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FARNESYL TRANSFERASE INHIBITORS

The present invention relates to novel benzoperhydroisoindole derivatives, to their preparation, to the pharmaceutical compositions which contain them and to their use in the preparation of medicaments.

The protein farnesyl transferase is an enzyme which catalyses the transfer of the farnesyl group from farnesyl pyrophosphate (FPP) to the terminal cysteine residue of the tetrapeptide sequence CAAX of a certain number of proteins and in particular of the p21Ras protein, which expresses the *ras* oncogene.

The *ras* (H-, N- or K-*ras*) oncogene is known to play a key role in cell signalling pathways and cell division processes. The mutation of the *ras* oncogene or its overexpression is often associated with human cancer: the mutated p21Ras protein is found in many human cancers and in particular in more than 50% of cancers of the colon and 90% of cancers of the pancreas (Kohl et al., Science, 260, 1834-1837, 1993).

The inhibition of farnesyl transferase and consequently of the farnesylation of the p21Ras protein blocks the ability of the mutated p21Ras protein to induce cell proliferation and to transform normal cells into cancerous cells.

Moreover, it has been demonstrated that farnesyl transferase inhibitors are also active with respect to tumoral cell lines which do not express mutated or

overexpressed *ras* but which exhibit the mutation of an oncogene or the overexpression of an oncoprotein, the signalling pathway of which uses the farnesylation of a protein, such as a normal *ras* (Nagasu et al., Cancer Research 55, 5310-5314, 1995; Sepp-Lorenzino et al., Cancer Research 55, 5302-5309, 1995).

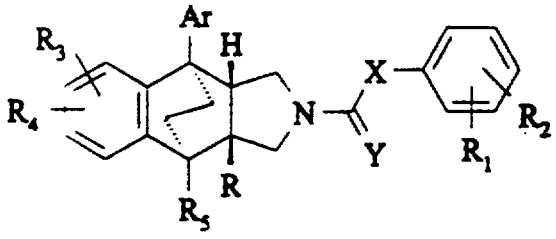
The inhibitors of farnesyl transferase are inhibitors of cell proliferation and consequently antitumour and antileukaemic agents.

It has now been discovered, and this is also the subject of this invention, that the novel products of general formula (I) presented hereinbelow possess, entirely surprisingly and unexpectedly, an inhibitory activity for farnesyl transferase and prove to be notable antitumour and antileukaemic agents.

In particular, it has been discovered, according to the invention, that the biological activity of the compounds according to the invention is very markedly improved, contrary to all expectations, by the presence of specific groups (represented by Ar hereinbelow) substituted at the 9 position of the benzoperhydroisoindole skeleton.

In particular, the corresponding compounds exhibit activities which are much higher than those obtained to date with compounds with similar structures but not exhibiting these Ar substituents.

The present invention relates to the novel compounds of general formula I



(I)

in which:

- Ar represents

  - a phenyl radical substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and the following radicals: alkyl containing 1 to 4 carbon atoms, such as methyl, alkenyl containing 2 to 4 carbon atoms, hydroxyl, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, formyl, alkylcarbonyl, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, cyano or trifluoromethyl, or alkoxy containing 1 to 4 carbon atoms, such as methoxy, the alkyl portion of which is optionally perhalogenated, such as trifluoromethoxy, or
  - a phenyl radical condensed with a 4- to 7-membered heterocycle containing one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, it being possible for the bicyclic system thus formed to be in particular chosen from 2,3-dihydro-1,4-benzo-

dioxin-6-yl or 2,3-dihydrobenzofuran-5-yl or 2,3-dihydrobenzopyran-6-yl radicals or

- an aromatic or non-aromatic polycyclic radical, such as 1- or 2-naphthyl or 5-indanyl or 1,2,3,4-tetra-hydronaphth-6-yl

- a 5- to 12-membered aromatic or non-aromatic heterocyclic radical incorporating one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, bonded to the condensed ring via a carbon-carbon bond, the said radical being substituted, if appropriate, by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and the following radicals: alkyl, alkenyl containing 2 to 4 carbon atoms, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, formyl, alkylcarbonyl, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, cyano or trifluoromethyl,

preferably Ar represents a 2,3-dihydro-1,4-benzodioxin-6-yl or 2,3-dihydrobenzofuran-5-yl radical or a phenyl radical substituted at the 4 position, preferably by a methyl, trifluoromethyl or methoxy radical; in particular, the 2,3-dihydro-1,4-benzodioxin-6-yl radical; very advantageously, Ar

represents a phenyl radical substituted at the 4 position by a methyl radical,

with, for all of these radicals, alkyl containing 1 to 4 carbon atoms,

- R represents

a radical of general formula

$$-(CH_2)_m-X_1-(CH_2)_n-Z$$

in which

- X_1 represents a single bond or an oxygen or sulphur atom,
- m represents an integer equal to 0 or 1,
- n represents an integer equal to 0, 1 or 2,
- one or more methylene radicals can be substituted by a carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, amino, alkylamino or dialkylamino radical with, for all of these radicals, alkyl containing 1 to 4 carbon atoms,
- Z represents
- a carboxyl radical,
- a $COOR_6$ radical, in which R_6 represents a straight or branched alkyl radical containing 1 to 3 carbon atoms, such as the methyl, or
- a radical of formula $CON(R_7)(R_8)$ in which
  - R_7 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms and
  - R_8 represents
    - a hydrogen atom,

- a hydroxyl radical,
- an arylsulphonyl radical, such as phenylsulphonyl, optionally substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,
- a 5- to 7-membered heterocycle incorporating one or more heteroatoms chosen from nitrogen, oxygen or sulphur atoms, it being possible for the said heterocycle to be bonded via a heteroatom,
- an amino radical optionally substituted by one or two radicals, which are identical or different, chosen from the following radicals:
  - alkyl containing 1 to 4 carbon atoms,
  - aryl, such as phenyl, optionally substituted by one or more radicals, which are identical or different, chosen from alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,
  - 5- to 7-membered heterocyclyl containing one or more heteroatoms chosen from nitrogen, oxygen and sulphur atoms,
  - arylcarbonyl, such as benzoyl,

optionally substituted by one or more radicals, which are identical or different, chosen from alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,

- an alkyloxy radical containing 1 to 6 straight- or branched-chain carbon atoms optionally substituted by a phenyl radical,
- a straight or branched alkyl radical containing 1 to 6 carbon atoms, such as methyl, optionally substituted by an amino, alkylamino, dialkylamino, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkyloxycarbonyl, carboxyl or cyano radical, an optionally substituted mono- or polycyclic aromatic radical having from 5 to 12 ring members which may or may not incorporate one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, it being possible for the said aromatic radical to be in particular the 2- or 3- or 4-pyridyl radical, preferably 3-pyridyl or 4-pyridyl, or the N-oxide of pyridine, or it also being possible for the said aromatic radical to be a phenyl radical optionally substituted by one or more halogen atoms or by one or more hydroxyl, amino or trifluoromethyl groups or by one or more

alkyl or alkenyl, alkoxy, alkylthio, alkylamino, alkylcarbonyl or C_2 to C_4 alkoxycarbonyl, carbamoyl, alkyl-carbamoyl or dialkylcarbamoyl, the alkyl part of which contains 1 to 8 carbon atoms, or formyl radicals, or alternatively a 1- or 2-naphthyl radical, or

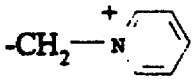
preferably, R represents a carboxyl radical or a -COOMe radical or alternatively a $-CON(R_7)(R_8)$ radical in which, when R_7 represents a hydrogen atom, R_8 represents a methyl radical substituted by the 3-pyridyl radical; very advantageously, R represents a carboxyl radical; very particularly advantageously, R represents a $-CON(R_7)(R_8)$ radical in which, when R_7 represents a hydrogen atom, R_8 represents a methyl radical substituted by the 3-pyridyl radical;

- Z represents

- a $PO(OR_9)_2$ radical in which R_9 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms, or

- an -NH-CO-T radical in which T represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms optionally substituted by an amino, carboxyl, alkyloxycarbonyl, hydroxyl, alkyloxy, mercapto or alkylthio radical, or

alternatively

- a  radical

having an anion, such as trifluoromethanesulphonate, as counterion,

with, for all of the radicals possessing an alkyl group provided in the definition of Z, alkyl containing 1 to 4 carbon atoms,

- R_1 and R_2, which are identical or different, represent a hydrogen atom, a halogen atom or an alkyl radical, an alkyloxy radical, such as methoxy, each optionally substituted by a dialkylamino radical, each alkyl part of which contains 1 to 4 carbon atoms or forms, with the nitrogen atom, a saturated heterocycle containing 5 or 6 ring members, an alkylthio radical or an alkyloxycarbonyl radical, or alternatively situated at the ortho position with respect to one another, R_1 and R_2 form a saturated or unsaturated heterocycle containing 1 or 2 heteroatoms chosen from nitrogen and oxygen, optionally substituted by a halogen atom or by an alkyl or alkyloxy radical,

preferably, one of the R_1 or R_2 symbols represents a hydrogen atom and the other of the symbols represents a methoxy radical, more advantageously attached at the *ortho* position of the phenyl ring,

with, for all of the radicals possessing an alkyl group provided in the definition of R_1 and R_2, alkyl

containing 1 to 4 carbon atoms,

- R_3 and R_4, which are identical or different, represent a hydrogen or halogen atom or an alkyl, hydroxyl, alkyloxy, alkylcarbonyloxy, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, alkyloxycarbonylamino, carboxyl, alkyloxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, formyl, alkylcarbonyl, cyano or trifluoromethyl radical,

preferably, either R_3 and R_4 each represent a hydrogen atom or alternatively one of the R_3 or R_4 symbols represents a hydrogen atom and the other of the R_3 or R_4 symbols represents a methoxy radical, more advantageously at the 5 position of the benzoperhydroisoindole nucleus;

very advantageously, R_3 and R_4 each represent a hydrogen atom;

with, for all of the radicals possessing an alkyl group provided in the definition of R_3 and R_4, alkyl containing 1 to 4 carbon atoms,

- R_5 represents a hydrogen atom or an alkyl radical or an alkylthio radical, with, for the definition of R_5, alkyl containing 1 to 4 carbon atoms;

preferably, R_5 represents a hydrogen atom or a methyl radical;

very advantageously, R_5 represents a hydrogen atom;

- X represents an oxygen or sulphur atom or one of the following groups: -NH-, -CO-, methylene,

alken-1,1-diyl, such as vinyldiyl, or cycloalkan-1,1-diyl containing 3 to 6 carbon atoms,

preferably, X represents a methylene or vinyldiyl group,

in a particularly advantageous way, X represents the vinyldiyl group,

and

- Y represents an oxygen or sulphur atom,

preferably, Y represents an oxygen atom,

in the racemic form or their optical isomers, as well as the salts of the product of general formula (I).

In the preceding and succeeding definitions,

- the "alkyl containing 1 to 8 carbon atoms" radicals or portions defines the methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl and octyl radicals and the corresponding *iso* isomers,

- the "alkyl containing 1 to 6 carbon atoms" radicals or portions defines the methyl, ethyl, propyl, butyl, pentyl and hexyl radicals and the corresponding *iso*, *sec* and *tert* isomers,

- the "alkyl containing 1 to 4 carbon atoms" radicals or portions defines the methyl, ethyl, propyl and butyl radicals and the corresponding *iso*, *sec* and *tert* isomers,

- "alkenyls containing 2 to 4 carbon atoms" defines the vinyl, allyl, propen-2-yl, buten-1-yl, buten-2-yl and buten-3-yl radicals and the corresponding *iso* isomers,

- "alkoxy containing 1 to 4 carbon atoms" defines the methoxy, ethoxy, propoxy and butoxy radicals and the corresponding *iso*, *sec* and *tert* isomers,
- "C_2 to C_4 alkoxycarbonyl" defines the methoxycarbonyl, ethoxycarbonyl and propoxycarbonyl radicals and the corresponding *iso*, *sec* and *tert* isomers.

Preferably, the compounds according to the invention exhibit a general formula (I) in which:

Ar represents a 2,3-dihydro-1,4-benzodioxin-6-yl or 2,3-dihydrobenzofuran-5-yl radical or a phenyl radical substituted at the 4 position, preferably by a methyl, trifluoromethyl or methoxy radical,

R represents a carboxyl radical or a -COOMe radical or alternatively a $-CON(R_7)(R_8)$ radical in which, when R_7 represents a hydrogen atom, R_8 represents a methyl radical substituted by the 3-pyridyl radical,

one of the R_1 or R_2 symbols represents a hydrogen atom and the other of the symbols represents a methoxy radical, more advantageously attached at the *ortho* position of the phenyl ring,

either R_3 and R_4 each represent a hydrogen atom or one of the R_3 or R_4 symbols represents a hydrogen atom and the other of the R_3 or R_4 symbols represents a methoxy radical, more advantageously at the 5 position of the benzoperhydroisoindole nucleus,

R_5 represents a hydrogen atom or a methyl radical,

X represents a methylene or vinyldiyl group,

Y represents an oxygen atom;

in the racemic form or their optical isomers, as well as their salts.

