobenzyl bromide, 71.97 g of the sodium salt of methanesulfinic acid and 150 mg of sodium iodide in 625 cm^3 of ethanol is heated under reflux, under an argon atmosphere, for about 16 hours. After cooling to a temperature in the region of 20°C, the reaction medium is diluted with 3 liters of ethyl acetate, washed with 500 cm^3 of water, 500 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulfate, filtered and evaporated under reduced pressure (50 mbar) at a temperature in the region of 40°C. The residue obtained is taken up in 300 cm^3 of ethyl ether, and the solid is filtered on sintered glass, rinsed with 200 cm^3 of ethyl ether, dried under reduced pressure at a temperature in the region of 20°C. 86 g of 3,5-difluorobenzyl methyl sulfone are thus obtained in the form of a white powder.

Example 81

(RS)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine may be prepared in the following manner: a mixture of

47 mg of 3-(pyridyl)-(4-chlorophenyl)bromomethane, 50 mg of (RS)-3-[(3,5-difluorophenyl)methylsulfonyl-methyl]azetidine hydrochloride and 58 mg of potassium carbonate in 2 cm^3 of acetonitrile, is stirred for about 3 hours at a temperature in the region of 20°C, for 2 hours at the reflux temperature of the solvent, for about 16 hours at a temperature in the region of 20°C and then for 1.5 hours at the reflux temperature of the solvent. A few granules of potassium iodide are then added and the reaction mixture is maintained for about 2 hours at the reflux temperature of the solvent. After cooling to a temperature in the region of 20°C, the reaction medium is purified by preparative thin-layer chromatography on silica [2 preparative Merck Kieselgel 60F254 plates; 20×20 cm; thickness 0.5 mm], eluting with a methanol-dichloromethane (2.5-97.5 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol-dichloromethane (10-90 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 11 mg of (RS)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine are obtained in the form of a colorless lacquer [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.59 (mt : 1H); 2.66 (s : 3H); 3.21 (mt : 2H); from 3.30 to 3.50 (mt : 1H); 3.67 (mt : 1H); 4.28 (broad d, J = 11 Hz : 1H); 4.32 (broad s : 1H); 6.84 (tt, J = 9 and 2 Hz : 1H);

6.95 (mt : 2H); 7.19 (broad dd, J = 8 and 5 Hz : 1H); from 7.20 to 7.40 (mt : 4H); 7.64 (broad d, J = 8 Hz : 1H); 8.45 (mt : 1H); 8.59 (very broad s : 1H].

(3-Pyridyl)-(4-chlorophenyl)bromomethane may be prepared in the following manner: a mixture of 150 mg of (3-pyridyl)-(4-chlorophenyl)methanol in 0.356 cm^3 of hydrobromic acid (at 33% in acetic acid) and 0.101 cm^3 of acetyl bromide is heated under reflux for 1 hour and then left at a temperature in the region of 20°C for 2 hours, before being concentrated under reduced pressure and coevaporated with a few cm^3 of toluene. 234 mg of (3-pyridyl)-(4-chlorophenyl)-bromomethane are thus obtained in the form of a gummy beige solid.

(3-Pyridyl)-(4-chlorophenyl)methanol may be prepared in the following manner: 0.5 cm^3 of 3-pyridinecarboxaldehyde is slowly added to a solution of 5.83 cm^3 of 4-chlorophenylmagnesium bromide (1 M solution in ethyl ether) in 5 cm^3 of tetrahydrofuran, under an inert argon atmosphere. After about 3 hours, 3 cm^3 of a saturated aqueous ammonium chloride solution and 10 cm^3 of water are added to the reaction medium. After stirring for 5 minutes at a temperature in the region of 20°C, the reaction medium is acidified to a pH of about 2 with a 1 N aqueous hydrochloric acid solution. The aqueous phase is extracted with 3 times 15 cm^3 of dichloromethane. The remaining aqueous phase is treated with 10 cm^3 of a 1 N aqueous sodium hydroxide

solution and reextracted with 3 times 15 cm^3 of ethyl acetate. The organic phases containing the ethyl acetate are combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. 466 mg of (3-pyridyl)-(4-chlorophenyl)methanol are thus obtained in the form of a bright yellow solid.

Example 82

(RS)-{1-[(4-Pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine may be prepared in the following manner: a mixture of 160 mg of (4-(pyridyl)-(4-chlorophenyl)bromomethane, 169 mg of (RS)-3-[(3,5-difluorophenyl)methylsulfonyl-methyl]azetidine hydrochloride and 94 mg of potassium carbonate in 5 cm^3 of acetonitrile, is stirred for about 17 hours at a temperature in the region of 20°C. A few granules of sodium iodide are then added and after stirring for 2 hours at a temperature in the region of 20°C, the reaction mixture is maintained for about 1.5 hours at the reflux temperature of the solvent. After cooling to a temperature in the region of 20°C, the reaction medium is purified by preparative thin-layer chromatography on silica [4 preparative Merck Kieselgel 60F254 plates; 20×20 cm; thickness 0.5 mm], eluting with a methanol-dichloromethane (2.5-97.5 by volume) mixture. After elution of the zone corresponding to the desired products with a methanol-dichloromethane (10-90 by volume) mixture, filtration on sintered glass and then evaporation of the solvents

under reduced pressure at a temperature in the region of 40°C, there are obtained a first mixture of diastereoisomers, that is to say 24 mg of (RS)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine in the form of a yellow lacquer, and a second mixture of diastereoisomers, that is to say 31 mg of (RS)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine in the form of a yellow foam. The first mixture of diastereoisomers has the characteristics are the following [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.62 (t, J = 7 Hz : 1H); 2.67 (s : 3H); 3.21 (broad t, J = 7 Hz : 2H); 3.42 (mt : 1H); 3.70 (broad t, J = 7 Hz : 1H); 4.28 (s : 1H); 4.28 (d, J = 11 Hz : 1H); 6.85 (tt, J = 9 and 2.5 Hz : 1H); 6.97 (mt : 2H); from 7.20 to 7.35 (mt : 6H); 8.52 (dd, J = 4.5 and 1.5 Hz : 2H).

The second mixture of diastereoisomers has the characteristics are the following [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.59 (t, J = 7 Hz : 1H); 2.67 (s : 3H); 3.26 (mt : 2H); from 3.35 to 3.50 (mt : 1H); 3.63 (broad t, J = 7 Hz : 1H); 4.28 (s : 1H); 4.28 (d, J = 11 Hz : 1H); 6.85 (tt, J = 9 and 2 Hz : 1H); 6.97 (mt : 2H); from 7.20 to 7.40 (mt : 6H); 8.50 (dd, J = 4.5 and 1.5 Hz : 2H).

(4-Pyridyl)-(4-chlorophenyl)bromomethane may be prepared in the following manner: a solution of

100 mg of (4-pyridyl)-(4-chlorophenyl)methanol in 0.24 cm^3 of hydrobromic acid (at 33% in acetic acid) is heated under reflux for 1 hour and then allowed to return to a temperature in the region of 20°C. 0.675 cm^3 of acetyl bromide is then added and the reaction mixture is heated under reflux for 1.5 hours and then allowed to return to a temperature in the region of 20°C before being concentrated under reduced pressure. 163 mg of (4-pyridyl)-(4-chlorophenyl)bromomethane are thus obtained in the form of a beige foam-gum.

(4-Pyridyl)-(4-chlorophenyl)methanol may be prepared in the following manner: 348 mg of sodium tetraborohydride are added, at a temperature in the region of 20°C, to a solution of 2 g of 4-(4-chlorobenzoyl)pyridine in 160 cm^3 of ethanol. After stirring for 2 hours at a temperature in the region of 20°C, 90 mg of sodium tetraborohydride are added. After about 1.5 hours at the same temperature, the reaction medium is diluted with 200 cm^3 of dichloromethane and 200 cm^3 of water. The pH of the aqueous phase is adjusted to a value of about 5 by addition of about 13 cm^3 of an aqueous 1 N hydrochloric acid solution. After decantation, the aqueous phase is extracted with 3 times 100 cm^3 of dichloromethane. The organic phases are combined, dried over magnesium sulfate, filtered and concentrated under reduced pressure. 2 g of (4-pyridyl)-(4-chlorophenyl)methanol are thus obtained in the form of a white powder.

Example 83

(RS)-{1-[(2-Chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine may be prepared in the following manner: a mixture of 300 mg of (2-chloropyrid-5-yl)-(4-chlorophenyl)bromomethane, 225 mg of (RS)-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-azetidine hydrochloride, 125 mg of potassium iodide and 521 mg of potassium carbonate in 5 cm^3 of acetonitrile, is heated for about 2 hours at the reflux temperature of the solvent. After cooling to a temperature in the region of 20°C, the reaction medium is filtered on sintered glass. The solid residue is rinsed with dichloromethane and the filtrates are evaporated under reduced pressure. 402 mg of a chocolate foam are thus obtained, which foam is purified by preparative thin-layer chromatography on silica [4 preparative Merck Kieselgel 60F254 plates; 20×20 cm; thickness 0.5 mm], eluting with a methanol-dichloromethane (2.5-97.5 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol-dichloromethane (10-90 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, there are obtained a first mixture of diastereoisomers, that is to say 14 mg of (RS)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine

in the form of a brown foam, and a second mixture of diastereoisomers, that is to say 10 mg of (RS)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine in the form of a beige foam.

The first mixture of diastereoisomers has the characteristics are the following: [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.57 (t, J = 7.5 Hz : 1H); 2.65 (s : 3H); from 3.15 to 3.30 (mt : 2H); 3.40 (mt : 1H); 3.63 (broad t, J = 7.5 Hz : 1H); 4.27 (d, J = 11 Hz : 1H); 4.31 (s : 1H); 6.84 (tt, J = 9 and 2 Hz : 1H); 6.95 (mt : 2H); from 7.20 to 7.35 (mt : 5H); 7.63 (dd, J = 8 and 2.5 Hz : 1H); 8.38 (d, J = 2.5 Hz : 1H).

The second mixture of diastereoisomers has the characteristics are the following: [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.57 (t, J = 7.5 Hz : 1H); 2.64 (s : 3H); 3.18 (broad t, J = 7.5 Hz : 2H); 3.38 (mt : 1H); 3.63 (broad t, J = 7.5 Hz : 1H); 4.24 (d, J = 11.5 Hz : 1H); 4.29 (s : 1H); 6.83 (tt, J = 9 and 2 Hz : 1H); 6.94 (mt : 2H); 7.20 (d, J = 8 Hz : 1H); from 7.20 to 7.35 (mt : 4H); 7.59 (dd, J = 8 and 2.5 Hz : 1H); 8.34 (d, J = 2.5 Hz : 1H).

2-(Chloropyrid-5-yl)-(4-chlorophenyl)bromomethane may be prepared in the following manner: 0.153 cm^3 of thionyl bromide is added to a solution of 100 mg of (2-chloropyrid-5-yl)-(4-chlorophenyl)methanol in 2 cm^3 of carbontetrachloride, under an inert argon atmosphere, at a temperature in the region of 0°C.

After 3.5 hours at a temperature in the region of 0°C, the reaction medium is concentrated under reduced pressure and coevaporated with a few cm^3 of toluene. 1.3 g of a brown liquid are thus obtained, which liquid is taken up in dichloromethane and supplemented with water and sodium dithionite. After decantation, the organic phase is dried over magnesium sulfate, filtered and concentrated to dryness under reduced pressure. 0.33 g of 2-(chloropyrid-5-yl)-(4-chlorophenyl)bromomethane is thus obtained in the form of a brown oil.

2-(Chloropyrid-5-yl)-(4-chlorophenyl)bromomethane may be prepared by carrying out the procedure in a manner similar to Example 84, starting with 22.5 cm^3 of 4-chlorophenylmagnesium bromide (1 M solution in ethyl ether) in 30 cm^3 of tetrahydrofuran, under an inert argon atmosphere, and 2.9 g of 2-chloropyridine-5-carboxaldehyde in 30 cm^3 of tetrahydrofuran. 3.42 g of 2-(chloropyrid-5-yl)-(4-chlorophenyl)methanol are thus obtained in the form of a pale green powder.

2-Chloropyridine-5-carboxaldehyde may be prepared according to the following reference:
G. Pandey, T.D. Bagul, A.K. Sahoo, J. Org. Chem., 1998, 63, 760-768.

Example 84

(RS)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine may be prepared in the following

manner: a mixture of 50 mg of 5-[bromo-(4-chlorophenyl)methyl]pyrimidine, 52.6 mg of (RS)-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-azetidine hydrochloride, 44 mg of potassium iodide and 73 mg of potassium carbonate in 2 cm^3 of acetonitrile, is heated for about 5 hours at the reflux temperature of the solvent. After cooling to a temperature in the region of 20°C, the reaction medium is purified by direct deposition on preparative thin-layer chromatography on silica [2 preparative Merck Kieselgel 60F254 plates; 20×20 cm; thickness 0.5 mm], eluting with a methanol-dichloromethane (2.5-97.5 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol-dichloromethane (10-90 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, there are obtained a first mixture of diastereoisomers, that is to say 8 mg of (RS)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine in the form of a yellow foam, and a second mixture of diastereoisomers, that is to say 6 mg of (RS)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidin-1-yl}methyl)-pyrimidine in the form of a yellow foam.

The first mixture of diastereoisomers has the characteristics are the following: [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.60 (broad t, J = 7 Hz :

1H); 2.66 (s : 3H); 3.24 (broad t, J = 7 Hz : 2H); 3.41 (mt : 1H); 3.66 (broad t, J = 7 Hz : 1H); 4.28 (d, J = 11.5 Hz : 1H); 4.33 (broad s : 1H); 6.84 (broad t, J = 9 Hz : 1H); 6.95 (mt : 2H); from 7.25 to 7.35 (mt : 4H); 8.71 (broad s : 2H); 9.08 (broad s : 1H).