According to the invention, the compounds of general formula (I) are preferably provided in the dextrorotatory form.

As it is possible for the technical effect of the compounds presented here, that is to say the biological activity, to be related to the specific nature of the Ar substituents defined as above, the compounds according to the invention are in particular the compounds of general formula (I) in which R, R_1, R_2, R_3, R_4, R_5, X and Y are defined as above and which can be characterized in that Ar represents

- a phenyl radical substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and the following radicals: alkyl containing 1 to 4 carbon atoms, such as methyl, alkenyl containing 2 to 4 carbon atoms, hydroxyl, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, formyl, alkylcarbonyl, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, cyano or trifluoromethyl, or alkoxy containing 1 to 4 carbon atoms, such as methoxy, the alkyl portion of which is optionally perhalogenated, such as trifluoromethoxy, or
- a phenyl radical condensed with a 4- to 7-membered heterocycle containing one or more heteroatoms chosen

from oxygen, nitrogen and sulphur atoms, it being possible for the bicyclic system thus formed to be in particular chosen from 2,3-dihydro-1,4-benzodioxin-6-yl or 2,3-dihydrobenzofuran-5-yl or 2,3-dihydrobenzopyran-6-yl radicals or

- an aromatic or non-aromatic polycyclic radical, such as 1- or 2-naphthyl or 5-indanyl or 1,2,3,4-tetrahydronaphth-6-yl

- a 5- to 12-membered aromatic or non-aromatic heterocyclic radical incorporating one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, bonded to the condensed ring via a carbon-carbon bond, the said radical being substituted, if appropriate, by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and the following radicals: alkyl, alkenyl containing 2 to 4 carbon atoms, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, formyl, alkylcarbonyl, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, cyano or trifluoromethyl,

preferably Ar represents a 2,3-dihydro-1,4-benzodioxin-6-yl or 2,3-dihydrobenzofuran-5-yl radical or a phenyl radical substituted at the 4 position, preferably by a methyl, trifluoromethyl or methoxy radical; in particular, the 2,3-dihydro-1,4-benzodioxin-6-yl radical; very advantageously, Ar represents

a phenyl radical substituted at the 4 position by a methyl radical.

The compounds of general formula I in which:

- Ar represents
  - a phenyl radical substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and alkyl, alkenyl containing 2 to 4 carbon atoms, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, formyl, alkylcarbonyl, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, cyano or trifluoromethyl radicals, or
  - a polycyclic aromatic radical, such as 1- or 2-napthyl or 5-indanyl, or
  - a 5- to 12-membered heterocyclic aromatic radical incorporating one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, bonded to the condensed ring via a carbon-carbon bond, the said radical being substituted, if appropriate, by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and the following radicals: alkyl, alkenyl containing

2 to 4 carbon atoms, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, formyl, alkylcarbonyl, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, cyano or trifluoromethyl, with, for all of these radicals, alkyl containing 1 to 4 carbon atoms,

- R represents a radical of general formula

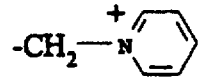
$$-(CH_2)_m-X_1-(CH_2)_n-Z$$

in which

- X_1 represents a single bond or an oxygen or sulphur atom,
- m represents an integer equal to 0 or 1,
- n represents an integer equal to 0, 1 or 2,
- the methylene radicals can be substituted by a carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, amino, alkylamino or dialkylamino radical with, for all of these radicals, alkyl containing 1 to 4 carbon atoms,
- Z represents
  - a carboxyl radical,
  - a $COOR_6$ radical, in which R_6 represents a straight or branched alkyl radical containing 1 to 3 carbon atoms, or
  - a radical of formula $CON(R_7)(R_8)$ in which

- R_7 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms and
- R_8 represents
  - a hydrogen atom,
  - a hydroxyl radical,
  - an amino, alkylamino or dialkylamino radical with alkyl containing from 1 to 4 carbon atoms,
  - an alkyloxy radical containing 1 to 6 straight- or branched-chain carbon atoms optionally substituted by a phenyl radical,
  - a straight or branched alkyl radical containing 1 to 6 carbon atoms, and preferably a methylene group, optionally substituted by an amino, alkylamino, dialkylamino, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkyloxycarbonyl, carboxyl or cyano radical, a mono- or polycyclic aromatic radical having from 5 to 12 ring members which may or may not incorporate one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms and, if appropriate, substituted, which can be a phenyl radical substituted by one or more halogen atoms

or by a hydroxyl, amino or trifluoromethyl group or by an alkyl or alkenyl, alkoxy, alkylthio, alkylamino, alkylcarbonyl or C_2 to C_4 alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, containing 1 to 8 carbon atoms, or formyl radical, or alternatively a 1-naphthyl or 2-naphthyl radical or,

- Z represents
  - a $PO(OR_9)_2$ radical in which R_9 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms, or
  - an -NH-CO-T radical in which T represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms optionally substituted by an amino, carboxyl, alkyloxycarbonyl, hydroxyl, alkyloxy, mercapto or alkylthio radical, or alternatively
  - a  radical

with, for all of the radicals possessing an alkyl group provided in the definition of Z, alkyl containing 1 to 4 carbon atoms,

- R_1 and R_2, which are identical or different, represent a hydrogen atom, a halogen atom or an alkyl radical, an alkyloxy radical optionally substituted by

a dialkylamino radical, each alkyl part of which contains 1 to 4 carbon atoms or forms, with the nitrogen atom, a saturated heterocycle containing 5 or 6 ring members, an alkylthio radical or an alkyloxycarbonyl radical, or alternatively

situated at the ortho position with respect to one another, R_1 and R_2 form a saturated or unsaturated heterocycle containing 1 or 2 heteroatoms chosen from nitrogen and oxygen, optionally substituted by a halogen atom or by an alkyl or alkyloxy radical,

with, for all of the radicals possessing an alkyl group provided in the definition of R_1 and R_2, alkyl containing 1 to 4 carbon atoms,

- R_3 and R_4, which are identical or different, represent a halogen atom or an alkyl, hydroxyl, alkyloxy, alkylcarbonyloxy, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, alkylcarbonyloxyamino, carboxyl, alkyloxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, formyl, alkylcarbonyl, cyano or trifluoromethyl radical,

with, for all of the radicals possessing an alkyl group provided in the definition of R_3 and R_4, alkyl containing 1 to 4 carbon atoms,

- R_5 represents a hydrogen atom,
- X represents an oxygen or sulphur atom or one of the following groups: -NH-, -CO-, methylene, alken-1,1-diyl, such as vinyldiyl, or cycloalkan-1,1-diyl

containing 3 to 6 carbon atoms, and

- Y represents an oxygen or sulphur atom,

in the racemic form, as well as the optical isomers of the product of general formula (I), are of very particular interest.

Mention will very particularly be made, as preferred compounds according to the present invention, of those represented in the general formula I in which R represents a radical

$$-(CH_2)_m-X_1-(CH_2)_n-CONH-CH_2-Ar'$$

with m, n and X_1 being as defined above and Ar' preferably representing therein a phenyl optionally substituted by one or more radicals chosen from alkoxys containing 1 to 4 carbon atoms, trifluoromethyl, 1- or 2-naphthyl, 2- or 3-furyl, 2- or 3-thienyl, 2- or 3-pyrrolyl, 2- or 3-indolyl, 2- or 3- or 4-quinolyl, 1- or 3- or 4-isoquinolyl, 2- or 3-benzofuryl, 2- or 3-benzothienyl, 2- or 4- or 5-pyrimidyl, 2- or 3-pyrazinyl, 2- or 4-quinazolyl, 1-phthalazinyl, 2- or 3- or 4-naphthyridinyl, 2- or 4-imidazolyl, 2- or 4-thiazolyl or 2- or 3- or 4-pyridyl, indanyl, chromanyl or thiochromanyl radical.

Mention may more particularly be made, as non-limiting illustration of the claimed compounds, of the following compounds:

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9]-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-(2-methoxyphenyl)-propenoyl-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-3a-N-benzylcarbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

(3aRS,4SR,9SR,9aRS)-3a-carbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

benzyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid

in the racemic form, as well as of their optical isomers.

Mention may also be made, according to the invention, of any compound of general formula (I) individually selected from:

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-(2-methoxyphenyl)-propenoyl-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-

benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-3a-N-benzylcarbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

(3aRS,4SR,9SR,9aRS)-3a-carbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

benzyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-

2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)-carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(4-pyridylmethyl)-carboxamide

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N',N'-dimethyl-carbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbo-hydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N',N'-pentamethylene-

carbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(methoxyphenyl)propenoyl]-9-(4-methylphenyl)-3a-phenylsulphonylaminocarbonyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(N-oxo-3-pyridyl)methylcarboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(4-methoxyphenyl)-carbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-methyl-N'-phenylcarbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(2-methylphenyl)carbohydrazide

methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-

carboxylic acid

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(2-thienylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(3,4,5-trimethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(4-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-

hexahydro-1H-benzo[f]isoindole-3a-N'-benzoyl-carbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenyl-carbohydrazide

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-9-(3,4-dichlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-chlorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-indolyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-

benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate acid

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)-carboxamide

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-

2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-

[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(3-pyridyl)carbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-thienylmethyl)carboxamide

(RS)- and (SR)-2-{(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carbonylamino}phenylacetic acids

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

methyl (3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

methyl (3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethyl-aminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3-aminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride

methyl (3aRS,4SR,9SR,9aRS)-9-(4-N,N-dimethylamino-phenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(4-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-hydroxy-4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-2-propenoyl]-4-methyl-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

in the racemic form or their optical isomers, as well as their salts.

In that which precedes and that which follows, the expression "optical isomer" or optically active form defines the pure form of the said optical

isomer or optionally the "enriched" mixture of the optical isomers, that is to say comprising predominantly the said optical isomer or the said form.

More preferably, mention may also be made, according to the invention, of any compound of general formula (I) individually selected from:

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-

methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-2-propenoyl]-4-methyl-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

in the racemic form or their optical isomers, as well as their salts.

Mention may be made, as very particularly advantageous optical isomer of the compounds of general formula (I) according to the invention, of any compound chosen individually from:

dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

laevorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-

benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide
laevorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide
dextrorotatary enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid
dextrorotatary enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid
dextrorotatary enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)-2-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid
dextrorotatary enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-2-propenoyl]-4-methyl-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid
or their salts.

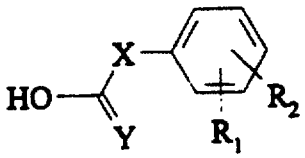
Mention may in particular be made of dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid
or its salts.

The Applicant Company additionally provides hereinbelow, without implied limitation of the present invention, various operating protocols as well as reaction intermediates liable to be of use in the preparation of the compounds of general formula (I). Of course, it is within the capability of a person skilled in the art to be inspired by these protocols and/or intermediates in developing analogous processes for the purpose of leading to these same compounds.

According to the invention, the claimed novel products of general formula (I) in which:

- Y represents an oxygen or sulphur atom and
- X represents one of the following groups: -CO-, methylene, alkene-1,1-diyl, such as vinyldiyl, or cycloalkane-1,1-diyl containing 3 to 6 carbon atoms,

can be obtained by reaction of an acid of general formula (II):

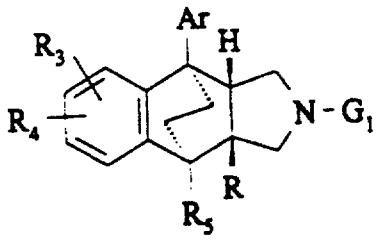


(II)

in which:

- R_1 and R_2 are defined according to the general formula I and X [lacuna] defined as above and
- Y represents an oxygen or sulphur atom,

of its methyl ester or of a derivative of this acid, such as a halide or the anhydride, with a product of general formula (III):



(III)

in which:

- Ar, R, R_3, R_4 and R_5 are defined according to the general formula I and
- G_1 represents a hydrogen atom (which can be obtained from a product of general formula (III) in which G_1 represents a protective group for an amino functional group, such as a benzyl, benzyloxycarbonyl, *tert*-butoxycarbonyl or vinyloxycarbonyl radical, by hydrogenolysis in the presence of a catalyst, such as palladium-on-charcoal, when G_1 represents a benzyl or benzyloxycarbonyl radical, or by hydrolysis in acidic medium, when G_1 represents a *tert*-butoxycarbonyl, vinyloxycarbonyl or benzyloxycarbonyl radical).

In that which follows, the definition for which G_1 represents a benzyl radical is given only by way of illustration and it is obvious to a person skilled in the art to adapt the various protocols to the other protective groups for an amino functional group, such as a benzyl, benzyloxycarbonyl, *tert*-butoxycarbonyl or vinyloxycarbonyl radical.

Generally, the reaction of the product of general formula (II), in the acid form, with the product of general formula (III) is carried out in an

organic solvent, such as a halogenated aliphatic hydrocarbon, such as dichloromethane, in the presence of a coupling agent, such as 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, 1,3-dicyclohexylcarbodiimide or benzotriazol-1-yloxytris-(dimethylamino)phosphonium hexafluorophosphate, and optionally of an activating agent, such as hydroxybenzotriazole, at a temperature of between 0°C and the reflux temperature of the reaction mixture.

The reaction of the product of general formula (II), in the form of the methyl ester, with a product of general formula (III) is generally carried out in an organic solvent, such as dioxane or a halogenated aliphatic hydrocarbon, such as dichloromethane, at a temperature of between 0°C and the reflux temperature of the reaction mixture.

The reaction of the product of general formula (II), in the halide form, with the product of general formula (III) is generally carried out in an organic solvent, such as a halogenated aliphatic hydrocarbon, such as dichloromethane, in the presence of a base (tertiary aliphatic amine) at a temperature of between 0°C and the reflux temperature of the reaction mixture.

The reaction of the product of general formula (II), in the anhydride form, with the product of general formula (III) is generally carried out in an organic solvent, such as a halogenated aliphatic

hydrocarbon, such as dichloromethane, in the presence of a base (tertiary aliphatic amine, pyridine or 4-dimethylaminopyridine) at a temperature of between 0°C and 50°C.

In addition, on conclusion of the reaction of II with III, it is optionally possible, when R represents or contains a $-COOR_6$ or $-PO(OR_9)_2$ radical with R_6 and R_9 representing an alkyl radical,

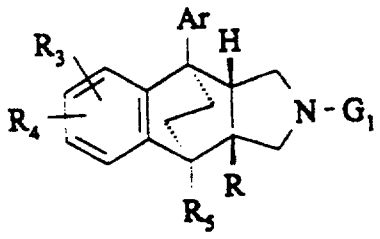
- to saponify the product obtained, in order to obtain a product of general formula (I) in which R represents or contains a carboxyl radical or
- to convert, by means of a nucleophilic agent, the product obtained, in order to obtain a product of general formula (I) in which R represents or contains a $-PO_3H_2$ radical.

The saponification of a product of general formula (I) in which R represents or contains an ester of general formula $-COOR_6$ into a product of general formula (I) in which R represents or contains a carboxyl radical is generally carried out by means of an inorganic base, such as sodium hydroxide or potassium hydroxide or sodium carbonate, in an organic solvent, such as an alcohol, for example methanol or ethanol, or such as an ether, for example dioxane, at a temperature of between 20°C and the reflux temperature of the solvent.

The conversion of a product of general formula (I) in which R represents or contains a $PO(OR_9)_2$

radical into a product of general formula (I) in which R represents or contains a PO_3H_2 radical is generally carried out by reaction with a nucleophilic agent, such as a trialkylsilyl (trimethylsilyl) halide (iodide), or with a sodium or lithium halide (sodium iodide) in the presence of a trialkylhalosilane (trimethylchlorosilane, trimethylbromosilane), the reaction being carried out in a solvent, such as carbon tetrachloride or acetonitrile, at a temperature of between 0 and 50°C, or by heating with an alkali metal halide (sodium iodide), followed by hydrolysis.

The present invention also relates to the products of general formula (III):



(III)

in which:

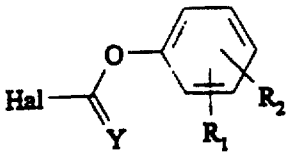
- Ar, R, R_3, R_4 and R_5 are defined according to the general formula I and
- G_1 represents a hydrogen atom or a protective group for an amino functional group, such as benzyl.

According to the invention, the novel products of general formula (I) in which:

- Y represents an oxygen or sulphur atom and
- X represents an oxygen atom

can be obtained by the reaction of a haloformate or of

a halothioformate of general formula (IV):



(IV)

in which:

- Y represents an oxygen or sulphur atom,
- R_1 and R_2 are defined as above and
- Hal represents a halogen atom,

with a product of general formula (III).

The reaction of the halide of general formula (IV) with the product of general formula (III) is generally carried out in organic or aqueous/organic medium, such as a dioxane/water mixture, in the presence of an inorganic base (sodium hydroxide) or organic base (triethylamine) at a temperature of between 0 and 50°C.

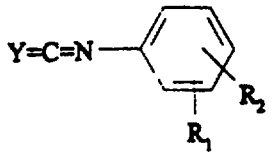
In the same way as above, when R represents or contains a $-COOR_6$ or $-PO(OR_9)_2$ radical, it is possible to saponify the product obtained, in order to obtain a product of general formula (I) in which R represents or contains a carboxyl radical, or to convert, by means of a nucleophilic agent, the product obtained into a product of general formula (I) in which R represents or contains a $-PO_3H_2$ radical.

According to the invention, the novel products of general formula (I) in which:

- Y represents an oxygen or sulphur atom and

- X represents an NH group

can be obtained by reaction of an isocyanate or of an isothiocyanate of general formula (V):



(V)

in which:

Y represents an oxygen or sulphur atom and

R_1 and R_2 are defined according to the general formula I with a product of general formula (III) as defined above.

The reaction of the product of general formula (V) with the product of general formula (III) is generally carried out in an inert organic solvent, such as tetrahydrofuran or toluene, in the presence of an activating agent, such as 4-dimethylaminopyridine or 4-pyrrolidinopyridine, at a temperature of between 0 and 50°C.

The reaction of V with II is optionally followed, when R represents or contains a $-COOR_6$ or $-PO(OR_9)_2$ radical in which R_6 or R_9 represent an alkyl radical, by the saponification of the product obtained, in order to obtain a product of general formula (I) in which R represents or contains a carboxyl radical, or by the conversion, by means of a nucleophilic agent, of the product obtained, in order to obtain a product of general formula (I) in which R represents or contains a

$-PO_3H_2$ radical. The optional conversion of the $-COOR_6$ and $PO(OR_9)_2$ radicals respectively by carboxyl and PO_3H_2 radicals is carried out under the conditions described above.

According to the invention, the novel products of general formula (I) in which:

- R represents a radical of general formula

$$-(CH_2)_m-X_1-(CH_2)_n-Z$$

with X_1, m and n defined as above and

Z representing a $-COOR_6$ radical with R_6 representing a straight or branched alkyl radical containing 1 to 3 carbon atoms,

can be obtained by esterification of a product of general formula (I) in which Z represents a carboxyl radical.

The esterification is generally carried out by means of an alcohol of general formula R_6-OH in which R_6 is defined as above, the reaction being carried out in acidic medium, or by means of an alkyl halide of general formula R_6-Hal in which Hal represents a halogen (iodine) atom, the reaction being carried out in alkaline medium (alkali metal or alkaline-earth metal carbonate, such as caesium carbonate), the reaction being carried out in an organic solvent, such as dimethylformamide, at a temperature of between 0 and 50°C.

According to the invention, the novel products of general formula (I) in which:

R represents a radical of general formula

$$-(CH_2)_m-X_1-(CH_2)_n-Z$$

in which:

X_1, m and n are defined as above and

Z represents a $-CON(R_7)(R_8)$ radical

in which:

R_7 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms and

R_8 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms optionally substituted by an amino, alkylamino containing 1 to 4 carbon atoms, dialkylamino, each alkyl part of which contains 1 to 4 carbon atoms, alkoxy containing 1 to 4 carbon atoms, alkylthio containing 1 to 4 carbon atoms, alkyloxycarbonyl, the alkyl part of which contains 1 to 4 carbon atoms, carboxyl, cyano, phenyl optionally substituted by one or more identical or different radicals chosen from alkoxy radicals containing 1 to 4 carbon atoms or trifluoromethyl radicals, 1- or 2-naphthyl, 2- or 3-furyl, 2- or 3-thienyl, 4- or 5-imidazolyl or 4- or 5-thiazolyl, or 2-, 3- or 4-pyridyl radical, or an indanyl or chromanyl radical

or alternatively

R_7 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms and

R_8 represents a hydroxyl, amino, alkyloxy containing 1 to 6 straight- or branched-chain carbon atoms optionally substituted by a phenyl radical, alkylamino

or dialkylamino, the alkyl parts of which contain 1 to 4 carbon atoms, radical,

or else preferably in which

- R_7 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms and
- R_8 represents
  - a hydrogen atom,
  - a hydroxyl radical,
  - an arylsulphonyl radical, such as phenylsulphonyl, optionally substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,
  - a 5- to 7-membered heterocycle incorporating one or more heteroatoms chosen from nitrogen, oxygen or sulphur atoms, it being possible for the said heterocycle to be bonded via a heteroatom,
  - an amino radical optionally substituted by one or two radicals, which are identical or different, chosen from the following radicals:
    - alkyl containing 1 to 4 carbon atoms,
    - aryl, such as phenyl, optionally substituted by one or more radicals, which

are identical or different, chosen from alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,

- 5- to 7-membered heterocyclyl containing one or more heteroatoms chosen from nitrogen, oxygen and sulphur atoms,

- arylcarbonyl, such as benzoyl, optionally substituted by one or more radicals, which are identical or different, chosen from alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,

- an alkyloxy radical containing 1 to 6 straight- or branched-chain carbon atoms optionally substituted by a phenyl radical,

- a straight or branched alkyl radical containing 1 to 6 carbon atoms, such as methyl, optionally substituted by an amino, alkylamino, dialkylamino, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkyloxycarbonyl, carboxyl or cyano radical, an optionally substituted mono- or polycyclic aromatic radical having from 5 to 12 ring members which may or may not incorporate one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, it being possible for the said

aromatic radical to be in particular the 2- or 3- or 4-pyridyl radical, preferably 3-pyridyl or 4-pyridyl, or the N-oxide of pyridine, or it also being possible for the said aromatic radical to be a phenyl radical optionally substituted by one or more halogen atoms or by one or more hydroxyl, amino or trifluoromethyl groups or by one or more alkyl or alkenyl, alkoxy, alkylthio, alkylamino, alkylcarbonyl or C_2 to C_4 alkoxycarbonyl, carbamoyl, alkyl-carbamoyl or dialkylcarbamoyl, the alkyl part of which contains 1 to 8 carbon atoms, or formyl radicals, or alternatively a 1- or 2-naphthyl radical,

preferably, R_7 represents a hydrogen atom and R_8 represents a methyl radical substituted by the 3-pyridyl radical,

can be obtained by reaction of a product of general formula:

$$HN(R_7)(R_8)$$

in which R_7 and R_8 are defined as above with a product of general formula (I) in which Z represents a carboxyl radical.

It is particularly advantageous:

- either first to react oxalyl chloride with a compound of general formula (I), in which R represents a carboxyl radical, in solution in

dichloromethane, in order to form the acid chloride as an intermediate, and then to react the compound of general formula $HN(R_7)(R_8)$, optionally in the presence of a base, such as triethylamine,

- or directly to react the compound of general formula $HN(R_7)(R_8)$ with a compound of general formula (I) in which R represents a carboxyl radical, in an organic solvent, such as an alcohol (ethanol) or a halogenated solvent, such as dichloromethane, in the presence of a coupling agent, such as N,N'-carbonyldiimidazole, 1,1-dicyclohexylcarbodiimide, 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide or benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate, at a temperature of between 0 and 50°C.

When at least one of the R_7 and R_8 symbols is substituted by an amino radical, it is particularly advantageous to protect it by a protective group, such as a *tert*-butoxycarbonyl, benzyloxycarbonyl or benzyl radical, prior to the coupling of the amine of general formula $HN(R_7)(R_8)$ to the appropriate acid and then to replace the protective group by a hydrogen atom, for example by hydrogenolysis by means of hydrogen in the presence of a catalyst, such as palladium-on-charcoal, when it represents a benzyl or benzyloxycarbonyl radical, or by hydrolysis in acidic medium, when it represents a *tert*-butoxycarbonyl or benzyloxycarbonyl radical.

When at least one of the R_7 and R_8 symbols is substituted by a carboxyl radical, it is particularly advantageous to protect it by a protective group, such as an alkyl radical optionally substituted by a phenyl radical, such as the benzyl radical, prior to the coupling of the amine of general formula $HN(R_7)(R_8)$ to the appropriate acid and then to replace the protective group by a hydrogen atom, for example by hydrogenolysis by means of hydrogen in the presence of a catalyst, such as palladium-on-charcoal, or by saponification under the conditions described above.

When, in the product of general formula (I), R_7 represents a hydrogen atom or an alkyl radical containing 1 to 6 carbon atoms and R_8 represents an alkyloxy radical substituted by a phenyl radical, the replacement of the alkyloxy radical, substituted by a phenyl radical, by a hydroxyl radical, carried out:

- either by hydrogenolysis in the presence of a catalyst, such as palladium-on-charcoal,
- or by treatment with aluminium chloride in the presence of anisole in an organic solvent, such as nitromethane, at a temperature of between -20°C and room temperature, when the alkyl radical substituted by a phenyl radical is a benzyl radical,

makes it possible to obtain a product of general formula (I) in which R_7 represents a hydrogen atom or an alkyl radical containing 1 to 4 carbon atoms and R_8 represents a hydroxyl radical.