The second mixture of diastereoisomers has the characteristics are the following: [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.61 (t, J = 7 Hz : 1H); 2.66 (s : 3H); 3.24 (broad t, J = 7 Hz : 2H); 3.43 (mt : 1H); 3.65 (broad t, J = 7 Hz : 1H); 4.28 (d, J = 11.5 Hz : 1H); 4.33 (s : 1H); 6.85 (tt, J = 9 and 2 Hz : 1H); 6.96 (mt : 2H); from 7.25 to 7.35 (mt : 4H); 8.69 (s : 2H); 9.06 (s : 1H).

5-[Bromo-(4-chlorophenyl)methyl]pyrimidine may be prepared in the following manner: 0.36 cm^3 of thionyl bromide is added to a solution of 205 mg of (4-chlorophenyl)pyrimidin-5-ylmethanol in 1 cm^3 of carbontetrachloride, and 1 cm^3 of dichloromethane, under an inert argon atmosphere, at a temperature in the region of 0°C. After 2.5 hours at a temperature in the region of 0°C, the reaction medium is brought to a temperature in the region of 20°C, concentrated under reduced pressure and coevaporated with a few cm^3 of toluene. The brown liquid obtained is taken up in 10 cm^3 of dichloromethane, washed with 5 cm^3 of a saturated aqueous sodium dithionite solution and then with water. After decantation, the organic phase is dried over magnesium sulfate, filtered and concentrated to dryness

under reduced pressure. 227 mg of a beige viscous liquid are thus obtained, which liquid is taken up in a minimum quantity of dichloromethane and purified by preparative thin-layer chromatography on silica [2 preparative Merck Kieselgel 60F254 plates; 20×20 cm, thickness 0.5 mm], eluting with a methanol-dichloromethane (2.5-97.5 by volume) mixture. After elution of the zone corresponding to the desired product with a methanol-dichloromethane (10-90 by volume) mixture, filtration on sintered glass and then evaporation of the solvents under reduced pressure at a temperature in the region of 40°C, 51 mg of 5-[bromo-(4-chlorophenyl)methyl]pyrimidine are obtained in the form of a yellow foam.

4-(Chlorophenyl)pyrimidin-5-ylmethanol may be prepared by carrying out the procedure in a manner similar to Example 83, 2.5 cm^3 of n-butyllithium (1.6 M solution in hexane) are added dropwise to a solution of 636 mg of 5-bromopyrimidine in 10 cm^3 of tetrahydrofuran, under an inert argon atmosphere, at a temperature in the region of -78°C. After 10 minutes at a temperature in the region of -78°C, a solution of 562 mg of 4-chlorobenzaldehyde in 1 cm^3 of tetrahydrofuran is added dropwise. After stirring for 30 minutes at a temperature in the region of -78°C, the temperature of the reaction medium is allowed to rise slowly to a temperature in the region of 20°C, and 15 cm^3 of a saturated aqueous ammonium chloride

solution, 60 cm^3 of ethyl acetate and 10 cm^3 of water are added successively. The aqueous phase is extracted with 15 cm^3 of ethyl acetate, the organic phases are combined, dried over magnesium sulfate, filtered on sintered glass and concentrated under reduced pressure (20 mbar) at a temperature in the region of 44°C. The bulk of the orange-colored oil obtained (1.09 g) is purified by chromatography on a column 30 mn in diameter filled with 60 g of medium silica (0.063-0.200 mm) at atmospheric pressure, eluting with a methanol/dichloromethane (0/100 to 7/93 by volume) gradient. The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure. 293 mg of 4-(chlorophenyl)pyrimidin-5-yl)methanol are thus obtained in the form of a yellow oil.

Example 85

The phenolic ester of 4-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}methylsulfonylmethyl)-3,6-dihydro-2H-pyridine-1-carbothioic acid may be prepared in the following manner: 0.140 g of 4-dimethylaminopyridine and then 0.042 cm^3 of methanesulfonyl chloride are added to a solution of 0.23 g of the phenolic ester of 4-({1-bis(4-chlorophenyl)methyl]-3-hydroxyazetidin-3-yl}methylsulfonylmethyl)-3,6-dihydro-2H-pyridine-1-carbothioic acid in 5 cm^3 of dichloromethane. The reaction mixture is stirred for 20 hours at 20°C and then diluted with

10 cm^3 of water. After decantation, the organic phase is successively washed with 100 cm^3 of water and 100 cm^3 of a saturated NaCl solution, dried over magnesium sulfate and then concentrated to dryness at 40°C under 2.7 kPa. The oil obtained is triturated for 45 minutes in 50 cm^3 of diisopropyl ether. The solid formed is filtered, providing 120 mg of the phenolic ester of 4-({1-[bis(4-chlorophenyl)methyl]azetidin-3-ylidene}methylsulfonylmethyl)-3,6-dihydro-2H-pyridine-1-carbothioic acid in the form of a beige solid melting at 184°C [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 2.53 (unresolved complex: 2H); 2.95 (s : 3H); 3.90 (unresolved complex: 2H); 4.04 (t, J = 5.5 Hz : 1H); 4.24 (mt : 3H); 4.49 (unresolved complex: 2H); 4.60 (mt : 1H); 5.90 (unresolved complex: 1H); from 7.05 to 7.50 (mt : 13H)].

The phenolic ester of 4-({1-[bis(4-chlorophenyl)methyl]-3-hydroxyazetidin-3-yl}methylsulfonylmethyl)-3,6-dihydro-2H-pyridine-1-carbothioic acid is prepared in the following manner: 0.52 g of potassium tert-butoxide is added to a mixture of 0.72 g of the phenolic ester of 4-methylsulfonylmethyl-3,6-dihydro-2H-pyridine-1-carbothioic acid and 0.708 g of 1-[bis(4-chlorophenyl)methyl]azetidin-3-one in 15 cm^3 of dry tetrahydrofuran cooled under an inert atmosphere to -78°C. The reaction mixture is stirred at -78°C for 4 hours and then 0.354 g of 1-[bis(4-chlorophenyl)-methyl]azetidin-3-one are added. After two hours at

-78°C, the temperature is allowed to return to 20°C. The reaction mixture is diluted in 100 cm^3 of water and then the tetrahydrofuran is evaporated off under 2.7 kPa at 40°C. The aqueous phase is extracted with twice 100 cm^3 of ethyl acetate. The organic extracts are combined and dried over magnesium sulfate, concentrated under 2.7 kPa at 40°C. The residue obtained is chromatographed on silica (200 g of silica, Amicon, 20-45 μm, porosity 60Angstroem, column 5 cm in diameter), eluting with a cyclohexane:ethyl acetate (6:4 by volume) mixture. The fractions with an Rf=11/64 (cyclohexane:ethyl acetate 6:4, silica plate, Merck reference 1.05719, Merck KGaA, 64721 Darmstatd, Germany) are combined and concentrated under 2.7 kPa at 40°C to give 240 mg of the phenolic ester of 4-({1-[bis(4-chlorophenyl)methyl]-3-hydroxyazetidin-3-yl}methylsulfonylmethyl)-3,6-dihydro-2H-pyridine-1-carbothioic acid.

The phenolic ester of 4-methylsulfonylmethyl-3,6-dihydro-2H-pyridine-1-carbothioic acid may be prepared in the following manner: 0.778 cm^3 of phenyl thiochloroformate is added to a solution of 1 g of 1-benzyl-4-methylsulfonylmethyl-1,2,3,6-tetrahydropyridine in 10 cm^3 of dichloromethane under an argon atmosphere. The solution instantly acquires a very dark amber color. The reaction mixture is stirred for 4 hours at 21°C and then diluted in 100 cm^3 of dichloromethane. The organic medium is washed with

twice 50 cm^3 of water, dried over magnesium sulfate and evaporated to dryness at 40°C under 2.7 kPa. The residue obtained is purified by chromatography on a silica cartridge (reference SIL-020-005, FlashPack, Jones Chromatography Limited, New Road, Hengoed, Mid Glamorgan, CF82 8AU, Great Britain), eluting with a cyclohexane:ethyl acetate 6:4 mixture (10 cm^3/min, 5-cm^3 fractions). The fractions with an Rf=12/74 (cyclohexane:ethyl acetate 1:1, silica plate, Merck reference 1.05719, Merck KGaA, 64271 Darmstatd, Germany) are combined and concentrated under 2.7 kPa at 40°C to give 700 mg of the phenolic ester of 4-methylsulfonylmethyl-3,6-dihydro-2H-pyridine-1-carbothioic acid.

1-Benzyl-4-methylsulfonylmethyl-1,2,3,6-tetrahydropyridine may be prepared in the following manner: a solution of 5.14 g of sodium borohydride and 25 g of sodium carbonate in 700 cm^3 of water is added dropwise over one hour, without exceeding a temperature of 5°C in the reaction medium, to a solution of 17.6 g of 1-benzyl-4-methylsulfonylmethylpyridinium bromide in 700 cm^3 of water cooled to 5°C. The reaction medium is stirred for four hours at 0°C and then the temperature is allowed to return to room temperature overnight. The yellow solid formed is isolated by filtration and dried under 2.7 kPa, giving 9.6 g of 1-benzyl-4-methylsulfonylmethyl-1,2,3,6-tetrahydropyridine having an Rf of 44/81 (dichloromethane:methanol, 95:5 by

volume, silica plate, Merck reference 1.05719, Merck KGaA, 64271 Darmstatd, Germany).

1-Benzyl-4-methylsulfonylmethylpyridinium bromide may be prepared in the following manner: 14 cm^3 of benzyl bromide are added to a solution of 10 g of 4-methylsulfonylmethylpyridine in 200 cm^3 of acetonitrile and then the mixture is heated under reflux for 3 hours and is then allowed to return to room temperature overnight. The solid formed is filtered, dried under vacuum at 2.7 kPa, giving 17.6 g of 1-benzyl-4-methylsulfonylmethylpyridinium bromide.

4-Methylsulfonylmethylpyridine may be prepared in the following manner: 14 g of sodium hydroxide pellets and then 35.7 g of sodium methanesulfinate are slowly added to a solution of 57.4 g of 4-chloromethylpyridine hydrochloride in 700 cm^3 of ethanol. After addition, the temperature is 28°C. The reaction mixture is heated under reflux for two hours and then allowed to return to room temperature overnight. The reaction medium is heated to 50°C and then filtered hot on paper. The filtrate is evaporated to dryness at 40°C under 2.7 kPa. The residue is recrystallized from 300 cm^3 of isopropanol, giving 29.6 g of 4-methylsulfonylmethylpyridine.

Example 86

(RS)-1-[2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)ethyl]-3-propylurea may be prepared by carrying out the

procedure in the following manner: 0.052 cm^3 of n-propyl isocyanate is added to a solution of 90 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethylamine in 5 cm^3 of tetrahydroduran. After stirring for about 72 hours at a temperature in the region of 20°C, the reaction mixture is filtered, concentrated to dryness under reduced pressure, and taken up in diisopropyl ether. The mixture obtained is filtered and concentrated to dryness under reduced pressure. 80 mg of a pale yellow solid are thus obtained, which solid is dissolved in 5 cm^3 of tetrahydrofuran, and to which 80 mg of scavenger resin are added. After stirring for about 18 hours at a temperature in the region of 20°C, the reaction mixture is filtered and then concentrated to dryness under reduced pressure. 36 mg of a pasty solid are thus obtained, which solid is purified by chromatography under pressure on a silica cartridge, eluting with a mixture of cyclohexane and ethyl acetate (50/50 by volume). Fractions 16 to 20 are combined and concentrated to dryness under reduced pressure. 6 mg of (RS)-1-[2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethyl]-3-propylurea are obtained in the form of an oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.88 (t, J = 7.5 Hz : 3H); from 1.35 to 1.60 (mt : 2H); from 2.25 to 2.55 and from 2.65 to 3.05 (2 series of mts : 6H in total); 3.04 (mt : 2H); 3.22 (mt : 1H); 3.38 (mt : 1H); 4.07 (mt: 1H); from 4.10 to

4.20 (mt : 1H); 4.17 (s : 1H); 6.62 (tt, J = 9 and 2.5 Hz : 1H); 6.82 (mt : 2H); from 7.20 to 7.45 (mt : 8H].

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)ethylamine may be prepared by carrying out the procedure in the following manner: 1.2 g of (RS)-2-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)methanesulfonic acid ethyl ester in solution in 10 cm^3 of methanol and then a solution of 30 cm^3 of ammonia in 30 cm^3 of methanol are introduced into an autoclave cooled by a bath of acetone and dry ice. The closed autoclave is shaken and heated to a temperature in the region of 60°C for 24 hours. After cooling to a temperature in the region of 20°C, the ammonia is allowed to evaporate in the air, at a tempeature in the region of 20°C, and then the remaining solution is concentrated to dryness under reduced pressure. A gum is thus obtained which is triturated with ethyl ether, at a temperature in the region of 20°C for about 16 hours. The insoluble matter obtained is filtered and dried in a desiccator for 3 hours. 830 mg of (RS)-2-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethylamine are thus obtained in the form of a whitish solid.

(RS)-2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)methanesulfonic acid ethyl ester may be prepared by carrying out the procedure in the following manner: 0.34 cm^3 of

methanesulfonyl chloride is added to a solution of 1.9 g of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethanol in 20 cm^3 of dichloromethane, at a temperature in the region of 20°C. After cooling of the reaction mixture to a temperature in the region of 10°C, 0.89 cm^3 of triethylamine is added. After stirring the solution for 20 hours at a temperature in the region of 20°C, 100 cm^3 of water are added dropwise followed by 150 cm^3 of dichloromethane. The organic phase separated after settling out is washed with twice 50 cm^3 of water, 50 cm^3 of a saturated aqueous sodium chloride solution, 50 cm^3 of water, and then dried over magnesium sulfate, filtered and evaporated to dryness under reduced pressure. The yellow foam thus obtained (2 g) is purified on a silica column (particle size 0.020 - 0.045 mm), at a pressure of 0.4 bar, eluting with a mixture of cyclohexane and ethyl acetate (80/20 by volume). Fractions 49 to 111 are combined and concentrated to dryness under reduced pressure. 1.2 g of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)methanesulfonic acid ethyl ester are obtained in the form of a white foam.

Example 87

(RS)-N-[2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)ethyl]cyclo-propanecarboxamide may be prepared by carrying out the procedure in the following manner: 0.018 cm^3 of

diisopropylcarbodiimide, 10 mg of cyclopropanecarboxylic acid, 16 mg of hydroxybenzotriazole hydrate and then 0.4 g of morpholine supported on polystyrene are added successively to a solution of 90 mg of (RS)-2-{1-[bis-(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethylamine in 5 cm^3 of tetrahydrofuran, at a temperature in the region of 20°C. The suspension obtained is stirred at a temperature in the region of 20°C for 20 hours. The reaction medium is filtered and concentrated to dryness under reduced pressure. 80 mg of a pasty product are thus obtained, which product is purified by passage over an SPE cartridge (SCX phase, 1 g of phase). 76 mg of a residue are thus obtained, which residue is purified by chromatography under pressure on a silica cartridge, eluting with a mixture of cyclohexane and ethyl acetate (70/30 by volume). Fractions 9 to 19 are combined and concentrated to dryness under reduced pressure. 12 mg of (RS)-N-[2-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethyl]-cyclopropanecarboxamide are obtained in the form of a colorless oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.70 (mt : 1H); from 0.80 to 1.00 (mt : 2H); from 1.15 to 1.35 (mt : 1H); from 2.35 to 2.55 and from 2.70 to 3.10 (2 series of mts : 7H in total); 3.26 (mt : 1H); 3.47 (mt : 1H); 4.19 (s : 1H); 5.63 (mt : 1H);

6.62 (tt, J = 9 and 2.5 Hz : 1H); 6.81 (mt : 2H); from 7.20 to 7.45 (mt : 8H)].

Example 88

(RS)-N-[2-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-2-(3,5-difluorophenyl)ethyl]-3-methylbutyramide may be prepared by carrying out the procedure in the following manner: 114 mg of HATU, 30.6 mg of isovaleric acid and then 0.2 g of morpholine supported on polystyrene are added to a solution of 45 mg of (RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethylamine in 5 cm^3 of tetrahydrofuran, at a temperature in the region of 20°C. The suspension obtained is stirred at a temperature in the region of 20°C for 20 hours. The reaction medium is filtered and concentrated to dryness under reduced pressure. 46 mg of an orange-colored oil are thus obtained, which oil is purified by chromatography under pressure on a cartridge of 5 g of silica, eluting with a mixture of cyclohexane and ethyl acetate (70/30 by volume). The fractions containing only the desired product are combined and concentrated to dryness under reduced pressure. 6 mg of (RS)-N-[2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethyl]-3-methylbutyramide are obtained in the form of a colorless oil [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 0.88 (d, J = 6.5 Hz : 3H); 0.91 (d, J = 6.5 Hz : 3H); from 1.85 to 2.10 (mt : 3H); from 2.30 to 2.55 and from 2.70 to 3.10 (2 series of

mts : 6H in total); 3.37 (mt : 2H); 4.19 (s : 1H); 5.45 (mt : 1H); 6.65 (tt, J = 9 and 2.5 Hz : 1H); 6.82 (mt : 2H); from 7.20 to 7.45 (mt : 8H)].

Example 89

(RS)-N-[2-{1-[Bis(4-chlorophenyl)methyl-azetidin-3-yl}-2-(3,5-difluorophenyl)ethyl]isobutyramide may be prepared by carrying out the procedure in the manner similar to Example 3 above: starting with 45 mg of (RS)-2-{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethylamine, 5 cm^3 of tetrahydrofuran, 114 mg of HATU, 26 mg of isobutyric acid and 0.2 g of morpholine supported on polystyrene, 10 mg of (RS)-N-[2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)ethyl]isobutyramide are obtained in the form of an opaque oil [^{1}H NMR spectrum (400 MHz, $(CD_3)_2SO$ d6, δ in ppm): 0.87 (d, J = 7 Hz : 3H); 0.93 (d, J = 7 Hz : 3H); from 2.15 to 2.85 (mt : 7H); from 3.00 to 3.25 (mt : 2H); 4.40 (s : 1H); from 7.00 to 7.20 (mt : 3H); 7.38 (mt : 4H); 7.52 (mt : 4H); 7.77 (mt : 1H)].

Example 90

{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,4-difluorophenyl)methanone may be prepared by carrying out the procedure in the following manner: 3 cm^3 of a 0.5 N solution of 3,4-difluorophenylmagnesium bromide in tetrahydrofuran are added to a solution of 128 mg of 1-[bis(4-chlorophenyl)methyl]azetidine-

3-carboxylic acid N-methoxy-N-methylamide in 3 cm^3 of tetrahydrofuran, cooled in a bath of acetone and dry ice. After stirring for 20 hours at a temperature in the region of 0°C, 10 cm^3 of water are added and then the reaction medium is stirred for 1 hour at a temperature in the region of 20°C. The aqueous phase separated by settling is extracted with 20 cm^3 of ethyl acetate. The combined organic phases are washed with twice 15 cm^3 of water, dried over magnesium sulfate and concentrated to dryness under reduced pressure. 123 mg of a residue are thus obtained, which residue is purified by chromatography under pressure on a cartridge of 20 g of silica, eluting with dichloromethane (stabilized on amylene). 47 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-3,4-difluorophenyl)methanone are thus obtained in the form of a white powder [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 3.34 (t, J = 7.5 Hz : 2H); 3.56 (t, J = 8 Hz : 2H); 4.05 (mt : 1H); 4.35 (s : 1H); from 7.15 to 7.40 (mt : 9H); 7.58 (dmt, J = 9 Hz : 1H); 7.70 (ddd, J = 9/7.5 and 2.5 Hz : 1H].

1-[Bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid N-methoxy-N-methylamide may be prepared by carrying out the procedure in the following manner: 2.65 cm^3 of 1-methylpiperidine are added to a suspension of 2.03 g of N,O-dimethylhydroxylamine hydrochloride in 40 cm^3 of dichloromethane, cooled to a temperature in the region of 0°C by an ice cold water bath. The yellow

solution obtained (solution A) is stored at a temperature in the region of 0°C. 2.65 cm^3 of 1-methylpiperidine and then 1.6 cm^3 of methyl chloroformate are added successively to a suspension of 7 g of 1-[bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid in 300 cm^3 of dichloromethane and 40 cm^3 of tetrahydrofuran, cooled to a temperature in the region of -8°C by an ice and isopropanol bath. After stirring for about 5 minutes at a temperature in the region of -8°C, solution A prepared above is added dropwise. After stirring for 10 minutes at a temperature in the region of -8°C, the cooling bath is removed, and the reaction mixture is stirred at a temperature in the region of 20°C for about 20 hours, and then washed with 3 times 150 cm^3 of water, and concentrated to dryness under reduced pressure. 8.19 g of a residue are thus obtained, which residue is purified under pressure on 500 g of Amicon silica (diameter of the particles: 20 - 45 ?m), eluting with an ethyl acetate/dichloromethane (8 - 92 by volume) mixture. 6.6 g of 1-[bis(4-chlorophenyl)methyl]-azetidine-3-carboxylic acid N-methoxy-N-methylamide are thus obtained in the form of a pale yellow oil.

1-[Bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid may be prepared in a manner similar to that described by ANDERSON A.G. and LOK R. *J. Org. Chem.*, **37**, 3953-3955 (1972) from 1-benzhydrylazetidin-

3-ol, using, as raw material, 1-[bis(4-chlorophenyl)-methyl]azetidin-3-ol.

Example 91

{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methanone may be prepared by carrying out the procedure as for {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,4-difluorophenyl)methanone, starting with 1.1 g of 1-[bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid N-methoxy-N-methylamide, 1.5 cm^3 of 1-bromo-3,5-difluorobenzene, and 316 mg of magnesium turnings. 880 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methanone are thus obtained in the form of a pale yellow viscous oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 3.34 (t, J = 7.5 Hz : 2H); 3.55 (t, J = 8 Hz : 2H); 4.03 (mt : 1H); 4.44 (s : 1H); 7.01 (tt, J = 9 and 2.5 Hz : 1H); from 7.20 to 7.40 (mt : 10H)].

Example 92

{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-cyclohexylmethanone may be prepared by carrying out the procedure as for {1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,4-difluorophenyl)methanone, starting with 284 mg of 1-[bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid N-methoxy-N-methylamide and 1.68 cm^3 of 2 N cyclohexylmagnesium chloride in THF. 116 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-cyclohexylmethanone are thus obtained in the form of a

yellow viscous oil [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm) : from 1.10 to 1.35 and from 1.55 to 1.85 (2 series of mt : 10H in total); 2.30 (mt : 1H); 3.14 (t, J = 8 Hz : 2H); 3.36 (t, J = 8 Hz : 2H); 3.56 (mt : 1H); 4.31 (s : 1H); from 7.20 to 7.35 (mt : 8H)].

Example 93

{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-phenylmethanone may be prepared by carrying out the procedure as for {1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,4-difluorophenyl)methanone, starting with 258 mg of 1-[bis(4-chlorophenyl)methyl]azetidine-3-carboxylic N-methoxy-N-methylamide and 1.02 cm^3 of 3 N phenylmagnesium bromide in THF. 208 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-phenylmethanone are thus obtained in the form of a yellow viscous oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 3.35 (t, J = 8 Hz : 2H); 3.57 (t, J = 8 Hz : 2H); 4.13 (mt : 1H); 4.35 (s : 1H); 7.25 (dmt, J = 8 Hz : 4H); 7.34 (dmt, J = 8 Hz : 4H); 7.45 (broad t, J = 8 Hz : 2H); 7.56 (tt, J = 8 and 1.5 Hz : 1H); 7.84 (dmt, J = 8 Hz : 2H)].

Example 94

(RS)-1-{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-1-(3,5-difluorophenyl)ethanol may be prepared by carrying out the procedure in the following manner: 0.167 cm^3 of a 3 N methylmagnesium bromide solution is added to a solution of 100 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-

(3,5-difluorophenyl)methanone in 4 cm^3 of tetrahydrofuran, cooled to a temperature of less than -40°C. After stirring for 20 hours at a temperature in the region of 0°C, 5 cm^3 of water are added and then the aqueous phase separated by settling is extracted with 5 cm^3 of ethyl acetate. The combined organic phases are dried over magnesium sulfate and concentrated to dryness under reduced pressure. 91 mg of a residue are thus obtained, which residue is purified by chromatography under pressure on a cartridge of 10 g of silica, eluting with an ethyl acetate/cyclohexane (1/9 by volume) mixture. 74 mg of (RS)-1-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-1-(3,5-difluorophenyl)ethanol are thus obtained in the form of a colorless oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 1.46 (s : 3H); 2.71 (mt : 1H); 2.82 (mt : 1H); 2.98 (t, J = 7.5 Hz : 1H); 3.24 (t, J = 7.5 Hz : 1H); 3.34 (mt : 1H); 4.31 (s : 1H); 4.33 (mf : 1H); 6.67 (tt, J = 9 and 2.5 Hz : 1H); 6.98 (mt : 2H); from 7.25 to 7.35 (mt : 8H)].

Example 95

{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methanone O-allyloxime may be prepared by carrying out the procedure in the following manner: a solution of 100 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)-methanone and 101 mg of O-allylhydroxylamine hydrochloride in 5 cm^3 of pyridine is stirred at a

temperature in the region of 20°C for 20 hours. 5 cm^3 of water are then added and the reaction mixture is extracted with twice 5 cm^3 of ethyl acetate. The combined organic phases are dried over magnesium sulfate and then concentrated to dryness under reduced pressure. 111 mg of a yellow oil are thus obtained, which oil is purified by chromatography under pressure on a cartridge of 20 g of silica (diameter of the particles from 0.04 to 0.063 mm), eluting with an ethyl acetate/cyclohexane (2/98 by volume) mixture. 68 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methanone O-allyloxime are thus obtained in the form of a colorless viscous oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm). A mixture of the 2 Z and E isomers is observed in the approximate proportions 65/35 or conversely; 2.84 and 3.11 (2 broad t, respectively J = 8 Hz and J = 7.5 Hz : 2H in total); 3.44 and 3.66 (2 broad t, respectively J = 7.5 Hz and J = 8 Hz : 2H in total); 3.58 and 3.81 (2 mts : 1H total); 4.16 and 4.30 (2 s : 1H in total); 4.59 (mt : 2H); 5.22 (dmt, J = 11 Hz : 1H); 5.27 (dmt, J = 18 Hz : 1H); 5.96 (mt : 1H); 6.80 (tt, J = 9 and 2.5 Hz : 1H); 6.91 (mt : 2H); from 7.20 to 7.35 (mt : 8H].