According to the invention, the novel products of general formula (I) in which:

- R represents a radical of general formula:

-NHCO-T

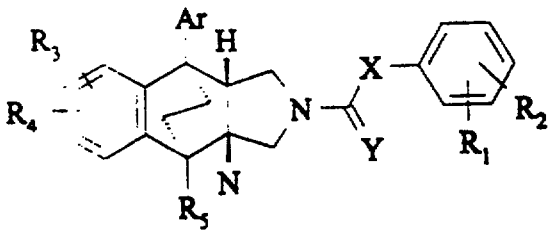
in which T represents a hydrogen atom or an alkyl radical (1 to 6 carbon atoms) optionally substituted by an amino, carboxyl, alkyloxycarbonyl, hydroxyl, alkyloxy, mercapto or alkylthio radical,

can be obtained by reaction of an acid of general formula:

T-CO-OH

in which T is defined as above

with a product of general formula VI:



(VI)

in which:

Ar, R_1, R_2, R_3, R_4, R_5, X and Y are defined according to the general formula I.

The reaction of the acid of general formula T-CO-OH, in the acid form, with a product of general formula (VI) is generally carried out in an organic solvent, such as a halogenated aliphatic hydrocarbon, such as dichloromethane, in the presence of a coupling agent, such as 1-ethyl-3-[3-(dimethylamino)propyl]-

carbodiimide hydrochloride, 1,1-dicyclohexylcarbodiimide or benzotriazol-1-oxytris(dimethylamino)-phosphonium hexafluorophosphate, optionally in the presence of an activating agent, such as hydroxybenzotriazole, at a temperature of between 0 and 50°C.

The reaction of the acid of general formula T-CO-OH, in the halide form, when T is other than a hydrogen atom, with the product of general formula (VI) is generally carried out in an organic solvent, such as a halogenated aliphatic hydrocarbon, such as dichloromethane, in the presence of a base (tertiary aliphatic amine) at a temperature of between 0 and 50°C.

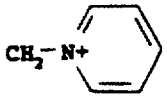
The reaction of the acid of general formula T-CO-OH, in the anhydride form, with the product of general formula (VI) is generally carried out in an organic solvent, such as a halogenated aliphatic hydrocarbon, such as dichloromethane, in the presence of a base (tertiary aliphatic amine, pyridine or 4-dimethylaminopyridine) at a temperature of between 0 and 50°C.

The reaction of a compound T-CO-OH with a compound VI can optionally be followed by replacement of the protected ester functional groups or amine functional groups carried by T by carboxyl or amino radicals respectively, under the conditions described above.

When T is substituted by an amino radical, it is particularly advantageous to protect it by a protective group, such as a benzyloxycarbonyl or *tert*-butoxycarbonyl radical, prior to the coupling of the acid of general formula T-CO-OH to the appropriate amine and then to replace the protective group by a hydrogen atom, for example by hydrogenolysis by means of hydrogen in the presence of a catalyst, such as palladium-on-charcoal, or by hydrolysis in acidic medium.

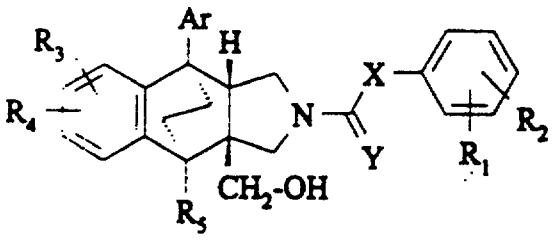
When T is substituted by a carboxyl radical, it is particularly advantageous to protect it by a protective group, such as a methyl, ethyl or benzyl radical, prior to the coupling of the acid of general formula T-CO-OH to the appropriate amine and then to replace the protective group by a hydrogen atom, for example by hydrogenolysis by means of hydrogen in the presence of a catalyst, such as palladium-on-charcoal, or by saponification under the conditions described above.

According to the invention, the novel products of general formula (I) in which: R represents a radical of general formula



can be obtained by reaction of an excess of pyridine and of a strong acid or of a derivative of this acid

with a product of general formula:



(VII)

in which Ar, R_1, R_2, R_3, R_4, R_5, X and Y are defined according to the general formula I.

The strong acid is preferably trifluoromethanesulphonic acid, optionally in the presence of trifluoromethanesulphonic anhydride.

According to the invention, the novel products of general formula (I) in which Y represents a sulphur atom can be obtained by thionation of a product of general formula (I) in which Y represents an oxygen atom.

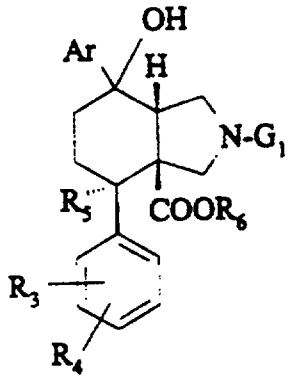
The thionation is generally carried out under the usual conditions by means of phosphorus pentasulphide, the reaction being carried out in an organic solvent, such as tetrahydrofuran, at a temperature of between 0 and 50°C.

According to the invention, the products of general formula (I) in which one of the R_1 or R_2 symbols represents an alkylcarbonyloxy radical can be obtained by acylation of a product of general formula (I) in which one of the R_1 or R_2 symbols represents a hydroxyl radical by means of an aliphatic acid or of a derivative of this acid, such as a halide or the

anhydride, under the usual esterification conditions.

As regards the intermediates described above, operating protocols and compounds useful in obtaining them are also provided hereinbelow.

Conventionally, the products of general formula (III) in which R represents a carboxyl radical or a radical of general formula $COOR_6$ can be obtained by the action of trifluoromethanesulphonic acid on a product of general formula (VIII):



(VIII)

in which:

- Ar, R_3, R_4 and R_5 are defined as above,
- G_1 represents a benzyl radical,
- R_6 represents an alkyl radical containing 1 to 3 carbon atoms

followed by replacement of the G_1 group by a hydrogen atom

- either by hydrogenolysis under the conditions described above, then, optionally, depending on the situation, by replacement of the hydrogen atom by a *tert*-butoxycarbonyl radical, by reaction with tert-butoxycarbonyl anhydride in an organic solvent, or

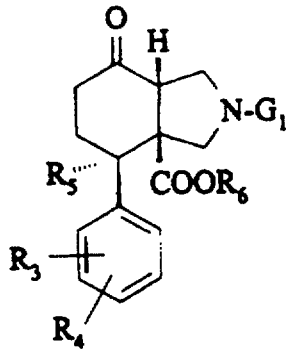
by a benzyloxycarbonyl radical, by reaction by benzyloxycarbonyl chloride in an organic solvent - or by reaction with an alkyl chloroformate, such as vinyl chloroformate or ethyl chloroformate or 2-chloroethyl chloroformate or 2,2,2-trichloroethyl chloroformate, in an organic solvent, such as dichloromethane, at a temperature of between 0°C and room temperature, followed by acid hydrolysis of the intermediate carbamate formed, generally using a 1 to 6M aqueous hydrochloric acid solution, optionally in an organic solvent, such as an alcohol, for example methanol or ethanol, or an ether, for example tetrahydrofuran or dioxane.

The intramolecular cyclization of Friedal-Crafts type of the product of general formula (VIII) to the product of general formula (III) can generally be carried out by the action of an excess, from 3 to 15 molar equivalents, of a strong acid, such as trifluoromethanesulphonic acid, optionally in the presence of trifluoromethanesulphonic anhydride as a catalytic amount or optionally added as successive additions, the reaction being carried out in an organic solvent, such as dichloromethane, at a temperature of between 0°C and the reflux temperature, for a few minutes to several days. It is also possible to carry out the intramolecular cyclization of Friedel-Crafts type by the action of a Lewis acid, such as aluminium chloride or titanium tetrachloride or boron

trifluoride, optionally in the form of a complex with diethyl ether, in an organic solvent, such as dichloromethane or nitromethane or nitrobenzene.

This reaction can optionally be followed by saponification of the product obtained and optionally followed, depending on the situation, by replacement of the benzyl radical by a hydrogen atom.

The product of general formula (VIII) can be obtained, for its part, conventionally by reaction of an organomagnesium derivative of general formula Ar-Mg-X, in which Ar is defined as above and X represents a halogen atom, or of an organolithium derivative of general formula Ar-Li, in which Ar is defined as above, with a product of general formula (IX):



(IX)

in which R_3, R_4, R_5, R_6 and G_1 are defined as above, under the usual conditions.

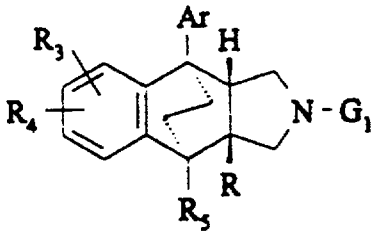
The reaction of an arylmagnesium derivative, obtained conventionally and optionally in the presence of anhydrous cerium(III) chloride under the conditions described by Imamoto (Tetrahedron Lett., 1985, p. 4763), with the ketone derivative of general formula

(IX) is generally carried out in an organic solvent, such as diethyl ether or tetrahydrofuran, the reaction being carried out at a temperature of between 0°C and the reflux temperature of the reaction mixture from a few minutes to 24 hours. However, it has been found to be particularly advantageous to carry out the reaction in toluene, optionally as a mixture with diethyl ether or tetrahydrofuran.

The reaction of an aryllithium derivative, obtained conventionally, with the ketone derivative of general formula (IX) is generally carried out in an organic solvent, such as diethyl ether or tetrahydrofuran, the reaction being carried out at a temperature of between -78° and -20°C for a few minutes to 4 hours. However, it has been found to be particularly advantageous to carry out the reaction in toluene, optionally as a mixture with diethyl ether or tetrahydrofuran.

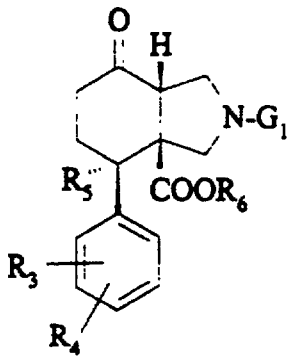
Advantageously, a preparation process has been developed, in the context of the present invention, which makes it possible to obtain the compounds of general formula (III) from compounds of general formula (IX) via the formation of a stable and characterizable intermediate of general formula (XV) characterized by the presence of an arylethylene functional group at the 7 position.

More specifically, the compounds of general formula (III)



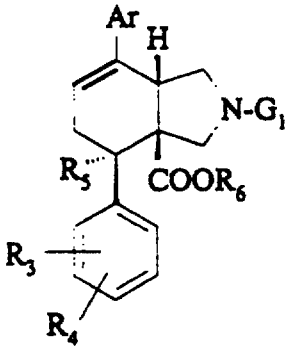
(III)

in which R_3, R_4, R_5, Ar and R are as defined in general formula I and G1 represents a benzyl radical, can be obtained from compounds of general formula (IX):



(IX)

in which R_3, R_4, R_5, R_6 and G_1 are as defined above, via the formation of an intermediate of general formula (XV)



(XV)

in which R_3, R_4, R_5, R_6, Ar and G_1 are as defined above.

The operating protocol developed successively involves:

- either the condensation, at the 7 position, of a ketone derivative of general formula (IX) with hydrazine, to result in a hydrazone, followed by reaction with iodine to result, according to the Barton reaction (J. Chem. Soc., 1962, p. 470), in an iodoethylene derivative; followed by a palladium coupling reaction with an arylboronic acid, the Suzuki reaction (Tetrahedron Lett., 1979, p. 3437), of general formula $Ar\text{-}B(OH)_2$ or optionally with the trimeric anhydride of arylboronic acid, in which Ar is defined as above, or with an arylstannane, the Stille reaction (Angew. Chem. Int. Ed. Engl., 1986, p. 508), of general formula $Ar\text{-}SnMe_3$ in which Ar is defined as above, in order to result in this arylethylene intermediate of general formula (XV), the conversion of which by intramolecular cyclization of Friedel-Crafts type results in the expected product (III),

- or the reaction of a ketone derivative of general formula (IX) with trifluoromethanesulphonic anhydride, in order to result in an enol triflate at the 7 position (Org. Synth., 1990, p. 116); followed by a palladium coupling reaction with an arylboronic acid, the Suzuki reaction (Tetrahedron Lett., 1979, p. 3437), of general formula $Ar\text{-}B(OH)_2$ in which Ar is defined as above, or with an arylstannane, the Stille reaction (Angew. Chem. Int. Ed. Engl., 1986, p. 508), of general formula $Ar\text{-}SnMe_3$ in which Ar is defined as above, in order to result in this arylethylene intermediate of

general formula (XV), the conversion of which by intramolecular cyclization of Friedel-Crafts type results in the expected product (III).

The ketone derivative of general formula (IX) is generally treated with an excess of hydrazine hydrate, from 3 to 20 molar equivalents, at reflux in a solvent, such as ethanol, from a few minutes to a few hours. The hydrazone thus obtained is then stirred with an excess of iodine, in the presence of an aliphatic tertiary amine, such as triethylamine, at a temperature in the region of 20°C for a few hours in order to result in an iodoethylene derivative.