Example 96

{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methanone O-ethyloxime may be prepared by carrying out the procedure as described for the preparation of {1-[bis(4-chlorophenyl)methyl]-

azetidin-3-yl}-(3,5-difluorophenyl)methanone O-allyloxime: starting with 100 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)-methanone and 90 mg of O-ethylhydroxylamine hydrochloride, 83 mg of {1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)methanone O-ethyloxime are thus obtained in the form of a colorless viscous oil [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm). A mixture of the 2 Z and E isomers is observed in the approximate proportions 65/35 or conversely; 1.25 and 1.27 (2 t, J = 7 Hz : 3H in total); 2.82 and 3.12 (2 broad t, respectively J = 8 Hz and J = 7.5 Hz : 2H in total); 3.45 and 3.66 (2 broad t, respectively J = 7.5 Hz and J = 8 Hz : 2H in total); 3.58 and 3.78 (2 mts : 1H total); from 4.05 to 4.20 (mt : 2H); 4.16 and 4.30 (2 s : 1H in total); 6.80 (tt, J = 9 and 2.5 Hz : 1H); 6.91 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 97

(RS)-1-[{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)methyl]-3-methylurea may be prepared in the following manner: 0.336 cm^3 of triethylamine and 0.384 cm^3 of diphenylphosphonoazide are added successively to a solution of 300 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride in 15 cm^3 anhydrous toluene, under an inert nitrogen atmosphere, at a temperature in the region of 20°C. The solution

obtained is stirred at a temperature in the region of 60°C for about 90 minutes. 2.6 cm^3 of a 2 M methylamine solution in tetrahydrofuran are added, the stirring is maintained at a temperature in the region of 20°C for about 12 hours, the reaction mixture is concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. The residue is taken up in 1 cm^3 of methanol and then deposited on a BOND-ELUT SCX VARIAN 5 g cartridge with the reference 1225-6027 conditioned with methanol. The cartridge is washed with methanol and eluted with 2 N ammoniacal methanol. The ammoniacal fractions are combined and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 250 mg of a light oil are thus obtained, which oil is taken up in 1 cm^3 of dichloromethane and then deposited on a cartridge 16 mn in diameter, filled with 5 g of silica of particle size 0.015-0.035 mm, conditioned and eluted with dichloromethane between 0 and 40 cm^3 and then eluted with a dichloromethane-ethyl acetate (80-20 by volume) mixture with the aid of a pumping system. The fractions between 50 and 80 cm^3 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 140 mg of (RS)-1-[{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]-3-methylurea are thus obtained in the form of a foam [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 2.66 (mt : 1H); 2.82 (d, J = 5 Hz

: 3H); 2.95 (mt : 1H); 3.03 (mt : 1H); 3.18 (mt : 2H); 4.24 (mt : 1H); 4.30 (s : 1H); 4.92 (t, J = 7 Hz : 1H); 5.36 (broad d, J = 7 Hz : 1H); 6.67 (tt, J = 9 and 2.5 Hz : 1H); 6.80 (mt : 2H); from 7.20 to 7.30 (mt : 8H)].

The preparation of {1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)acetic acid hydrochloride has been described in the patent "carbon-containing derivatives", example 77.

Example 98

(RS)-1-[{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)methyl]-3-isopropylurea may be prepared in the following manner: 3 cm^3, that is 0.1 mM of a freshly prepared solution of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)isocyanatomethyl]azetidine are added to a solution of 17 µl of isopropylamine in 1 cm^3 of anhydrous toluene, under an inert nitrogen atmosphere, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. The solid residue is taken up in 1 cm^3 of methanol and then deposited on a BOND-ELUT SCX VARIAN 500 mg cartridge with the reference 1210-2040, conditioned with methanol. The cartridge is washed with methanol and then eluted with 2 N ammoniacal methanol. The ammoniacal fractions are combined and concentrated to

dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. The solid residue thus obtained is taken up in 1 cm^3 of dichloromethane and then deposited on an IST FlashPack cartridge with the reference SIL 016-002, filled with 2 g of silica (0.065-0.090 mm), conditioned with dichloromethane and eluted with a dichloromethane-ethyl acetate (90-10 by volume) mixture with the aid of a pumping system. The fractions between 20 and 38 cm^3 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 14 mg of (RS)-1-[{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)-methyl]-3-isopropylurea are thus obtained in the form of a white foam [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 1.14 (d, J = 6.5 Hz : 3H); 1.15 (d, J = 6.5 Hz : 3H); 2.66 (mt : 1H); 2.92 (broad dd, J = 8 and 5.5 Hz : 1H); 3.01 (broad dd, J = 8 and 5.5 Hz : 1H); 3.16 (t, J = 8 Hz : 1H); 3.20 (t, J = 8 Hz : 1H); 3.85 (mt : 1H); 4.06 (d, J = 8 Hz : 1H); 4.29 (s : 1H); 4.91 (t, J = 7 Hz : 1H); 5.17 (d, J - 6.5 Hz : 1H); 6.66 (tt, J = 9 and 2 Hz : 1H); 6.78 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

(RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)isocyanatomethyl]azetidine may be prepared in the following manner: 0.126 cm^3 of triethylamine and 0.195 cm^3 of diphenylphosphonoazide are added successively to a solution of 150 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-

(3,5-difluorophenyl)acetic acid hydrochloride in 9 cm^3 of anhydrous toluene, under an inert nitrogen atmosphere, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 50°C for about 1 hour. The mixture is allowed to cool and (RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)isocyanatomethyl]azetidine is thus obtained in solution in toluene and will be subsequently used in this form.

Example 99

(RS)-1-[{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)methyl]-3-isobutylurea may be prepared in the following manner: 3 cm^3, that is 0.1 mM of a freshly prepared solution of (RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)isocyanatomethyl]azetidine are added to a solution of 20 µl of isobutylamine in 1 cm^3 of anhydrous toluene, under an inert nitrogen atmosphere, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. The solid residue is taken up in 1 cm^3 of methanol and then deposited on a BOND-ELUT SCX VARIAN 500 mg cartridge with the reference 1210-2040 conditioned with methanol. The cartridge is washed with methanol and then eluted with 2 N ammoniacal methanol. The ammoniacal fractions

are combined and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. The residue thus obtained is taken up in 1 cm^3 of dichloromethane and then deposited on an IST FlashPack cartridge with the reference SIL 016-002 filled with 2 g of silica (0.065-0.090 mm), conditioned with dichloromethane and eluted with a dichloromethane-ethyl acetate (90-10 by volume) mixture with the aid of a pumping system. The fractions between 0 and 15 cm^3 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 14 mg of (RS)-1-[{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]-3-isobutylurea are thus obtained in the form of a white foam [^{1}H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 0.89 (d, J = 6.5 Hz : 3H); 0.90 (d, J = 6.5 Hz : 3H); 1.74 (mt : 1H); 2.66 (mt : 1H); from 2.90 to 3.25 (mt : 6H); 4.29 (s and mt : 2H in total); 4.90 (t, J = 7 Hz : 1H); 5.34 (broad d, J = 6.5 Hz : 1H); 6.66 (tt, J = 9 and 2 Hz : 1H); 6.80 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 100

N-Methyl-N-phenyl-1-[bis(4-chlorophenyl)-methyl]azetidine-3-carboxamide may be prepared in the following manner: 0.039 cm^3 of N-methylaniline, 87 mg of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, 0.063 cm^3 of triethylamine and then 4 mg of hydroxybenzotriazol hydrate are added successively to a solution of 100 mg of 1-[bis(4-chlorophenyl)-

methyl]azetidine-3-carboxylic acid in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on an IST FlashPack cartridge with the reference SIL 016-005 filled with 5 g of silica (0.065-0.090 mm), conditioned with dichloromethane and eluted with a gradient of dichloromethane-ethyl acetate mixture (the percentage of ethyl acetate varying from 0 to 5 by volume) with the aid of a pumping system, collecting 1.5 cm^3 fractions. Fractions 3 to 15 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 50°C. 95 mg of 1-[bis(4-chlorophenyl)methyl]azetidine-N-methyl-N-phenyl-3-carboxamide are thus obtained in the form of a cream-colored foam [^1H NMR spectrum (400 MHz, $CDCl_3$, δ in ppm): 3.08 (mt : 2H); 3.21 (mt : 3H); 3.27 (s : 3H); 4.35 (s : 1H); 7.06 (d, J = 7.5 Hz : 2H); from 7.15 to 7.45 (mt : 11H)].

Example 101

1-[Bis(4-chlorophenyl)methyl]azetidine-N-benzyl-N-methyl-3-carboxamide may be prepared in the following manner: 0.0213 cm^3 of N-benzylmethylamine is added to a suspension of 150 mg of 1-[bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid activated on TFP resin (165 µM) in 2 cm^3 of dichloromethane. The suspension is stirred at a temperature in the region of 20°C for 22 hours and then filtered on sintered glass. The solid residue is washed again with twice 1 cm^3 of

dichloromethane. The filtrates are combined and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 38 mg of 1-[bis(4-chlorophenyl)methyl]azetidine-N-benzyl-N-methyl-3-carboxamide are thus obtained in the form of a colorless gum [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.78 (s : 3H); from 3.25 to 3.55 (mt : 5H); 4.38 (mt : 2H); 4.57 (s : 1H); from 7.15 to 7.40 (mt : 13H].

1-[Bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid activated on TFP resin may be prepared in the following manner: 2 g of 1-[bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid, 73 mg of 4-dimethylaminopyridine, 0.927 cm^3 of 1,3-diisopropylcarbodiimide are added to a suspension of 2.7 g of TFP resin (free phenol functional group, 1.1 mmol/g, that is 2.975 mM) in 40 cm^3 of anhydrous dimethylformamide. After stirring for 19 hours at a temperature in the region of 20°C, the suspension is filtered, the resin is washed with 40 cm^3 of dimethylformamide, 40 cm^3 of tetrahydrofuran, 40 cm^3 of dichloromethane and then dried under vacuum to a constant weight. 3.6 g of 1-[bis(4-chlorophenyl)-methyl]azetidine-3-carboxylic acid activated on TFP resin are thus obtained.

1-[Bis(4-chlorophenyl)methyl]azetidine-3-carboxylic acid may be prepared in a manner similar to that described by ANDERSON A.G. and LOK R., *J. Org. Chem.*, **37**, 3953-3955 (1972) from 1-benzhydrylazetidin-

3-ol, using, as raw material, 1-[bis(4-chlorophenyl)-methyl]azetidin-3-ol.

The TFP resin (free phenol functional group) may be prepared according to the procedure described in patent WO9967228.

Example 102

(RS)-[{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]methylamine may be prepared in the following manner: 0.099 cm^3 of methylamine is added to a solution of 108 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methanone in 2 cm^3 of anhydrous 1,2-dichloroethane, followed successively by 84 mg of sodium triacetoxyborohydride and 0.014 cm^3 of acetic acid. After stirring for 12 hours at a temperature in the region of 20°C, 0.992 cm^3 of methylamine, 85 mg of sodium triacetoxyborohydride and then 0.143 cm^3 of acetic acid are again added successively. The solution obtained is stirred at a temperature in the region of 20°C for about 24 hours and then washed with 4 cm^3 of a saturated sodium bicarbonate solution. The organic phase is separated by settling and then dried over magnesium sulfate, filtered and then concentrated under reduced pressure (2.7 kPa). The residue thus obtained is purified on an IST FlashPack cartridge with the reference SIL 016-002 filled with 2 g of silica (0.065-0.090 mm) conditioned with dichloromethane and eluted with a gradient of dichloromethane-methanol

mixture (the percentage of methanol varying from 0 to 6 by volume) with the aid of a pumping system, collecting 1 cm^3 fractions. Fractions 8 to 18 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 50°C. 66 mg of [{1-[bis(4-chlorophenyl)-methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]-methylamine are thus obtained in the form of a colorless honey [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 2.25 (s : 3H); 2.60 (mt : 1H); 2.68 (t, J = 7 Hz : 1H); 2.94 (t, J = 7 Hz : 1H); 3.02 (broad t, J = 7 Hz : 1H); 3.34 (broad t, J = 7 Hz : 1H); 3.58 (d, J = 9 Hz : 1H); 4.25 (s : 1H); 6.67 (tt, J = 9 and 2.5 Hz : 1H); 6.80 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 103

(RS)-[{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]isobutylamine may be prepared in the following manner: 0.028 cm^3 of isobuthylamine is added to a solution of 109 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methanone in 2 cm^3 of anhydrous 1,2-dichloroethane, followed successively by 85 mg of sodium triacetoxyborohydride and 0.015 cm^3 of acetic acid. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a cartridge filled with 5 g of silica, conditioned with dichloromethane and eluted with a gradient of dichloromethane-ethyl acetate mixture (the percentage of ethyl acetate varying from 0

to 10 by volume) with the aid of a pumping system. The fractions containing the desired product are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 8 mg of (RS)-[{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]isobutylamine are thus obtained [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.85 (d, J = 7 Hz : 3H); 0.87 (d, J = 7 Hz : 3H); 1.63 (mt : 1H); 2.15 (dd, J = 11 and 7.5 Hz : 1H); 2.25 (dd, J = 11 and 7 Hz : 1H); 2.57 (mt : 1H); 2.70 (t, J = 7 Hz : 1H); 2.92 (t, J = 7 Hz : 1H); 3.01 (broad t, J = 7.5 Hz : 1H); 3.33 (broad t, J = 7.5 Hz : 1H); 3.66 (d, J = 9 Hz : 1H); 4.25 (s : 1H); 6.66 (tt, J = 9 and 2.5 Hz : 1H); 6.81 (mt : 2H); from 7.20 to 7.35 (mt : 8H)].