The ketone derivative of general formula (IX) is generally treated:

- either with trifluoromethanesulphonic anhydride in the presence of an organic base, such as 2,6-di-*tert*-butyl-4-methylpyridine, in an organic solvent, such as dichloromethane, at a temperature in the region of room temperature for a few hours, according to Stang (Synthesis, 1980, p. 283),
- or with a bis(trifluoromethylsulphonyl)amide, such as N,N-bis(trifluoromethylsulphonyl)aniline, according to MacMurry (Tetrahedron Lett., 1983, p. 979), or 2-[N,N-bis(trifluoromethylsulphonyl)amino]pyridine, according to Comins (Tetrahedron Lett., 1992, p. 979), in the presence of a base, such as lithium diisopropylamide, in an organic solvent, such as dichloromethane or 1,2-dimethoxyethane,

in order to result in an enol triflate.

The coupling between the iodoethylene derivative or the enol triflate obtained above and an arylboronic acid obtained conventionally and optionally isolated in the trimeric anhydride form is generally carried out by stirring in a two-phase system composed of an organic solvent, preferably a mixture of toluene and methanol, and of a basic aqueous solution, preferably a 2N sodium carbonate solution, in the presence of a catalytic amount of palladium(0) derivative, preferably tetrakis(triphenylphosphine)-palladium, at a temperature in the region of the reflux temperature for a few hours, in order to result in the arylethylene compound of general formula (XV).

The coupling between the iodoethylene derivative or the enol triflate obtained above with an arylstannane obtained conventionally is generally carried out by stirring in a polar aprotic organic solvent, preferably dimethylformamide or N-methylpyrrolidone, in the presence of a catalytic amount of palladium(0) derivative, preferably tetrakis(triphenylphosphine)palladium, at a temperature of between 50° and 100°C for a few hours, in order to result in the arylethylene compound of general formula (XV).

The intramolecular cyclization of Friedel-Crafts type of the compound of general formula (XV) to the product of general formula (III) is generally

carried out under the conditions described above for the intramolecular cyclization of the products of general formula (VIII).

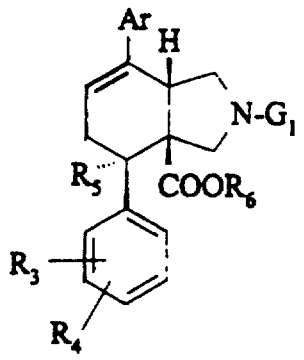
Advantageously, a second preparation process has additionally been developed, in the context of the present invention, which makes it possible to obtain the compounds of general formula (III) as defined above from the compounds of general formula (IX) via the formation of the intermediate of general formula (XV), which can optionally be isolated. This second process is very particularly advantageous when the aryl radical Ar represents a phenyl nucleus substituted, at the para or meta-para or meta-para-meta' positions, by electron-donating groups or a heterocyclic radical which is naturally rich in electrons or a heterocyclic radical suitably substituted by electron-donating groups. This second process consists in directly reacting, according to tandem intermolecular and then intramolecular cyclization reactions of Friedel-Crafts type, an aromatic or heterocyclic hydrocarbon Ar-H with a compound of general formula (IX) in an organic solvent in the presence of an excess of strong acid, such as trifluoromethanesulphonic acid, or optionally of a Lewis acid, such as aluminium chloride.

The procedure developed consists in condensing the product of general formula (IX) with an excess of trifluoromethanesulphonic acid (from 5 to 20 molar equivalents) in an organic solvent, such as

dichloromethane, at a temperature in the region of room temperature, for a few hours to several days. According to the number of molar equivalents in the concentration of trifluoromethanesulphonic acid, as well as the nature of the Ar radical and of the substituents which it carries, this reaction results either directly in the compounds of general formula (III) or in the compounds of general formula (XV) as intermediates, which are then cyclized as described above to compounds of general formula (III).

In addition, the compounds of general formula (I) or (III) can be obtained by functionalization of the substituents of the aromatic ring Ar of the corresponding compounds of general formula (I) or (III), by application or adaptation of the known methods for standard functionalizations, such as, and without implied limitation: functional substitution reactions (for example the replacement of a halogen atom by a cyano group by a palladium coupling), dealkylation reactions (for example by BBr_3) or alkylation reactions (in particular alkylation/ cyclization reactions by the action of BBr_2).

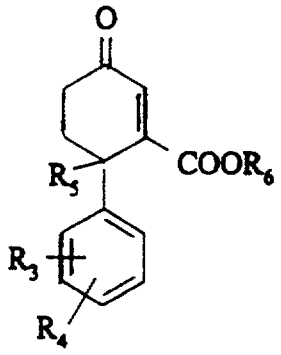
Another subject of the present invention also relates to these compounds of general formula (XV):



(XV)

in which R_3, R_4, R_5 and Ar are as defined in general formula I, G_1 represents a benzyl radical and R_6 represents an alkyl radical containing 1 to 3 carbon atoms, in the racemic form, and to their optical isomers.

The product of general formula (IX), in the racemic form or its optical isomers, in which R_3, R_4, R_5, R_6 and Ar are as defined in general formula I and G_1 represents a benzyl radical can be obtained by reaction of an N-trialkylsilylmethyl-N-(alkoxy-methyl)amine carrying a protective group for the amine functional group, such as a benzyl radical, for example N-trimethylsilylmethyl-N-(n-butoxymethyl)benzylamine, which can be prepared under the conditions described in Chem. Pharm. Bull., 276 (1985), with a cyclohexenone derivative of general formula:



(X)

in which R_3, R_4, R_5 and R_6 are defined as above, in the racemic form or its optical isomers.

The reaction is generally carried out in an organic solvent, such as a halogenated aliphatic hydrocarbon, for example dichloromethane, in the presence of a strong acid, such as trifluoroacetic acid, at a temperature of between 0°C and the reflux temperature of the reaction mixture.

The products of general formula (X) can be obtained by esterification of 3-oxo-6-phenylcyclohex-1-ene-1-carboxylic acids, in which R_3, R_4 and R_5 are defined as above, by means of an aliphatic alcohol containing 1 to 3 carbon atoms, in the presence of an inorganic base, such as hydrochloric acid or sulphuric acid, at a temperature of between 0°C and the reflux temperature of the reaction mixture, or by means of an alkyl halide (iodide), in the presence of an organic base, such as 1,8-diazabicyclo[5.4.0]undec-7-ene, or an inorganic base, such as caesium carbonate, the reaction being carried out in a solvent chosen from tetrahydrofuran, dimethylformamide, acetone or dioxane.

3-Oxo-6-phenylcyclohex-1-ene-1-carboxylic acids, in which R_3, R_4 and R_5 are defined as above, can be obtained from 3-oxo-6-phenylcyclohexane-1-ol-1-carboxylic acids, in which R_3, R_4 and R_5 are defined as above, either by thermal dehydration, by heating at a temperature in the region of 190°C (according to J. Org. Chem., 1971, p. 3707) or by heating in refluxing toluene in the presence of p-toluenesulphonic acid, or by reacting with an inorganic base, such as sodium hydroxide, at a temperature of between 0 and 50°C.

3-Oxo-6-phenylcyclohexane-1-ol-1-carboxylic acids, in which R_3, R_4 and R_5 are defined as above, can be obtained by reaction of phenylpyruvic acids, or optionally of the corresponding esters, more particularly in the case where R_5 does not represent a hydrogen atom, the phenyl nucleus of which is optionally substituted by substituents defined by R_3 and R_4, with methyl vinyl ketone, the reaction generally being carried out in aqueous/alcoholic medium, such as a methanol/water mixture, in the presence of an inorganic base, such as sodium hydroxide (according to J. Org. Chem., 1971, 3707).

Phenylpyruvic acids, the phenyl nucleus of which is optionally substituted by substituents defined by R_3 and R_4, can be obtained, more particularly in the case where R_5 represents a hydrogen atom, either by hydrolysis of the corresponding a-acetamidocinnamic

acids, by heating in hydrochloric acid, according to Org. Synth., 1943, p. 519, or by hydrolysis of the corresponding benzalhydantoins, by heating in 20% sodium hydroxide solution, according to Org. Synth. Coll. Vol. V, p. 627.

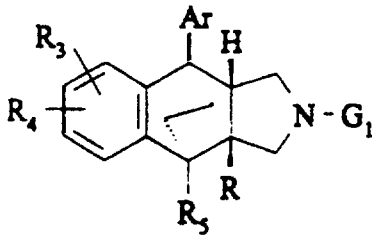
a-Acetamidocinnamic acids, the phenyl nucleus of which is optionally substituted by substituents defined by R_3 and R_4, can be obtained, from the corresponding benzaldehydes according to Org. Synth., 1939, p. 1, by reaction with N-acetylglycine in refluxing acetic anhydride in the presence of sodium acetate. The intermediate azlactones thus obtained are then hydrolysed to a-acetamidocinnamic acids by heating at reflux in aqueous acetone.

Benzalhydantoins, the phenyl nucleus of which is optionally substituted by substituents defined by R_3 and R_4, can be obtained by heating the corresponding benzaldehydes, according to Org. Synth. Coll. Vol. V, p. 267, with hydantoin in the presence of an organic base, such as piperidine, at a temperature in the region of 130°C.

Phenylpyruvates, the phenyl nucleus of which is optionally substituted by substituents defined by R_3 and R_4, can be obtained, more particularly in the case where R_5 does not represent a hydrogen atom but an alkyl or alkylthio radical, from 2-phenylalkanoic acids, the phenyl nucleus of which is optionally substituted by substituents defined by R_3 and R_4, by reaction of the

corresponding dianion, generally obtained by reaction of an organic base, such as n-butyllithium, with the acid, with ethyl oxalate at a temperature in the region of -70°C, followed by decarboxylation, the reaction being carried out under the conditions described in Tetrahedron Lett., 1981, 2439-42.

The products of general formula (III)



(III)

in which R represents a radical

$$(CH_2)_m\text{-}X_1(CH_2)_n\text{-}Z$$

in which:

m is equal to 0,

X_1 represents a bond,

n is equal to 0 and

Z represents a $-COOR_6$ or $-CON(R_7)(R_8)$ radical

can be obtained from a product of general formula (VIII), in which R represents a carboxyl radical, by esterification and amidation under the conditions described above, followed by cyclization by the action of trifluoromethanesulphonic acid under the conditions described above.

The products of general formula (III) in which R represents a radical

$$(CH_2)_m\text{-}X_1(CH_2)_n\text{-}Z$$

in which:

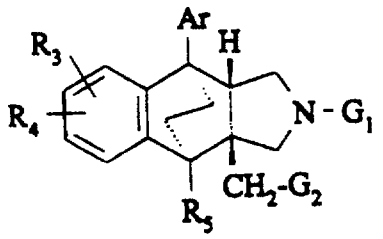
m is equal to 1,

X_1 represents a bond,

n is equal to 0 and

Z represents a $-COOR_6$, $-CON(R_7)(R_8)$ or $PO(OR_9)_2$ radical

can be obtained from a product of general formula:



(XI)

in which Ar, R_3, R_4 and R are defined as above, G_1 represents a protective group for the amine functional group (benzyl, benzyloxycarbonyl or *tert*-butoxycarbonyl and G_2 represents a leaving group, such as a trifluoromethylsulphonyloxy radical.

More particularly, in order to obtain a product of general formula (III) in which R represents a radical

$$-(CH_2)_m-X_1(CH_2)_n-Z$$

in which:

m is equal to 1,

X_1 represents a bond,

n is equal to 0 and

Z represents a carboxyl, $-COOR_6$, in which R_6 repressents an alkyl radical, or $-CON(R_7)(R_8)$ radical,

it is particularly advantageous to use the corresponding nitrile as an intermediate, which nitrile

can be obtained by reaction of an alkali metal cyanide with the product of general formula (XI), the reaction being carried out in a polar organic solvent, such as dimethyl sulphoxide, at a temperature of between 0 and 50°C, which nitrile is hydrolysed to the corresponding acid, which can then be esterified or amidated under the usual conditions.

More particularly, in order to obtain a product of general formula (III) in which R represents a radical

$$(CH_2)_m\text{-}X_1(CH_2)_n\text{-}Z$$

in which:

m is equal to 1,

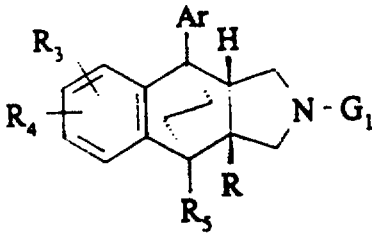
X_1 represents a bond,

n is equal to 0 and

Z represents a $-PO(OR_9)_2$ radical,

it is particularly advantageous to react a trialkyl phosphite with a product of general formula (XI) and then, optionally, to convert the phosphonate obtained to the corresponding phosphonic acid.

The products of general formula (III)



(III)

in which:

- R represents a $(CH_2)_m\text{-}X_1\text{-}(CH_2)_n\text{-}Z$ radical with m

equal to 1, X_1 representing an oxygen or sulphur atom, n equal to 1 or 2 and Z representing a carboxyl, $-COOR_6$, in which R_6 represents an alkyl radical, or $-CON(R_7)(R_8)$ radical and

- G_1 represents a protective group for the amine functional group

can be obtained by reaction of an ester or of an amide of general formula:

$$H-X_1-(CH_2)_n-Z$$

in which X_1, n and Z are defined as above with a product of general formula (XI), the reaction being carried out in an anhydrous organic solvent, such as dioxane, in the presence of an alkali metal hydride, such as sodium hydride, optionally followed, depending on the situation, by saponification of the product of general formula (III) thus obtained.

The products of general formula (III) in which:

- m is equal to 1,
- X_1 represents a bond,
- n is equal to 1, with it being possible for the methylene group to be substituted by a carboxyl or alkoxycarbonyl or carbamoyl or alkylcarbamoyl or dialkylcarbamoyl radical,
- G_1 represents a protective group for the amine functional group and
- Z represents a carboxyl, $-COOR_6$, in which R_6 represents an alkyl radical, or $-CON(R_7)(R_8)$ radical,

can be obtained by reaction of a malonic acid, anionized beforehand, or of a malonic acid derivative, preferably a diester, with a product of general formula (XI), the reaction being carried out in an anhydrous organic solvent, such as dioxane, in the presence of an alkali metal hydride, such as sodium hydride, at a temperature of between 0°C and the reflux temperature of the reaction mixture, followed, depending on the situation, by saponification, esterification, amidation or decarboxylation of the product of general formula (III) thus obtained.

The products of general formula (III) in which:

R represents an -NH-CO-T radical in which T is defined as above

can be obtained by amidation of a product of general formula (III) in which:

- R_3 is defined as above,
- G_1 represents a protective group of the amine functional group and
- R represents an amino radical

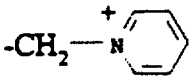
by means of an acid of general formula T-CO-OH in which T is defined as above, under the conditions described above for the amidation of a product of general formula (VI).

The products of general formula (III) in which R represents an amino radical or the products of general formula (VI) can be obtained according to the

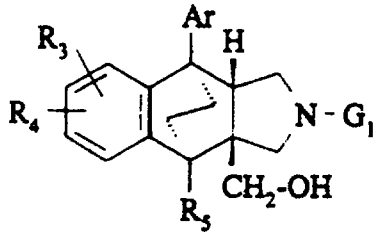
methods which make it possible to convert a carboxyl radical to an amino radical without affecting the remainder of the molecule.

The carboxyl functional group of a product of general formula (III) or (I) is generally converted to the amino radical via an isocyanate which can be obtained by pyrolysis of the acid azide, which can itself be obtained by reaction of an alkali metal azide with the corresponding acid halide. The intermediate isocyanate thus obtained is conventionally condensed with benzyl alcohol and then the benzyl carbamate obtained is converted to the amino radical, either by hydrogenolysis or by acid hydrolysis under the conditions described above.

The products of general formula (III) in which R represents

- a  radical

can be obtained by reaction of pyridine and of a strong acid or of a derivative of this acid with a product of general formula (XII):



(XII)

in which Ar, R_3, R_4 and R_5 are defined as above and G_1

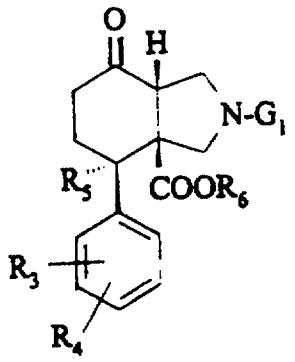
represents a protective group for the amine functional group.

The products of general formula (VII) or of general formula (XII) can be obtained respectively by reduction of a product of general formula (I) or of a product of general formula (III) in which R represents a radical of general formula -$COOR_6$ in which R_6 preferably represents an alkyl radical containing 1 to 3 carbon atoms.

The reduction is generally carried out by means of a lithium aluminium hydride, the reaction being carried out in an organic solvent, such as an ether, for example tetrahydrofuran, at a temperature of between 0 and 50°C.

According to the invention, the products of general formula (I), in which Ar, R_1, R_2, R_3, R_4, R_5, X and Y are defined as above and R represents a $COOR_6$ radical in which R_6 is defined as above, can also be obtained from a product of general formula (IX) in which R_3, R_4, R_5 and R_6 are defined as above and G_1 represents a hydrogen atom.

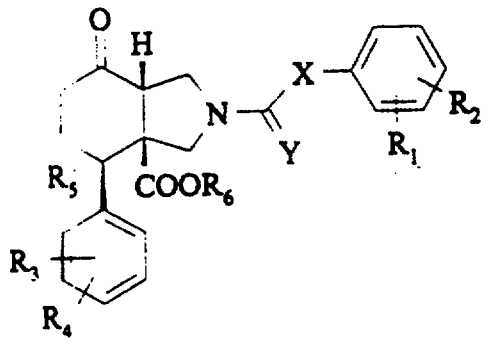
According to the invention, the product of general formula (IX)



(IX)

in which G_1 represents a hydrogen atom, is obtained from the product of general formula (IX), in which G_1 represents a protective group for the amino functional group, under the conditions described above for the preparation of a product of general formula (III) in which G_1 represents a hydrogen atom.

The product of general formula (IX) in which G_1 represents a hydrogen atom is converted to the product of general formula:



(XIII)

in which R_1, R_2, R_3, R_4, R_5, R_6, X and Y are defined as above, the reaction being carried out, depending on the meanings of X and Y, in the following way:

- the products of general formula (XIII), in which Y represents an oxygen or sulphur atom and X represents a

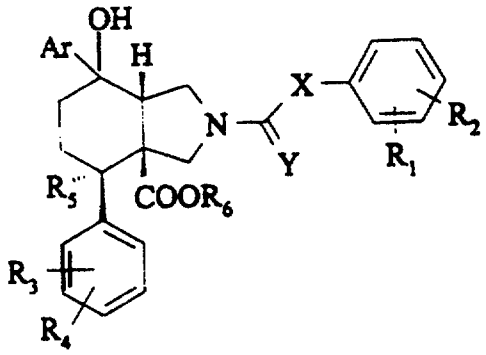
-CO-, methylene, vinyldiyl, alkene-1,1-diyl or cycloalkane-1,1-diyl group, can be obtained by reaction of an acid of general formula (II) or of its chloride or of its anhydride with a product of general formula (IX) in which G_1 represents a hydrogen atom, the reaction being carried out under the conditions described above for the reaction of a product of general formula (II) with a product of general formula (III) in which G_1 represents a hydrogen atom,

- the products of general formula (XIII), in which Y represents an oxygen or sulphur atom and X represents an oxygen atom, can be obtained by reaction of a haloformate or of a halothioformate of general formula (IV) with a product of general formula (IX) in which G_1 represents a hydrogen atom, the reaction being carried out under the conditions described above for the reaction of a product of general formula (IV) with a product of general formula (III) in which G_1 represents a hydrogen atom,

- the products of general formula (XIII), in which Y represents an oxygen or sulphur atom and X represents an NH group, can be obtained by reaction of an isocyanate or of an isothiocyanate of general formula (V) with a product of general formula (IX) in which G_1 represents a hydrogen atom, the reaction being carried out under the conditions described above for the reaction of a product of general formula (V) with a product of general formula (III) in which G_1 represents

a hydrogen atom.

The product of general formula (XIII) is converted to the product of general formula:



(XIV)

in which Ar, R_1, R_2, R_3, R_4, R_5, R_6, X and Y are defined as above, by reaction of a metallic derivative of general formula Ar-Mg-X or Ar-Li, in which X represents a halogen atom, with a product of general formula (XIII), the reaction being carried out under the conditions described above for the reaction of an organomagnesium or organolithium derivative of general formula Ar-Mg-X or Ar-Li with a product of general formula (IX).

The product of general formula (XIV) is converted to the product of general formula (I), in which Ar, R_1, R_2, R_3, R_4, R_5, R_6, X and Y are defined as above, by the action of trifluoromethanesulphonic acid or of a Lewis acid on the product of general formula (XIV), the reaction being carried out under the conditions described above for the action of trifluoromethanesulphonic acid or of a Lewis acid on a product of general formula (VIII).

The reaction of an aromatic hydrocarbon or of an aromatic heterocycle Ar-H, as defined above, in the presence of trifluoromethanesulphonic acid or of a Lewis acid, with a product of general formula (XIII), in which R_1, R_2, R_3, R_4, R_5, R_6, X and Y are defined as above, results in a product of general formula (I) in which Ar is defined as above and R represents a $COOR_6$ radical in which R_6 represents an alkyl radical containing 1 to 3 carbon atoms.

According to the invention, the products of general formula (I) in which:

- Ar, R_1, R_2, R_3, R_4, R_5, X and Y are defined as above and
- R represents a radical

$$(CH_2)_m-X_1-(CH_2)_n-Z$$

in which m, n, X_1 and Z are defined as above can also be prepared from a product of general formula (VII) under the conditions described above for the preparation of the products of general formula (III) from a product of general formula (XI), after replacement of the hydroxyl radical of the product of general formula (VII) by a leaving group, such as a trifluoromethanesulphonyloxy radical.

The reaction mixtures obtained by the various processes described above are treated according to conventional physical methods (evaporation, extraction, distillation, chromatography, crystallization, for example) or conventional chemical methods (formation of

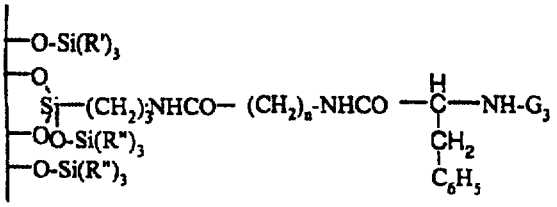
salts, for example).

The compounds of formula (I) can optionally be converted into 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.

The optical isomers of the products of general formula (I) can be obtained according to the usual separation methods from the corresponding racemic product. It is particularly advantageous to carry out the separation by high performance liquid phase chromatography using a chiral stationary phase of modified Pirkle type, elution being carried out with a suitable solvent.

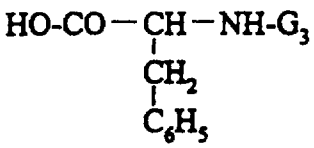
Use may preferably be made, as chiral stationary phase, of a phase in which the chiral selector, which is preferably 3,5-dinitrophenylalanine, is kept at a distance from the silica by an aminoalkyl arm containing 3 to 14 carbon atoms attached to the amine functional groups of an aminopropyl silica, the free silanol functional groups of which are blocked by trialkylsilyl radicals.

This chiral phase may be defined by the following structure:



in which the R′ symbols, which are identical or different, and the R" symbols, which are identical or different, represent alkyl radicals containing 1 to 10 carbon atoms, G_3 represents an electron-withdrawing group and n represents an integer between 3 and 13 inclusive, the porosity of which is in the region of 100 Å.

The chiral phase can be prepared by reaction of an aminopropyl silica with the anhydride of an aminoalkanoic acid containing 4 to 14 carbon atoms, the amine functional group of which is protected by a protective group, such as the *tert*-butoxycarbonyl radical, followed by blocking a part of the silanol functional groups by $Si(R')_3$ radicals as defined above, then, after removal of the protective groups for the amine functional group, by amidation by means of an amino acid of general formula:



in which G_3 is defined as above, and finally blocking of the residual silanol functional groups by $Si(R")_3$

radicals as defined above.

Generally, the reaction of the anhydride of a protected aminoalkanoic acid with the aminopropyl silica is carried out in an anhydrous organic solvent, such as dimethylformamide, at a temperature in the region of 20°C.

Blocking of the silanol functional groups by $-Si(R'_3)$ groups as defined above is carried out by reaction of a halotrialkylsilane with the aminopropyl silica, which has been grafted by aminoalkanoyl residues, in an organic solvent, such as methylene chloride, in the presence of a basic agent, such as pyridine.

Removal of the protective groups from the aminoalkanoyl residues is generally carried out, when the protective group is a *tert*-butoxycarbonyl radical, by the action of trifluoroacetic acid in an organic solvent, such as methylene chloride.

Amidation by means of phenylalanine in which the amine functional group is protected is carried out in the presence of a coupling agent, such as N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, in an anhydrous organic solvent, such as dimethylformamide.

Blocking the residual silanol functional groups by $-Si(R")_3$ radicals as defined above is generally carried out by means of trialkylsilyl-imidazole in an organic solvent, such as methylene chloride.

The aminopropyl silica can be prepared by reaction of aminopropyltriethoxysilane with a silica in which the porosity is in the region of 100 Å in the presence of imidazole in an anhydrous organic solvent, such as an aromatic hydrocarbon, for example toluene.

As shown in the examples below, the novel products of general formula (I), which inhibit farnesyl transferase and the farnesylation of the Ras protein, exhibit notable antitumour and antileukaemic properties.

Another subject of the present invention is any pharmaceutical composition containing at least one product of general formula [lacuna] in combination with one or more pharmaceutically acceptable diluents or adjuvants, whether inert or biologically active.
The novel products of general formula (I) can be provided in the form of non-toxic and pharmaceutically acceptable salts. These non-toxic salts comprise salts with inorganic acids (hydrochloric, sulphuric, hydrobromic, phosphoric, nitric acids) or with organic acids (acetic, propionic, succinic, maleic, hydroxymaleic, benzoic, fumaric, methanesulphonic, trifluoroacetic or oxalic acids) or with inorganic bases (sodium hydroxide, potassium hydroxide, lithium hydroxide, calcium hydroxide) or organic bases (tertiary amines, such as triethylamine, piperidine, benzylamine), depending on the nature of the compounds of general formula (I).