Example 104

(RS)-[{1-[Bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]butylamine may be prepared in the following manner: 0.0265 cm^3 of n-butylamine is added to a solution of 108 mg of {1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methanone in 2 cm^3 of anhydrous 1,2-dichloroethane, followed successively by 95 mg of sodium triacetoxyborohydride and 0.0143 cm^3 of acetic acid. After stirring for about 16 hours at a temperature in the region of 20°C, 0.0265 cm^3 of n-butylamine, 85 mg of sodium triacetoxyborohydride and then 0.143 cm^3 of acetic acid are again successively added. The solution obtained is stirred at a

temperature in the region of 20°C for about 24 hours and then washed with 4 cm^3 of a saturated sodium bicarbonate solution. The organic phase is separated by settling and then dried over magnesium sulfate, filtered and then concentrated under reduced pressure (2.7 kPa). The residue thus obtained is purified on an IST FlashPack cartridge with the reference SIL 016-002 filled with 2 g of silica (0.065-0.090 mm), conditioned with dichloromethane and eluted with a gradient of dichloromethane-methanol mixture (the percentage of methanol varying from 0 to 6 by volume) with the aid of a pumping system, collecting 1 cm^3 fractions. Fractions 25 to 30 are combined and concentrated to dryness under reduced pressure (2.7 kPa) at 50°C. 37 mg of RS)-[{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]butylamine are thus obtained in the form of a colorless honey [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.85 (t, J = 7.5 Hz : 3H); from 1.20 to 1.50 (mt : 4H); 2.37 (broad t, J = 7 Hz : 2H); 2.56 (mt : 1H); 2.67 (t, J = 7 Hz : 1H); 2.89 (t, J = 7 Hz : 1H); 2.99 (broad t, J = 7 Hz : 1H); 3.32 (broad t, J = 7 Hz : 1H); 3.67 (d, J = 9 Hz : 1H); 4.24 (s : 1H); 6.65 (tt, J = 9 and 2.5 Hz : 1H); 6.80 (mt : 2H); from 7.20 to 7.35 (mt : 8H].

Example 105

(RS)-N-[{1-[Bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)methyl]-3-methylbutyramide may be prepared in the following

manner: 0.025 cm^3 of N,N'-diisopropylcarbodiimide, 10 mg of hydroxybenzotriazole hydrate, 30 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-C-(3,5-difluorophenyl)methylamine are added successively to a solution of 0.017 cm^3 of isovaleric acid in 2 cm^3 of anhydrous dichloromethane, at a temperature in the region of 20°C. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours. The reaction medium is deposited on a BOND-ELUT SCX VARIAN 500 mg cartridge with the reference 1210-2040, conditioned with methanol. The cartridge is washed with methanol and then eluted with 2N ammoniacal methanol. The ammoniacal fractions are combined and concentrated to dryness under reduced pressure (2.7 kPa) at a temperature in the region of 40°C. 35 mg of (RS)-N-[{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-(3,5-difluorophenyl)methyl]-3-methylbutyramide are thus obtained in the form of a yellow honey [^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ in ppm): 0.98 (d, J = 5 Hz : 6H); from 2.05 to 2.25 (mt : 3H); 2.71 (mt : 1H); 2.90 (mt : 1H); 3.00 (mt : 1H); 3.20 (mt : 2H); 4.30 (s : 1H); 5.14 (t, J = 7.5 Hz : 1H); 6.48 (broad d, J = 7.5 Hz : 1H); 6.67 (tt, J = 9 and 2.5 Hz : 1H); 6.75 (mt : 2H); from 7.20 to 7.40 (mt : 8H)].

(RS)-C-{1-[Bis(4-chlorophenyl)-methyl]azetidin-3-yl}-C-(3,5-difluorophenyl)methylamine may be prepared in the following manner: to a solution

of 216 mg of (RS)-{1-[bis(4-chlorophenyl)methyl]-azetidin-3-yl}-(3,5-difluorophenyl)methanone in 10 cm^3 of methanol, followed successively by 385 mg of ammonium acetate and 29 mg of sodium cyanoborohydride. The solution obtained is stirred at a temperature in the region of 20°C for about 12 hours and then made lukewarm at 45°C for 6 h. 29 mg of sodium cyanoborohydride are added to this solution. The stirring is continued at a temperature in the region of 20°C for 72 hours. The reaction medium is poured into a mixture of 30 cm^3 of ice-cold water with 5 cm^3 of a 4 N aqueous sodium hydroxide solution, and then extracted with twice 30 cm^3 of ethyl acetate, the organic phase is extracted with twice 30 cm^3 of N hydrochloric acid, the aqueous phase thus obtained is alkalinized with a normal aqueous sodium hydroxide solution and then extracted with three times 20 cm^3 of ethyl acetate. The combined organic phases are dried over magnesium sulfate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa) at 40°C. 35 mg of (RS)-C-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-C-(3,5-difluorophenyl)methylamine are thus obtained in the form of a yellow honey.

The medicaments according to the invention consist of a compound of formula (I) or an isomer or a salt of such a compound, in the pure state or in the form of a composition in which it is combined with any other pharmaceutically compatible product which may be

inert or physiologically active. The medicaments according to the invention may be used orally, parenterally, rectally or topically.

As solid compositions for oral administration, tablets, pills, powders (gelatine capsules, sachets) or granules may be used. In these compositions, the active ingredient according to the invention is mixed with one or more inert diluents, such as starch, cellulose, sucrose, lactose or silica, under an argon stream. These compositions may also comprise substances other than diluents, for example one or more lubricants such as magnesium stearate or talc, a coloring, a coating (sugar-coated tablets) or a glaze.

As liquid compositions for oral administration, there may be used pharmaceutically acceptable solutions, suspensions, emulsions, syrups and elixirs containing inert diluents such as water, ethanol, glycerol, vegetable oils or paraffin oil. These compositions may comprise substances other than diluents, for example wetting, sweetening, thickening, flavoring or stabilizing products.

Sterile compositions for parenteral administration may be preferably solutions which are aqueous or nonaqueous, suspensions or emulsions. As solvent or vehicle, there may be used water, propylene glycol, polyethylene glycol, vegetable oils, in particular olive oil, injectable organic esters, for

example ethyl oleate or other suitable organic solvents. These compositions may also contain adjuvants, in particular wetting, isotonizing, emulsifying, dispersing and stabilizing agents. Sterilization may be carried out in several ways, for example by asepticizing filtration, by incorporating sterilizing agents into the composition, by irradiation or by heating. They may also be prepared in the form of sterile solid compositions which may be dissolved at the time of use in sterile water or any other injectable sterile medium.

Compositions for rectal administration are suppositories or rectal capsules which contain, in addition to the active product, excipients such as cocoa butter, semisynthetic glycerides or polyethylene glycols.

Compositions for topical administration may be, for example, creams, lotions, collyria, collutoria, nasal drops or aerosols.

In human therapy, the compounds according to the invention are particularly useful for the treatment and/or prevention of psychoses including schizophrenia, anxiety disorders, depression, epilepsy, neurodegeneration, cerebellar and spinocerebellar disorders, cognitive disorders, cranial trauma, panic attacks, peripheral neuropathies, glaucomas, migraine, Parkinson's disease, Alzheimer's disease, Huntington's chorea, Raynaud's syndrome, tremor, obsessive-

compulsive disorder, senile dementia, thymic disorders, Tourette's syndrome, tardive dyskinesia, bipolar disorders, cancers, movement disorders induced by medicaments, dystonia, endotoxemic shocks, hemorrhagic shocks, hypotension, insomnia, immunological diseases, multiple sclerosis, vomiting, asthma, appetite disorders (bulimia, anorexia), obesity, memory disorders, intestinal transit disorders, in weaning from chronic treatments and alcohol or drug abuse (opioids, barbiturates, cannabis, cocaine, amphetamine, phencyclide, hallucinogens, benzodiazepines for example), as analgesics or potentiators of the analgesic activity of the narcotic and nonnarcotic drugs.

The doses depend on the desired effect, the duration of the treatment and the route of administration used; they are generally between 5 mg and 1000 mg per day orally for an adult with unit doses ranging from 1 mg to 250 mg of active substance.

In general, the doctor will determine the appropriate dosage depending on the age, weight and any other factors specific to the subject to be treated.

The following examples illustrate the compositions according to the invention:

EXAMPLE A

Gelatin capsules containing a dose of 50 mg of active product and having the following composition are prepared according to the usual technique:

- Compound of formula (I) ..... 50 mg
- Cellulose ..... 18 mg
- Lactose ..... 55 mg
- Colloidal silica ..... 1 mg
- Sodium carboxymethylstarch ..... 10 mg
- Talc ..... 10 mg
- Magnesium stearate ..... 1 mg

EXAMPLE B

Tablets containing a dose of 50 mg of active product and having the following composition are prepared according to the usual technique:

- Compound of formula (I) ..... 50 mg
- Lactose ..... 104 mg
- Cellulose ..... 40 mg
- Polyvidone ..... 10 mg
- Sodium carboxymethylstarch ..... 22 mg
- Talc ..... 10 mg
- Magnesium stearate ..... 2 mg
- Colloidal silica ..... 2 mg
- Mixture of hydroxymethylcellulose, glycerin, titanium oxide (72-3.5-24.5) qs 1 finished film-coated tablet containing 245 mg

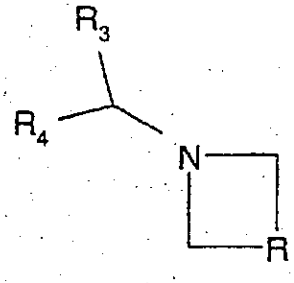
EXAMPLE C

An injectable solution containing 10 mg of active product having the following composition is prepared:

- Compound of formula (I)	10 mg
- Benzoic acid	80 mg
- Benzyl alcohol	0.06 ml
- Sodium benzoate	80 mg
- Ethanol, 95%	0.4 ml
- Sodium hydroxide	24 mg
- Propylene glycol	1.6 ml
- Water	qs 4 ml

CLAIMS

1. Compound of formula



(I)

in which

R represents a radical CR_1R_2, $C=C(R_5)SO_2R_6$ or $C=C(R_7)SO_2alk$,

or R_1 represents a hydrogen atom and R_2 represents a radical $-C(R_8)(R_9)(R_{10})$, $-C(R_8)(R_{11})(R_{12})$, $-CO-NR_{13}R_{14}$, $-CH_2-CO-NR_{13}R_{14}$, $-CH_2-CO-R_6$, $-CO-R_6$, -CO-cycloalkyl, $-SO-R_6$, $-SO_2-R_6$, $-C(OH)(R_{12})(R_6)$, $-C(OH)(R_6)(alkyl)$, $-C(=NOalk)R_6$, $-C(=NO-CH_2-CH=CH_2)R_6$, $-CH_2-CH(R_6)NR_{31}R_{32}$, $-CH_2-C(=NOalk)R_6$, $-CH(R_6)NR_{31}R_{32}$, $-CH(R_6)NHSO_2alk$, $-CH(R_6)NHCONHalk$ or $-CH(R_6)NHCOalk$,

or R_1 represents an alkyl, $NH-R_{15}$, cyano, $-S-alk-NR_{16}R_{17}$, $-CH_2-NR_{18}R_{19}$, or $-NR_{20}R_{21}$ radical and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$,

R_3 and R_4, which are identical or different, represent either an alkyl or cycloalkyl radical, or an aromatic

chosen from phenyl, naphthyl or indenyl, these aromatics being unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, formyl, hydroxyl, trifluoromethyl, trifluoromethoxy, -CO-alk, cyano, -COOH, -COOalk, $-CONR_{22}R_{23}$, $-CO-NH-NR_{24}R_{25}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl or $-alk-NR_{24}R_{25}$ radicals; or a heteroaromatic chosen from the benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, imidazolyl, isochromanyl, isoquinolyl, pyrrolyl, pyridyl, pyrimidinyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, -COOH, -COOalk, $-CO-NH-NR_{24}R_{25}$, $-CONR_{22}R_{23}$, $-alk-NR_{24}R_{25}$, alkylsulfanyl, alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl or hydroxyalkyl radicals,

R_5 represents a hydrogen atom or an alkyl radical,

R_6 represents a radical Ar or Het,

R_7 represents a cycloalkyl, heterocycloalkyl or heterocyclenyl radical optionally substituted by a -CSO-phenyl radical,

R_8 represents a hydrogen atom or an alkyl radical,

R_9 represents a radical $-CO-NR_{26}R_{27}$, -COOH, -COOalk, $-CH_2OH$, -NH-CO-NH-alk, $-CH_2-NHR_{28}$ or -NHCOOalk,

R_{10} represents a radical Ar or Het,

R_{11} represents a radical $-SO_2$-alk, $-SO_2$-Ar or $-SO_2$-Het,

R_{12} represents a hydrogen atom or a radical Ar or Het,

R_{13} represents a hydrogen atom or an alkyl radical,

R_{14} represents a radical Ar, Het, -alk-Ar or -alk-Het,

R_{15} represents an alkyl, cycloalkyl or $-alk-NR_{29}R_{30}$ radical,

R_{16} and R_{17}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{16} and R_{17} together form with the nitrogen atom to which they are attached a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle optionally containing one or more other heteroatoms chosen from

oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl radicals,

R_{18} represents a hydrogen atom or an alkyl radical,

R_{19} represents a hydrogen atom or an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, $-SO_2$alk, -CO-NHalk or -COOalk radical,

or alternatively R_{18} and R_{19} form with the nitrogen atom to which they are attached a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle optionally containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl radicals,

$-NR_{20}R_{21}$ represents a 3- to 8-membered saturated or unsaturated monocyclic heterocycle optionally containing another heteroatom chosen from oxygen, nitrogen and sulfur,

R_{22} and R_{23}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{22} and R_{23} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and

being optionally substituted with one or more alkyl radicals,

R_{24} and R_{25}, which are identical or different, represent a hydrogen atom or an alkyl, -COOalk, cycloalkyl, alkylcycloalkyl, -alk-O-alk or hydroxyalkyl radical or alternatively R_{24} and R_{25} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo, hydroxyalkyl, -alk-O-alk or $-CO-NH_2$ radicals,

R_{26} and R_{27}, which are identical or different, represent a hydrogen atom or an alkyl, hydroxyalkyl, cycloalkyl, cycloalkylalkyl, -alk-COOalk, -alk-Ar, -alk-Het, Het or $-alk-N(alk)_2$ radical, R_{26} and R_{27} may also form with the nitrogen atom to which they are attached a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle optionally containing one or more other heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted with one or more alkyl or alkoxy radicals or halogen atoms,

R_{28} represents a $-CH_2$-alk, benzyl, $-SO_2$alk, -CONHalk, -COalk, cycloalkylalkylcarbonyl, cycloalkylcarbonyl or $-CO-(CH_2)_nOH$ radical,

n is equal to 1, 2 or 3,

R_{29} and R_{30}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{29} and R_{30} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{31} and R_{32}, which are identical or different, represent a hydrogen atom or an alkyl, Ar or -alk-Ar radical or alternatively R_{31} and R_{32} together form with the nitrogen atom to which they are attached a heterocycle chosen from aziridinyl, azetidinyl, pyrrolidinyl and piperidinyl,

alk represents an alkyl or alkylene radical,

Ar represents a phenyl or naphthyl radical optionally substituted with one or more substituents chosen from a halogen atom or an alkyl, alkoxy, -CO-alk, cyano, -COOH, -COOalk, $-CONR_{22}R_{23}$, $-CO-NH-NR_{24}R_{25}$, alkylsulfanyl,

alkylsulfinyl, alkylsulfonyl, alkylsulfanylalkyl, alkylsulfinylalkyl, alkylsulfonylalkyl, hydroxyalkyl, -alk-$NR_{24}R_{25}$, -$NR_{24}R_{25}$, alkylthioalkyl, formyl, hydroxyl, CF_3, OCF_3, Het, -O-alk-NH-cycloalkyl or SO_2NH_2 radical,

Het represents a 3- to 10-membered unsaturated or saturated mono- or bicyclic heterocycle containing one or more heteroatoms chosen from oxygen, sulfur and nitrogen and optionally substituted with one or more halogen atoms or alkyl, alkoxy, alkoxycarbonyl, -$CONR_{22}R_{23}$, hydroxyl, hydroxyalkyl, oxo or SO_2NH_2 radicals,

the alkyl and alkylene radicals and portions and the alkoxy radicals and portions are in the form of a straight or branched chain and contain 1 to 6 carbon atoms, the cycloalkyl radicals contain 3 to 10 carbon atoms and the heterocycloalkyl and heterocyclenyl radicals contain 3 to 10 carbon atoms,
their optical isomers and their salts with an inorganic or organic acid.

2. Compound according to claim 1, for which Het is chosen from benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, chromanyl, 2,3-dihydrobenzofuryl, 2,3-dihydrobenzothienyl, furyl, indolinyl, indolyl, isochromanyl, isoquinolyl, piperidyl, pyrrolyl, pyridyl, pyrimidinyl, quinolyl,

1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinolyl, thiazolyl and thienyl.

3. Compound of formula (I) according to claim 1, for which when R_{16} and R_{17} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

4. Compound of formula (I) according to claim 1, for which when R_{18} and R_{19} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

5. Compound of formula (I) according to claim 1, for which the heterocycle formed by $NR_{20}R_{21}$ is an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl, piperazinyl or imidazolyl ring.

6. Compound of formula (I) according to claim 1, for which when R_{22} and R_{23} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

7. Compound of formula (I) according to claim 1, for which when R_{24} and R_{25} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

8. Compound of formula (I) according to claim 1, for which when R_{26} and R_{27} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

9. Compound of formula (I) according to claim 1, for which when R_{29} and R_{30} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle, the latter is an azetidinyl, pyrrolidinyl, piperidinyl, morpholinyl, thiamorpholinyl or piperazinyl ring.

10. Compound of formula (I) according to claim 1, for which:

R represents a radical CR_1R_2,

either R_1 represents a hydrogen atom and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ or $C(R_8)(R_9)(R_{10})$,

or R_1 represents an alkyl radical and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$,

R_3 and R_4, which are identical or different, represent either a phenyl which is unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_{22}R_{23}$, hydroxyalkyl or $-alk-NR_{24}R_{25}$ radicals; or a heteroaromatic chosen from the pyridyl, pyrimidinyl, thiazolyl and thienyl rings, it being possible for these heteroaromatics to be unsubstituted or substituted with one or more halogen atoms or alkyl, alkoxy, hydroxyl, trifluoromethyl, trifluoromethoxy, cyano, $-CONR_{22}R_{23}$, $-alk-NR_{24}R_{25}$ or hydroxyalkyl radicals,

R_8 represents a hydrogen atom,

R_9 represents a $-CO-NR_{26}R_{27}$, -COOalk, $-CH_2OH$, -NH-CO-NH-alk, $-CH_2-NHR_{28}$ or -NHCOOalk radical,

R_{10} represents a radical Ar or Het,

R_{11} represents a radical $-SO_2$-alk, $-SO_2$-Ar or $-SO_2$-Het,

R_{12} represents represents a hydrogen atom or a radical Ar or Het,

R_{22} and R_{23}, which are identical or different, represent a hydrogen atom or an alkyl radical or alternatively R_{22} and R_{23} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated mono- or bicyclic heterocycle optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl radicals,

R_{24} and R_{25}, which are identical or different, represent a hydrogen atom or an alkyl, cycloalkyl, alkylcycloalkyl or hydroxyalkyl radical or alternatively R_{24} and R_{25} together form with the nitrogen atom to which they are attached a 3- to 10-membered saturated or unsaturated mono- or bicyclic heterocycle optionally containing another heteroatom chosen from oxygen, sulfur and nitrogen and being optionally substituted with one or more alkyl, -COalk, -COOalk, -CO-NHalk, -CS-NHalk, oxo or $-CO-NH_2$ radicals,

Ar represents a phenyl or naphthyl radical optionally substituted with 1 or 2 subtituents chosen from a halogen atom or an alkyl, alkoxy, -CO-alk, cyano, -COOalk, $-CONR_{22}R_{23}$, alkylsulfonyl, hydroxyalkyl, $-alk-NR_{24}R_{25}$, $-NR_{24}R_{25}$, hydroxyl, CF_3, OCF_3, -O-alk-NH-cycloalkyl or SO_2NH_2 radical,

Het represents a benzofuryl, benzothiazolyl, benzothienyl, benzoxazolyl, furyl, isoquinolyl, pyrrolyl, pyridyl, quinolyl, 1,2,3,4-tetrahydroisoquinolyl, 1,2,3,4-tetrahydroquinolyl, thiazolyl or thienyl ring,

their optical isomers and their salts with an inorganic or organic acid.

11. Compound chosen from the following compounds:

(RS)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine,

(R)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine,

(S)-1-[bis(4-chlorophenyl)methyl)]-3-[(3,5-difluorophenyl)(methylsulfonyl)methyl]azetidine,

(RS)-1-[bis(4-chlorophenyl)methyl)]-3-[(pyrid-3-yl)(methylsulfonyl)methyl]azetidine,

(R)-1-[bis(4-chlorophenyl)methyl)]-3-[(pyrid-3-yl)(methylsulfonyl)methyl]azetidine,

(S)-1-[bis(4-chlorophenyl)methyl)]-3-[(pyrid-3-yl)(methylsulfonyl)methyl]azetidine,

(RS)-1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluoro-phenyl)methylsulfonylmethyl]azetidine,

(R)-1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluoro-phenyl)methylsulfonylmethyl]azetidine,

(S)-1-[bis(3-fluorophenyl)methyl]-3-[(3,5-difluoro-phenyl)methylsulfonylmethyl]azetidine,

1-[bis(4-chlorophenyl)methyl]-3-(RS)-{[3-azetidin-1-yl-phenyl]methylsulfonylmethyl}azetidine,

1-[bis(4-chlorophenyl)methyl]-3-(R)-{[3-azetidin-1-yl-phenyl]methylsulfonylmethyl}azetidine,

1-[bis(4-chlorophenyl)methyl]-3-(S)-{[3-azetidin-1-yl-phenyl]methylsulfonylmethyl}azetidine,

(RS)-1-[3({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]pyrrolidine,

(R)-1-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]pyrrolidine,

(S)-1-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethyl)phenyl]pyrrolidine,

(RS)-N-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}methylsulfonylmethyl)phenyl]-N-methylamine,

(R)-N-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]-N-methylamine,

(S)-N-[3-({1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-methylsulfonylmethyl)phenyl]-N-methylamine,

(RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bistrifluoromethylphenyl)methylsulfonylmethyl]azetidine,

(R)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bistrifluoromethylphenyl)methylsulfonylmethyl]azetidine,

(S)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-bistrifluoromethylphenyl)methylsulfonylmethyl]azetidine,

1-[bis(4-chlorophenyl)methyl]-3-(phenylsulfonylmethyl)azetidine,

(RS)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-3-methylazetidine,

(R)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]-3-methylazetidine,

(S)-1-[bis(4-chlorophenyl)methyl]-3-[(3,5-difluoro-phenyl)methylsulfonylmethyl]-3-methylazetidine,

(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylacetamide,

(R)-2-{1-[bis(4-chlorophenyl)methyl]azeditin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylacetamide,

(S)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclohexylacetamide,

(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isobutylacetamide,

(R)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isobutylacetamide,

(S)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isobutylacetamide,

(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylmethylacetamide,

(R)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylmethylacetamide,

(S)-2-{1-bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-cyclopropylmethylacetamide,

(RS)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isopropylacetamide,

(R)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isopropylacetamide,

(S)-2-{1-[bis(4-chlorophenyl)methyl]azetidin-3-yl}-2-(3,5-difluorophenyl)-N-isopropylacetamide,

(RS)-1-[bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluorophenyl)-1-methylsulfonylethyl]azetidine,

(R)-1-[bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluorophenyl)-1-methylsulfonylethyl]azetidine,

(S)-1-[bis(4-chlorophenyl)methyl]-3-[1-(3,5-difluorophenyl)-1-methylsulfonylethyl]azetidine,

(RS)-1-[bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(R)-1-[bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(S)-1-[bis(4-fluorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RS)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SS)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RR)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SR)-{1-[(3-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RS)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SS)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RR)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SR)-{1-[(4-pyridyl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RS)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine,

(SR)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine,

(RR)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine,

(SS)-5-((4-chlorophenyl)-{3-[(3,5-difluorophenyl)-methylsulfonylmethyl]azetidin-1-yl}methyl)pyrimidine,

(SS)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(RR)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

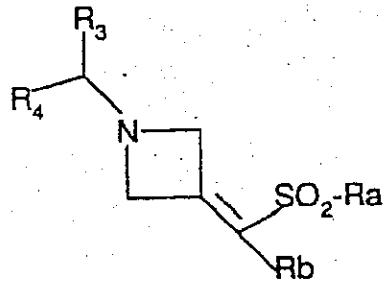
(RS)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

(SR)-{1-[(2-chloropyrid-5-yl)-(4-chlorophenyl)methyl]-3-[(3,5-difluorophenyl)methylsulfonylmethyl]azetidine,

their optical isomers and their pharmaceutically acceptable salts with an inorganic or organic acid.

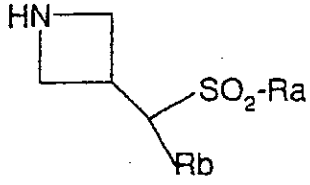
12. Process for preparing the compounds of formula (I) according to claim 1 for which R represents

a radical CR_1R_2, in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_{11})(R_{12})$ in which R_8 represents a hydrogen atom, R_{11} represents a radical $-SO_2-Ar$, $-SO_2-Het$ or $-SO_2alk$ and R_{12} represents a hydrogen atom or a radical Ar or Het, characterized in that a derivative of formula:



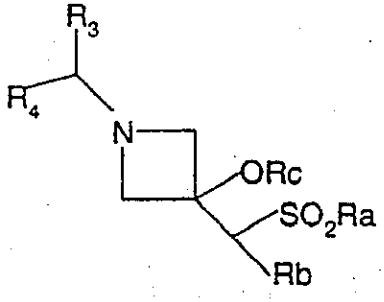
in which Ra represents an alkyl, Het or Ar radical and Rb represents a hydrogen atom or an Ar, Het or alkyl radical, Ar and Het having the same meanings as in claim 1, is reduced, the product isolated and optionally converted to a salt with an inorganic or organic acid.

13. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2, in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_{11})(R_{12})$ in which R_8 represents a hydrogen atom, R_{11} represents a radical $-SO_2-Ar$, $-SO_2-Het$ or $-SO_2alk$ and R_{12} represents a hydrogen atom or a radical Ar or Het, characterized in that a derivative $R_3CH(Br)R_4$ is reacted with a derivative of formula:



in which Ra represents an alkyl, Het or Ar radical and Rb represents a hydrogen atom or an Ar, Het or alkyl radical, Ar and Het having the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

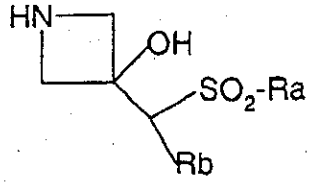
14. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical $C=C(R_5)SO_2R_6$ or $C=C(R_7)SO_2alk$, characterized in that a derivative of formula:



in which either Ra represents a radical Ar or Het and Rb represents a hydrogen atom or an alkyl radical, or Ra represents an alkyl radical and Rb represents a cycloalkyl, heterocycloalkyl or heterocyclenyl radical optionally substituted with a radical -CSO-phenyl, Rc represents a hydrogen atom or an acetyl radical, R_3, R_4, Ar and Het having the same meanings as in claim 1, is

dehydrated, the product isolated and optionally converted to a salt with an inorganic or organic acid.