The present invention also relates to the use of the compounds of general formula (I) according to the invention in the preparation of pharmaceutical compositions useful in inhibiting farnesyl transferase and more particularly in inhibiting farnesylation of the *ras* oncogene.

In particular, the present invention relates to the use of the compounds of general formula (I) according to the invention in the preparation of pharmaceutical compositions useful in the treatment of diseases related to cell proliferations by inhibition of farnesyl transferase and in particular in the treatment of diseases related to cell proliferations overexpressing any one of the H-Ras, N-Ras or K-Ras oncoproteins or exhibiting a mutation of any one of the corresponding *ras* oncogenes.

The invention relates in particular to the use of the compounds of general formula (I) according to the invention in the preparation of pharmaceutical compositions useful in the treatment of diseases related to cell proliferations, malignant or benign, of cells of various tissues and/or organs, comprising muscle, bone or connective tissues, the skin, the brain, the lungs, the sexual organs, the lymphatic or renal systems, mammary or blood cells, the liver, the digestive system, the colon, the pancreas and the thyroid or adrenal glands,

and including the following pathologies: psoriasis,

restenosis, solid tumours, Kaposi's sarcoma, carcinomas, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanomas, teratocarcinomas, gliomas, multiple myelomas, chronic lymphocytic leukaemias, acute or chronic granulocytic lymphomas, and cancers, such as cancers of the pancreas, colon, lung, ovary, breast, brain, prostate, liver, stomach, bladder or testicles.

The invention very particularly relates to the use of the compounds of general formula (I) according to the invention, preferably the compound described in Example 3, in the preparation of pharmaceutical compositions useful in the treatment of cancers, such as cancers of the pancreas, colon, lung, ovary, breast, brain, prostate, liver, stomach, bladder or testicles, and more advantageously cancer of the colon and pancreas, in particular of the colon.

The compounds according to the invention can also be useful in the preparation of medicaments in the treatment and/or the prevention of pathological conditions related to cell signalling pathways, associated with farnesyl transferase, or to their consequences or symptoms.

The compounds according to the present invention can advantageously be used in in the preparation of medicaments in the treatment and/or the prevention of diseases associated with cell signalling

pathways related to Ras. Thus, the compounds according to the invention can be used in the preparation of medicaments in the treatment and/or the prevention of the rejection of grafts (such as allografts) (O'Donnel et al. 1995, Kidney International, vol. 48, suppl. 52, pp. 29-33).

The compounds according to the invention can also be useful in the preparation of medicaments for inhibiting angiogenesis and acting on tumour growth (J. Rak et al., Cancer Research, 55, 4575-4580, 1995), it being possible for these antiangiogenic properties also to be useful in the treatment of certain forms of blindness relating to retinal vascularization.

The compounds according to the invention can also be useful in the preparation of medicaments in the treatment and/or the prevention

- of diseases related to (pro- or anti-)apoptotic dysfunctioning comprising in particular the abovementioned cancers;
- of delta hepatitis and associated viruses (J.S. Glenn et al., Science, 256, 1331-1333, 1992), as well as, and in a non-limiting way, the Herpes, Pox, Epstein-Barr and Sindbis viruses and adenoviruses);
- of inflammatory and/or autoimmune diseases, such as, by way of illustration, polyarthritides, polyarticular rheumatisms, intestinal inflammations, pulmonary oedemas, myocardial infarctions, fibroses, the various forms of lupus erythematosus, such as Kaposi's sarcoma,

immunoglomerulonephritides or autoimmune diabetes;

- cardiovascular diseases (arteriosclerosis or other arterial lesions) or restenosis following angioplasty or vascular surgery;

- bone diseases, of regulation of bone metabolism, for example Paget's disease, hypercalcaemia, bony metastases or osteoporosis;

- diseases associated with a high level of cholesterol, such as hypercholesterolaemia, hyperlipidaemia, hyperpoproteinaemia, nephrotic hyperlipidaemia or artherosclerosis (Massey et al., Lancet, 347, 102-103, 1996);

- neurodegenerative disorders, such as Parkinson's disease, Alzheimer's disease, amyotrophic lateral sclerosis, neurological disorders associated with viral diseases, such as AIDS, retinites, or spinocerebellar atrophies or degenerations);

and in the prevention and/or the treatment of the following diseases: in particular AIDS and also polycystic kidney (D.L. Schaffner et al., American Journal of Pathology, 142, 1051-1060, 1993), neurofibromatoses, pulmonary fibroses, arthrites, psoriasis, glomerulonephritides, hypertrophic scar formations or endotoxin shocks;

as well as myeliodysplastic syndromes, aplastic anaemia, ischaemic lesions associated with infarctions, lesions associated with strokes and, arrhythmias, atheroscleroses, liver diseases due to toxins or

alcohol, haematological diseases, including in particular chronic or aplastic anaemia, degenerative diseases of the muscle-skeleton system, including in particular osteoporosis and arthritis, cystic fibroses, multiple scleroses, liver diseases or pain related to cancer.

The said treatment can in particular be carried out by inhibition of tumour growth, in particular by inhibition of farnesyl transferase, or alternatively by inhibition of the growth of tumours expressing the activated *ras* oncogene.

The therapeutic treatment may also be carried out conjointly with other therapeutic treatments including antineoplastic medicaments, monoclonal antibodies, immunological therapies or radiotherapies or biological-response modifiers. The response modifiers include, without implied limitation, lymphokines and cytokines such as interleukins, interferons (α, β or δ) and TNF. Other chemotherapeutic agents which are useful in the treatment of disorders due to abnormal cell proliferation include, without implied limitation, alkylating agents such as nitrogen mustards, for instance mechlorethamine, cyclophosphamide, melphalan and chlorambucil, alkyl sulphonates such as busulphan, nitrosoureas such as carmustine, lomusine, semustine and streptozocin, triazenes such as dacarbazine, antimetabolites such as folic acid analogues, for instance methotrexate,

pyrimidine analogues such as fluorouracil and cytarabine, purine analogues such as mercaptopurine and thioguanine, natural products such as vinca alkaloids, for instance vinblastine, vincristine and vendesine, epipodophyllotoxins such as etoposide and teniposide, antibiotics such as dactinomycin, daunorubicin, doxorubicin, bleomycin, plicamycin and mitomycin, enzymes such as L-asparaginase, various agents such as coordination complexes of platinum, for example cisplatin, substituted ureas such as hydroxyurea, methylhydrazine derivatives such as procarbazine, adrenocorticoid suppressants such as mitotane and aminoglutethimide, hormones and antagonists such as adrenocorticosteroids such as prednisone, progestins such as hydroxyprogesterone caproate, methoxyprogesterone acetate and megestrol acetate, oestrogens such as diethylstilboestrol and ethinyloestradiol, antioestrogens such as tamoxifen, and androgens such as testosterone propionate and fluoxymesterone.

Another subject of the present invention is any combination of a product of general formula (I) with one or more compatible and pharmacologically active compounds and/or a radiotherapy treatment, in order to obtain a synergic therapeutic effect, the said compounds preferably being active principles known for their inhibitory activity with respect to cell proliferation and particularly for their activity in

the treatment of cancer; they may preferably be anti-proliferative compounds acting, at any one of the stages of the *ras* oncogene signalling pathway, as an inhibitor of tyrosine kinase, or another inhibitor of farnesyl transferase, or an inhibitor of HMG-Co-reductase, or the cytotoxic compounds commonly used in the treatment of cancer.

The products according to the invention can be used to prevent or delay the appearance or the reappearance of pathological conditions or to treat these pathological conditions.

The products according to the invention can be administered orally, parenterally or or intraperitoneally or rectally, preferably orally. The compositions for oral administration comprise tablets, pills, powders or granules. In these compositions, the active product according to the invention is mixed with one or more inert diluents, such as sucrose, lactose or starch. These compositions can comprise substances other than diluents, for example a lubricant such as magnesium stearate.
As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, for example wetting, sweetening or flavouring products.

The compositions according to the invention for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous sterile solutions. As solvent or vehicle, propylene glycol, a polyethylene glycol, vegetable oils, especially olive oil, or injectable organic esters, for example ethyl oleate, may be employed. These compositions can also contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilization may be carried out in several ways, for example using a bacteriological filter, by incorporating sterilizing agents in the composition or by heating. They may also be prepared in the form of sterile solid compositions which can be dissolved at the time of use in sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, besides the active product, excipients such as cocoa butter.

The doses used for implementing the methods according to the invention are those which permit a prophylactic treatment or a maximum therapeutic response. The doses vary according to the administration form, the particular product selected and the features specific to the subject to be treated. In general, the doses are those which are therapeutically effective in the treatment of disorders due to an abnormal cell proliferation and in particular a cytostatic treatment. The products according to the invention can be

administered as often and as long as necessary to obtain the desired therapeutic effect.

The doses are generally, in man, between 0.1 and 10,000 mg/kg per day, preferably between 100 and 2000 mg/kg per day, preferably by the oral route. It is understood that, in order to choose the most appropriate dosage, account should be taken of the administration route, the weight of the patient, his general state of health, his age and all the factors which can influence the effectiveness of the treatment. Generally, the doctor will determine the appropriate posology according to the age, weight and all the other factors specific to the subject to be treated. Compositions according to the invention are illustrated in Example 105.

The following examples are presented by way of illustration of the present invention and do not limit the present invention.

EXAMPLE 1

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

358 g (2.52 mol) of methyl iodide and 361 g (2.38 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene are successively added to a solution of 428 g (1.98 mol) of (RS)-3-oxo-6-phenylcyclohex-1-ene-1-carboxylic acid,

which can be obtained according to J. Org. Chem., 1971, 36, 3707, in 4.5 cm^3 of acetone and then the reaction mixture is brought to reflux for five hours. The acetone is subsequently distilled off and then the residue is stirred with 2.5 dm^3 of water. After cooling to 10°C, the precipitate formed is filtered off, washed with ice-cold water and then dried at 30°C. 423 g (93%) of methyl (RS)-3-oxo-6-phenylcyclohex-1-ene-1-carboxylate are thus obtained in the form of a yellow powder, the characteristics of which are as follows:

- melting point = 66°C
- N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): 2.1-2.4 (mt, 4H, H at 4 and at 5), 3.72 (s, 3H, CH_3), 4.25 (dt, 1H, H at 6), 6.88 (s, 1H, H at 2), 7.2-7.52 (mt, 5H, aromatic protons).

Stage B

A solution of 170 g (0.77 mol) of methyl (RS)-3-oxo-6-phenylcyclohex-1-ene-1-carboxylate and of 0.9 cm^3 of trifluoroacetic acid in 880 cm^3 of dichloromethane is brought to reflux. 256.3 g (0.913 mol) of N-n-butoxymethyl-N-[(trimethylsilyl)methyl-benzylamine, which can be obtained according to Chem. Pharm. Bull., 1985, 276, are then added over 15 minutes at reflux. The reaction mixture is then cooled to 20°C. After addition of 20 cm^3 of a saturated aqueous sodium hydrogencarbonate solution, the organic phase is separated by settling, washed with water and then stirred with 900 g of silica (63-200 mesh) for

30 minutes. The silica is filtered off and then washed with 1.5 cm^3 of dichloromethane. After concentrating the solvent under reduced pressure, 270 g of a brown oil are then obtained, which oil is taken up in 800 cm^3 of cyclohexane and 770 cm^3 of a normal aqueous methanesulphonic acid solution. After separation by settling, the organic phase is washed with two times 200 cm^3 of water. The combined aqueous phases are washed with two times 200 cm^3 of cyclohexane, then neutralized by addition of sodium hydrogencarbonate and extracted with 400 cm^3 and then two times 200 cm^3 of ethyl acetate. The combined organic phases are then washed with a half-saturated sodium chloride solution, dried over sodium sulphate and then concentrated under reduced pressure. 248 g (90%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenylocta-hydroisoindole-3a-carboxylate are then obtained in the form of an orange-coloured oil, the characteristics of which are as follows:

- N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): 2.4-2.65 (mt, 4H, H at 5 and at 6), 2.85 (2 dt, 2H, H at 1), 3.02 (2 dt, 2H, H at 3), 3.2 (2 dt, 1H, H at 4), 3.35 (mt, 1H, H at 7a), 3.5 (2 dt, 2H, benzyl H), 7-7.3 (mt, 10H, aromatic protons).