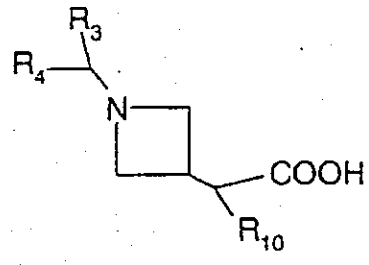
15. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical $C=C(R_5)SO_2R_6$ or $C=C(R_7)SO_2alk$, characterized in that $R_3CH(Br)R_4$ is reacted with a derivative of formula:



in which either Ra represents a radical Ar or Het and Rb represents a hydrogen atom or an alkyl radical, or Ra represents an alkyl radical and Rb represents a cycloalkyl, heterocycloalkyl or heterocyclenyl radical optionally substituted with a radical -CSO-phenyl, Rc represents a hydrogen atom or an acetyl radial, R_3, R_4, Ar and Het having the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

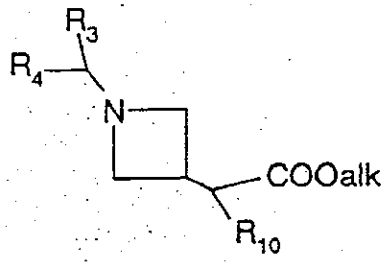
16. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_9)(R_{10})$ in which R_8 represents a hydrogen atom, R_9 represents a radical $-CO-NR_{26}R_{27}$ and R_{10} represents a radical Ar or Het, characterized in that an amine $HNR_{26}R_{27}$ in which R_{26} and

R_{27} have the same meanings as in claim 1, is reacted with an acid of formula:



in which R_3, R_4 and R_{10} have the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

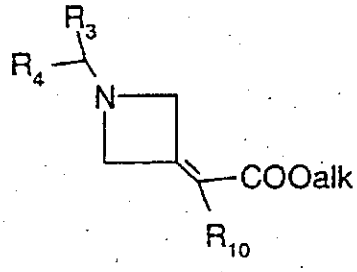
17. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_9)(R_{10})$ in which R_8 represents a hydrogen atom, R_9 represents a radical -COOH and R_{10} represents a radical Ar or Het, characterized in that the corresponding ester of formula:



in which R_3, R_4 and R_{10} have the same meanings as in claim 1 and alk represents an alkyl radical (1-6C in the form of a straight or branched chain, is

hydrolyzed, the product isolated and optionally converted to a salt with an inorganic or organic acid.

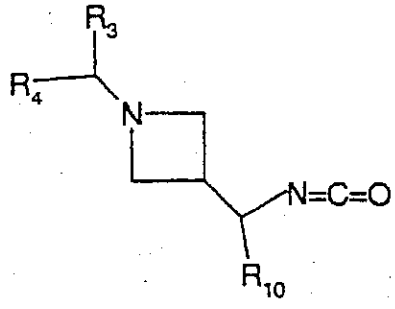
18. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_9)(R_{10})$ in which R_8 represents a hydrogen atom, R_9 represents a radical -COOalk or $-CH_2OH$ and R_{10} represents a radical Ar or Het, characterized in that a compound of formula:



in which R_3, R_4 and R_{10} have the same meanings as in claim 1 and alk represents an alkyl radical (1-6C in the form of a straight or branched chain), is reduced, the product isolated and optionally converted to a salt with an inorganic or organic acid.

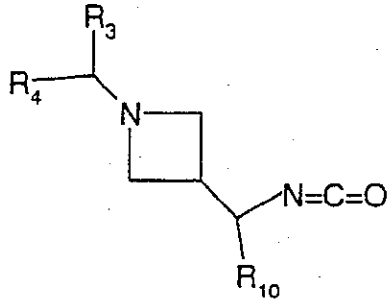
19. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_9)(R_{10})$ in which R_8 represents a hydrogen atom, R_9 represents a radical -NHCOOalk and R_{10} represents a radical Ar or Het, characterized in that an alcohol alkOH for which alk

represents an alkyl radical (1-6C in the form of a straight or branched chain) is reacted with a derivative of formula:



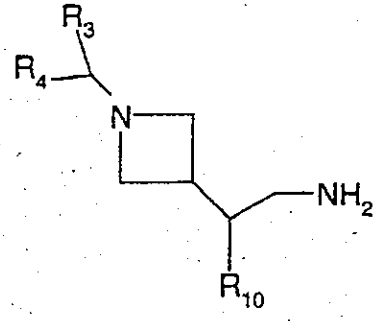
in which R_3, R_4 and R_{10} have the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

20. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a hydrogen atom and R_2 represents a radical $C(R_8)(R_9)(R_{10})$ in which R_8 represents a hydrogen atom, R_9 represents a radical -NH-CO-NH-alk and R_{10} represents a radical Ar or Het, characterized in that an amine $alkNH_2$ for which alk represents an alkyl radical (1-6C in the form of a straight or branched chain) is reacted with a derivative of formula:



in which R_3, R_4 and R_{10} have the same meanings as in formula (I), the product isolated and optionally converted to a salt with an inorganic or organic acid.

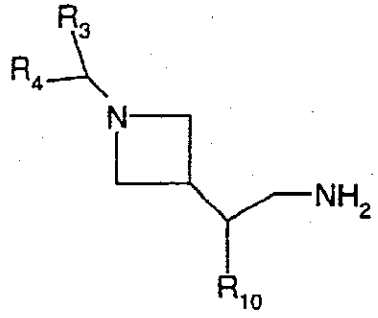
21. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-C(R_8)(R_9)(R_{10})$, R_8 is a hydrogen atom, R_9 is a radical $-CH_2-NHR_{28}$, R_{28} represents a $-CH_2$-alk or benzyl radical and R_{10} represents a radical Ar or Het, characterized in that a derivative of formula:



in which R_3, R_4 and R_{10} have the same meanings as in claim 1, is reacted with an aldehyde RdCHO for which Rd represents a $-CH_2$-alk or benzyl radical and alk represents an alkyl radical (1-6C in the form of a straight or branched chain), the product isolated and

optionally converted to a salt with an inorganic or organic acid.

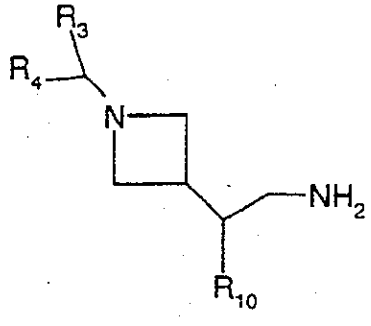
22. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-C(R_8)(R_9)(R_{10})$, R_8 is a hydrogen atom, R_9 is a radical $-CH_2-NHR_{28}$, R_{28} represents a radical $-SO_2alk$ and R_{10} represents a radical Ar or Het, characterized in that an amine of formula:



in which R_3, R_4 and R_{10} have the same meanings as in claim 1, is reacted with a derivative $ClSO_2Re$ for which Re represents an alkyl radical (1-6C in the form of a straight or branched chain), the product isolated and optionally converted to a salt with an inorganic or organic acid.

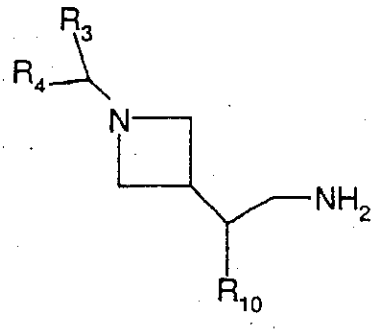
23. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-C(R_8)(R_9)(R_{10})$, R_8 is a hydrogen atom, R_9 is a radical $-CH_2-NHR_{28}$, R_{28} represents a

radical -CO-NHalk and R_{10} represents a radical Ar or Het, characterized in that a derivative of formula:



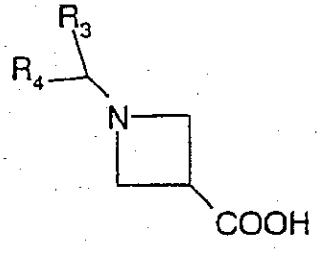
in which R_3, R_4 and R_{10} have the same meanings as in claim 1, is reacted with a derivative RfNCO for which Rf represents an alkyl radical (1-6C in the form of a straight or branched chain), the product isolated and optionally converted to a salt with an inorganic or organic acid.

24. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-C(R_8)(R_9)(R_{10})$, R_8 is a hydrogen atom, R_9 is a radical $-CH_2-NHR_{28}$, R_{28} represents a -COalk, cycloalkylalkylcarbonyl, cycloalkylcarbonyl or $-CO-(CH_2)_nOH$ radical and R_{10} represents a radical Ar or Het, characterized in that a derivative of formula:



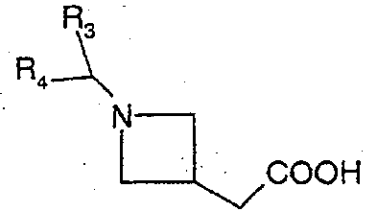
in which R_3, R_4 and R_{10} have the same meanings as in claim 1, is reacted with an acid HOOCRg for which Rg represents an alkyl (1-6C in the form of a straight or branched chain), cycloalkyl(3-10C)alkyl(1-6C in the form of a straight or branched chain), cycloalkyl(3-10C) or $-(CH_2)_nOH$ radical and n is equal to 1, 2 or 3, the product isolated and optionally converted to a salt with an inorganic or organic acid.

25. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 is a radical $-CONR_{13}R_{14}$, characterized in that an amine $HNR_{13}R_{14}$ in which R_{13} and R_{14} have the same meanings as in claim 1, is reacted with a derivative of formula:



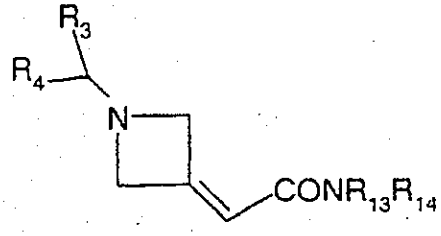
in which R_3 and R_4 have the same meanings as in formula (I), the product isolated and optionally converted to a salt with an inorganic or organic acid.

26. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 is a radical $-CH_2-CONR_{13}R_{14}$, characterized in that an amine $HNR_{13}R_{14}$ in which R_{13} and R_{14} have the same meanings as in claim 1, is reacted with a derivative of formula:



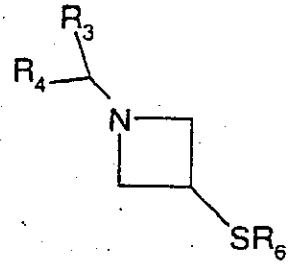
in which R_3 and R_4 have the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

27. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 is a radical $-CH_2-CONR_{13}R_{14}$, characterized in that a derivative of formula:



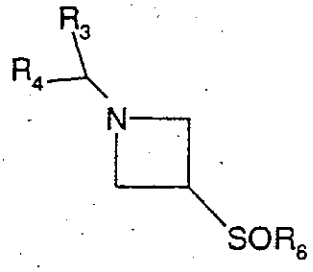
in which R_3, R_4, R_{13} and R_{14} have the same meanings as in claim 1, is reduced, the product isolated and optionally converted to a salt with an inorganic or organic acid.

28. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-SOR_6$, characterized in that a derivative of formula:



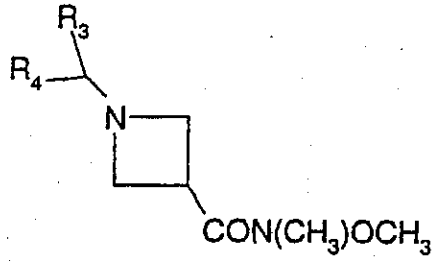
in which R_3, R_4 and R_6 have the same meanings as in claim 1, is oxidized, the product isolated and optionally converted to a salt with an inorganic or organic acid.

29. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-SO_2R_6$, characterized in that a derivative of formula:



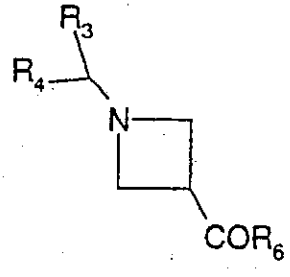
in which R_3, R_4 and R_6 have the same meanings as in claim 1, is oxidized, the product isolated and optionally converted to a salt with an inorganic or organic acid.

30. Process for preparing compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-COR_6$ or -CO-cycloalkyl, characterized in that a derivative of formula:



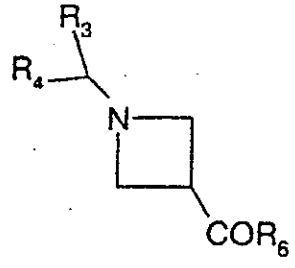
in which R_3 and R_4 have the same meanings as in claim 1, is reacted with a derivative RhMgBr for which Rh has the same meanings as R_6 in claim 1 or else represents a radical cycloalkyl(3-10C), the product isolated and optionally converted to a salt with an inorganic or organic acid.

31. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-C(OH)(R_6)(R_{12})$ or $-C(OH)(R_6)$(alkyl), characterized in that a derivative of formula:



in which R_3, R_4 and R_6 have the same meanings as in claim 1, is reacted with a derivative RiMgBr for which Ri has the same meanings as R_{12} in claim 1, or else represents an alkyl radical (1-6C in the form of a straight or branched chain), the product isolated and optionally converted to a salt with an inorganic or organic acid.

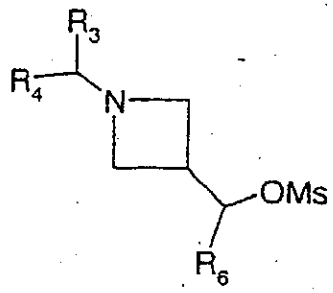
32. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-C(=NOalk)R_6$ or $-C(=NO-CH_2-CH=CH_2)R_6$, characterized in that a derivative of formula:



in which R_3, R_4 and R_6 have the same meanings as in claim 1, is reacted with a derivative $RjONH_2$ for which Rj represents an alkyl radical (1-6C in the form of a straight or branched chain) or $-CH_2-CH=CH_2$, the product isolated and optionally converted to a salt with an inorganic or organic acid.

33. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2

represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} represent hydrogen atoms, characterized in that aqueous ammonia is reacted with a derivative of formula:



in which R_3, R_4 and R_6 have the same meanings as in claim 1 and Ms represents a methylsulfonyloxy radical, the product isolated and optionally converted to a salt with an inorganic or organic acid.

34. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is an alkyl, Ar or -alk-Ar radical, characterized in that a halide $HalR_{31}$ is reacted with a corresponding compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} are hydrogen atoms, the product isolated and optionally converted to a salt with an inorganic or organic acid.

35. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2

represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} are alkyl, Ar or -alk-Ar radicals, characterized in that a halide $HalR_{32}$ is reacted with a corresponding compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is an alkyl, Ar or -alk-Ar radical), the product isolated and optionally converted to a salt with an inorganic or organic acid.

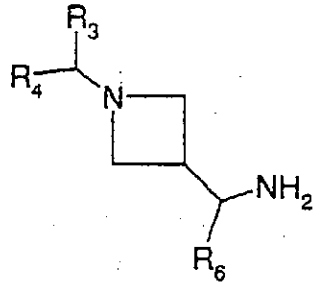
36. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is a (2-6C) alkyl or -(2-6C)alk-Ar radical, characterized in that an aldehyde RaCHO for which Ra is an alkyl or -alk-Ar radical is reacted with a corresponding compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} are hydrogen atoms, the product isolated and optionally converted to a salt with an inorganic or organic acid.

37. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is an alkyl, Ar or -alk-Ar radical and R_{32} is a (2-6C) alkyl or -(2-6C)alk-Ar radical, characterized in that an

aldehyde RaCHO for which Ra is an alkyl or -alk-Ar radical is reacted with a corresponding compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is an alkyl, Ar or -alk-Ar radical, the product isolated and optionally converted to a salt with an inorganic or organic acid.

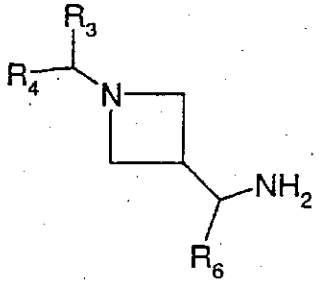
38. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} form with the nitrogen atom to which they are attached a heterocycle chosen from aziridinyl, azetidinyl, pyrrolidinyl and piperidinyl, characterized in that a dihalide Hal-(2-5C)alk-Hal is reacted with a corresponding compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} and R_{32} are hydrogen atoms, the product isolated and optionally converted to a salt with an inorganic or organic acid.

39. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NHSO_2alk$, characterized in that a derivative of formula:



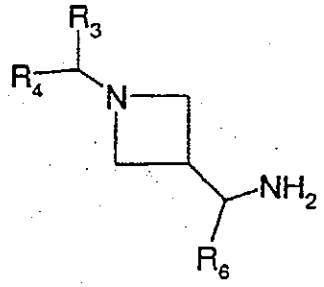
in which R_3, R_4 and R_6 have the same meanings as in claim 1, is reacted with a derivative $ClSO_2alk$ for which alk represents an alkyl radical (1-6C in the form of a straight or branched chain), the product isolated and optionally converted to a salt with an inorganic or organic acid.

40. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NHCONHalk$, characterized in that a derivative of formula:



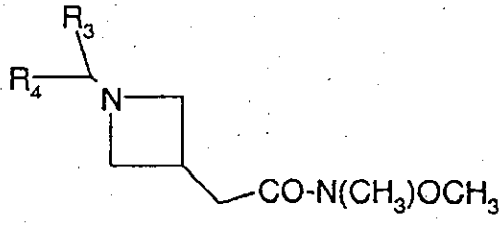
in which R_3, R_4 and R_6 have the same meanings as in claim 1, is reacted with a derivative alkNCO for which alk represents an alkyl radical (1-6C in the form of a straight or branched chain), the product isolated and optionally converted to a salt with an inorganic or organic acid.

41. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical or $-CH(R_6)NHCOR_{31}$, characterized in that a derivative of formula:



in which R_3, R_4 and R_6 have the same meanings as in claim 1, is reacted with a derivative $R_{31}COOH$ for which R_{31} has the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

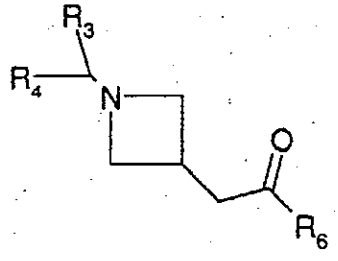
42. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH_2-COR_6$, characterized in that a derivative of formula:



in which R_3 and R_4 have the same meanings as in claim 1, is reacted with a derivative of formula R_6MgBr for which

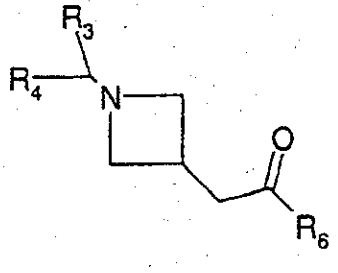
R_6 has the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

43. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH_2-CH(R_6)-NR_{31}R_{32}$, characterized in that a derivative of formula:



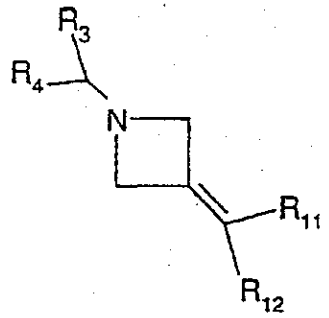
in which R_3 and R_4 have the same meanings as in claim 1, is reacted with a derivative of formula $HNR_{31}R_{32}$ for which R_{31} and R_{32} have the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

44. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH_2-C(=NOalk)R_6$, characterized in that a derivative of formula:



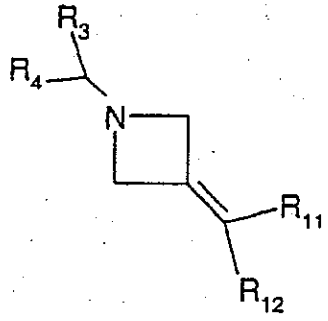
in which R_3 and R_4 have the same meanings as in claim 1, is reacted with a derivative of formula $alkONH_2$ for which alk represents an alkyl radical (1-6C in the form of a straight or branched chain), the product isolated and optionally converted to a salt with an inorganic or organic acid.

45. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a cyano radical and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ in which R_8 is a hydrogen atom, characterized in that a derivative of formula:



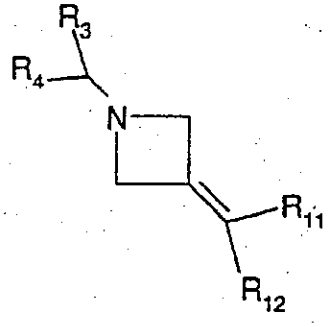
in which R_3, R_4, R_{11} and R_{12} have the same meanings as in claim 1, is reacted with sodium cyanide, the product isolated and optionally converted to a salt with an inorganic or organic acid.

46. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a radical $-S-alk-NR_{16}R_{17}$ and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ in which R_8 is a hydrogen atom, characterized in that a derivative of formula:



in which R_3, R_4, R_{11} and R_{12} have the same meanings as in claim 1, is reacted with a derivative HS-alk-$NR_{16}R_{17}$ for which alk represents an alk radical represents an alkyl radical (1-6C in the form of a straight or branched chain) and R_{16} and R_{17} have the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

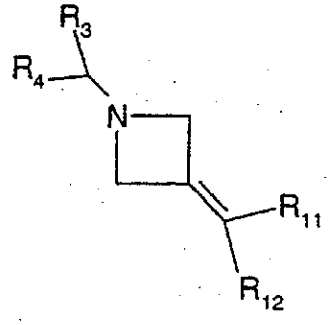
47. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a radical $-NHR_{15}$ and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ in which R_8 is a hydrogen atom, characterized in that a derivative of formula:



in which R_3, R_4, R_{11} and R_{12} have the same meanings as in claim 1, is reacted with a derivative H_2NR_{15} for which

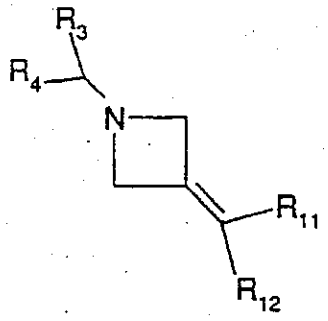
R_{15} has the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid.

48. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents an alkyl radical and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ in which R_8 is a hydrogen atom, characterized in that a derivative of formula:



in which R_3, R_4, R_{11} and R_{12} have the same meanings as in claim 1, is reacted with a derivative alkMHal for which alk represents an alkyl radical (1-6C in the form of a straight or branched chain) and M represents a metal, the product isolated and optionally converted to a salt with an inorganic or organic acid.

49. Process for preparing the compounds of formula (I) according to claim 1, for which R represents a radical CR_1R_2 in which R_1 represents a radical $-NR_{20}R_{21}$ and R_2 represents a radical $-C(R_8)(R_{11})(R_{12})$ in which R_8 is a hydrogen atom, characterized in that a derivative of formula:



in which R_3, R_4, R_{11} and R_{12} have the same meanings as in claim 1, is reacted with a derivative $HNR_{20}R_{21}$ for which $NR_{20}R_{21}$ has the same meanings as in claim 1, the product isolated and optionally converted to a salt with an inorganic or organic acid

50. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} and R_{19} represent hydrogen atoms, characterized in that a corresponding compound of formula (I) for which R_1 represents a cyano radical is reduced, the product isolated and optionally converted to a salt with an inorganic or organic acid.

51. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} represents a hydrogen atom and R_{19} represents an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, -SO_2alk, -CO-NHalk or -COOalk radical, characterized in that a halide $HalR_{19}$, Hal represents a halogen, is reacted with a corresponding

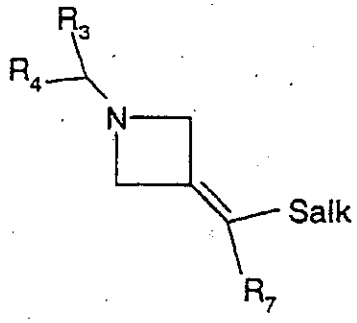
compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} and R_{19} represent a hydrogen atom, the product isolated and optionally converted to a salt with an inorganic or organic acid.

52. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} represents an alkyl radical and R_{19} represents an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, -SO_2alk, -CO-NHalk or -COOalk radical, characterized in that an alkylhalide is reacted with a corresponding compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 represents a radical -alk-$NR_{18}R_{19}$, R_{18} represents a hydrogen atom, and R_{19} represents an alkyl, cycloalkyl, cycloalkylalkyl, cycloalkylcarbonyl, -SO_2alk, -CO-NHalk or -COOalk radical, the product isolated and optionally converted to a salt with an inorganic or organic acid.

53. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which either R_1 represents a hydrogen atom and R_2 represents a radical -$C(R_8)(R_9)(R_{10})$ or -$C(R_8)(R_{11})(R_{12})$, or R_1 represents an alkyl, NH-R_{15}, cyano, -S-alk-$NR_{16}R_{17}$, -alk-$NR_{18}R_{19}$ or -$NR_{20}R_{21}$ radical and R_2 represents a radical -$C(R_8)(R_{11})(R_{12})$ and R_8 represents an alkyl radical, characterized in that a corresponding compound of formula (I) for which R_8 is a hydrogen atom

is alkylated, the product isolated and optionally converted to a salt with an inorganic or organic acid.

54. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical $C=C(R_7)SO_2alk$, characterized in that a derivative of formula:



in which R_3, R_4 and R_7 have the same meanings as in claim 1 and alk represents an alkyl radical (1-6C in the form of a straight or branched chain), is oxidized, the product isolated and optionally converted to a salt with an inorganic or organic acid.

55. Process for preparing the compounds of formula (I) according to claim 1 for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CH(R_6)NR_{31}R_{32}$, R_{31} is a hydrogen atom and R_{32} is an alkyl radical, characterized in that a corresponding compound of formula (I) for which R represents a radical CR_1R_2 in which R_1 is a hydrogen atom and R_2 represents a radical $-CO-R_6$, is reacted with an amine $HNR_{31}R_{32}$ for which R_{31} is a hydrogen atom and R_{32} is an alkyl radical, the product isolated and

optionally converted to a salt with an inorganic or organic acid.

56. Pharmaceutical composition containing, as active ingredient, at least one compound of formula (I) according to one of claims 1 to 11.