Stage C

5.1 cm^3 of 4-bromotoluene and 1 g of magnesium turnings in 100 cm^3 of diethyl ether are heated at reflux for one hour. 100 cm^3 of toluene are added and

the mixture is heated to 60°C under a stream of nitrogen. After cooling to a temperature in the region of 5°C, a solution of 10 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 80 cm^3 of toluene is added. The reaction mixture is stirred for one hour at a temperature in the region of 20°C and then hydrolysed with 100 cm^3 of a saturated aqueous ammonium chloride solution. The aqueous phase is separated by settling and extracted with two times 75 cm^3 of ethyl acetate. The organic phases are combined, washed successively with 100 cm^3 of distilled water and 100 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture, 9 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(4-methylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate are obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 164°C
- ^1H N.M.R. spectrum (250 MHz, $CDCl_3$, d in ppm): 1.84 and 2.60 (d mt and mt, J = 12.5 Hz, each 1H, CH_2 at 5), from 2.05 to 2.20 (mt, 2H, 1H of the CH_2 at 1 and 1H of the CH_2 at 6), 2.32 (s, 3H, $ArCH_3$), 2.40 and 2.95 (2d, J = 10.5 Hz, each 1H, CH_2 at 3), 2.45 (mt, 1H, the other H of the CH_2 at 6), 2.64 (mt, 1H, the other H of the CH_2

at 1), 2.85 (mt, 1H, H at 7a), 3.32 (s, 3H, $COOCH_3$), 3.40 and 3.70 (2d, J = 1.25 Hz, each 1H, NCH_2Ar), 3.50 (dd, J = 12.5 and 3 Hz, 1H, H at 4), 6.68 (s, 1H, OH at 7), from 7.00 to 7.50 (mt, 10H, aromatic H at 4 and aromatic H of the benzyl), 7.12 and 7.40 (2d, J = 8 Hz, each 2H, H at the ortho and meta positions of the aromatic at 7).

Stage D

A mixture of 29 cm^3 of trifluoromethanesulphonic acid and of 100 cm^3 of dichloromethane is added dropwise to a solution of 20 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(4-methylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate in 200 cm^3 of dichloromethane maintained at a temperature in the region of 0°C. The reaction mixture is stirred for 30 minutes at a temperature in the region of 0°C and 2 hours at a temperature in the region of 20°C and is then cooled to a temperature in the region of 0°C. 50 cm^3 of distilled water are then added and then the pH of the aqueous phase is brought to between 8 and 9 by addition of a 4N aqueous sodium hydroxide solution. The organic phase is separated by settling, washed successively with 100 cm^3 of distilled water and 100 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After recrystallization from isopropanol, 18.2 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-4,9-ethano-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-

benzo[f]isoindole-3a-carboxylate are thus obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 158°C
- ^1H N.M.R. spectrum (300 MHz, CDCl3, d in ppm): 1.61, 1.90 and 2.67 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), from 2.50 to 2.60 (mt, 2H, 1H of the CH_2 at 1 and 1H [lacuna] CH_2 at 3), 2.57 (s, 3H, $ArCH_3$), 2.95 (d, J = 10 Hz, the other H of the CH_2 at 1), 3.37 (d, J = 10 Hz, the other H of the CH_2 at 3), 3.44 (broad d, J = 10 Hz, 1H, H at 9a), 3.54 and 3.85 (2d, J = 12.5 Hz, each 1H, NCH_2Ar), 3.57 (broad s, 1H, H at 4), 3.72 (s, 3H, $COOCH_3$), 6.70 (broad d, J = 7.5 Hz, 1H, H at 8), from 7.10 to 7.60 (mt, 12H, H at 5, H at 6, H at 7, H at the ortho and meta positions of the aromatic at 9 and aromatic H of the benzyl).

Stage E

18 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-4,9-ethano-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, in solution in 250 cm^3 of methanol, are reduced by 7.8 g of ammonium formate in the presence of 2 g of 10% (w/w) palladium-on-charcoal by heating at reflux for two hours. After cooling, the catalyst is separated by filtration and rinsed with three times 50 cm^3 of methanol and the filtrate is concentrated under reduced pressure. The residue is dissolved in 200 cm^3 of ethyl acetate and the organic phase is washed successively with 100 cm^3 of a

saturated aqueous sodium hydrogen carbonate solution, 100 cm^3 of distilled water and 100 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. By stirring in 100 cm^3 of pentane, the oil obtained crystallizes. By filtration, 13.2 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 118°C
- ^1H N.M.R. spectrum (250 MHz, $CDCl_3$, d in ppm): 1.56, 1.78 and 2.24 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.42 (s, 3H, $ArCH_3$), 2.79 and 2.96 (2 dd, respectively J = 12.5 and 5.5 Hz and J = 1.25 and 8 Hz, each 1H, CH_2 at 1), 3.10 and 3.39 (2 d, J = 12.5 Hz, each 1H, CH_2 at 3), 3.30 (mt, 1H, H at 9a), 3.51 (broad s, 1H, H at 4), 3.60 (s, 3H, $COOCH_3$), 6.56 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.95 to 7.45 (mt, 7H, H at 5, H at 6, H at 7 and H at the ortho and meta positions of the aromatic at 9).

Stage F

36.6 g of (2-methoxyphenyl)acetic acid, in suspension in 110 cm^3 of bis(dimethylamino)methane, are cooled to a temperature in the region of 0°C. 110 cm^3 of acetic anhydride are added dropwise, the temperature of the reaction mixture not exceeding 40°C. The reaction mixture is stirred for 24 hours at a temperature in the

region of 20°C and then cooled to a temperature in the region of 0°C. 500 cm^3 of distilled water are then added and stirring is continued for 2 hours at a temperature in the region of 0°C. The solid which has appeared is separated by filtration, washed with three times 100 cm^3 of distilled water and dried under reduced pressure at 40°C. 23 g of 2-(2-methoxyphenyl)propenoic acid are thus obtained in the form of a cream solid, the characteristics of which are as follows:

- melting point = 145°C
- ^1H N.M.R. spectrum (200 MHz, d6-DMSO, d in ppm): 3.74 (s, 3H, $ArOCH_3$), 5.71 and 6.15 (2d, J = 0.5 Hz, each 1H, $=CH_2$), from 6,90 to 7.50 (mt, 4H, aromatic H), from 11.5 to 13.5 (very broad unresolved peak, 1H, COOH).

Stage G

A solution of 3.05 cm^3 of oxalyl chloride in 150 cm^3 of dichloromethane is added dropwise to a solution of 6.31 g of 2-(2-methoxyphenyl)propenoic acid in 150 cm^3 of dichloromethane containing 5 drops of N,N-dimethylformamide. The reaction mixture is stirred for a further two hours at a temperature in the region of 20°C, then cooled to a temperature in the region of 0°C and run dropwise into a solution of 12.3 g of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate in 250 cm^3 of dichloromethane and 10 cm^3 of triethylamine, the temperature being

maintained in the region of 0°C. The reaction mixture is stirred for a further one hour at a temperature in the region of 0°C, then for one hour at a temperature in the region of 20°C and poured into 200 cm^3 of distilled water. The organic phase is separated by settling, washed with two times 200 cm^3 of distilled water and then 200 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture, 14.9 g of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 152°C
- ^1H N.M.R. spectrum (250 MHz, d6-DMSO, at a temperature of 383 K, d in ppm): 1.44, 1.68 and from 2.00 to 2.30 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.40 (s, 3H, $ArCH_3$), from 3.35 to 3.50 (mt, 3H, CH_2 at 1 and H at 9a), 3.46 (mt, 1H, H at 4), 3.55 (s, 3H, $COOCH_3$), 3.60 and 4.10 (2d, J = 12.5 Hz, each 1H, CH_2 at 3), 3.73 (s, 3H, $ArOCH_3$), 5.54 and 5.70 (2s, each 1H, $=CH_2$), 6.46 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.40 (mt, 11H, H at 5, H at 6, H at 7, H at the ortho and meta positions of the aromatic at 9 and

aromatic H at the ortho, meta and para positions with respect to the OCH_3).

EXAMPLE 2

Preparation of (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

14.7 g of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate are heated at reflux for six hours in 400 cm^3 of ethanol in the presence of 43.5 cm^3 of a normal aqueous sodium hydroxide solution. The reaction mixture is subsequently concentrated under reduced pressure and the resiude dissolved in 250 cm^3 of distilled water. The aqueous phase is washed with three times 200 cm^3 of diethyl ether and then acidified with a 4N aqueous hydrochloric acid solution to a pH in the region of 2. The crystals which appear are separated off by filtration, washed with three times 400 cm^3 of distilled water and then 200 cm^3 of petroleum ether and dried under reduced pressure at 40°C. 12.6 g of (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are thus obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 142°C
- ^{1}H N.M.R. spectrum (400 MHz, d6-DMSO, at a temperature of 413 K, d in ppm): 1.42, 1.65, 2.00 and 2.15 (4 mts, each 1H, CH_2CH_2), 2.40 (s, 3H, $ArCH_3$), from 3.20 to 3.40 (mt, 3H, CH_2 at 1 and H at 9a), 3.55 (mt, 1H, H at 4), 3.60 and 4.06 (2d, J = 12.5 Hz, each 1H, CH_2 at 3), 3.68 (s, 3H, OCH_3), 5.53 and 5.70 (2 s, each 1H, $=CH_2$), 6.45 (broad d, J = 7.5 Hz, 1H, H at 8), 6.95 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to the OCH_3), 7.03 (broad d, J = 7.5 Hz, 1H, aromatic H at the ortho position with respect to the OCH_3), from 6.90 to 7.30 (mt, 9H, H at 5, H at 6, H at 7 and aromatic H at the meta positions with respect to the OCH_3 and aromatic H at the ortho and meta positions of the aromatic at 9).

EXAMPLE 3

Isolation of the dextrorotatory enantiomer of (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

500 mg of (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are resolved on a chiral silica column, carrying (3,5-dinitrobenzoyl)-S-phenylalanine grafts, elution being carried out with a mixture of dichloromethane, of isopropanol and of n-heptane (85/10/5 by volume). On collecting the second fraction

eluted (retention time 60 minutes), 220 mg of the dextrorotatory enantiomer are obtained after concentrating under reduced pressure, the characteristics of which enantiomer are as follows:

- melting point = 225°C
- mass spectrum (EI): M/Z = 493 (M^+) and 449 (M^+-CO_2)
- optical rotation: $[\alpha]^{20}_{365}$ = + 63.3 +/- 1.0° (c = 0.5, methanol).

The chiral silica can be prepared in the following way:

948 g of aminopropyl silica (100 Å, 10 µm, NH_2; Macherey-Nagel) are suspended in 3 dm^3 of N,N-dimethylformamide in a 6-dm^3 three-necked flask. 180 g of the anhydride of N-(*tert*-butoxycarbonyl)-11-aminoundecanoic acid are added and the reaction mixture is stirred for 18 hours at a temperature in the region of 20°C. The silica is separated by filtration and washed successively with 2 times 2500 cm^3 of dichloromethane and then 2 times 2500 cm^3 of N,N-dimethylformamide. The silica, thus washed, is resuspended in 3 litres of N,N-dimethylformamide and 180 g of the anhydride of N-(*tert*-butoxycarbonyl)-11-aminoundecanoic acid are added and then the reaction mixture is stirred for 18 hours at a temperature in the region of 20°C. The silica is separated by filtration, washed successively with 2 times 2500 cm^3 of dichloromethane, 2 times 2500 cm^3 of tetrahydrofuran, 2 times 2500 cm^3 of methanol and 2 times 2500 cm^3 of

diethyl ether and then dried under reduced pressure at a temperature in the region of 20°C. 971 g of silica, denoted by the term "BOC-C_{11}-C_3-silica", are thus obtained in the form of a white powder, the structure of which is confirmed by the infrared spectrum and the elemental analysis (found) of which is: C % = 9.85, H % = 2.05, N % = 1.05.

971 g of "BOC-C_{11}-C_3-silica" silica are suspended in 2500 cm^3 of dichloromethane and 470 g of imidazole in a 6-dm^3 three-necked flask. 850 cm^3 of dimethyloctylchlorosilane are added dropwise and the reaction mixture is stirred for 16 hours at a temperature in the region of 20°C. The solid obtained is separated by filtration and washed successively with 2 times 2500 cm^3 of dichloromethane, two times 2500 cm^3 of methanol, 2 times 2500 cm^3 of tetrahydrofuran, 2 times 2500 cm^3 of dichloromethane and 2 times 2500 cm^3 of diethyl ether and then dried under reduced pressure at a temperature in the region of 20°C. 1179 g of silica, denoted by the term "BOC-C_{11}-C_3-silica-O-$Si(CH_3)_2(CH_2)_7CH_3$", are thus obtained in the form of a white powder, the structure of which is confirmed by the infrared spectrum and the elemental analysis (found) of which is: C % = 13.9, H % = 2.83, N % = 1.16.

1178 g of "BOC-C_{11}-C_3-silica-O-$Si(CH_3)_2(CH_2)_7CH_3$" silica are suspended in 2500 cm^3 of a 5 % by volume solution of trifluoroacetic acid in

dichloromethane in a 6-dm^3 three-necked flask. The reaction mixture is stirred at 20°C. The silica is separated by filtration and washed successively with 2 times 2500 cm^3 of dichloromethane, 2 times 2500 cm^3 of a dichloromethane/diisopropylethylamine (70/30 by volume) mixture, 2500 cm^3 of dichloromethane, 2 times 2500 cm^3 of tetrahydrofuran, 2 times 2000 cm^3 of methanol and 2 times 2000 cm^3 of diethyl ether and then dried under reduced pressure at a temperature in the region of 50°C. 1080.5 g of silica, denoted by the term "C_{11}-C_3-silica-O-$Si(CH_3)_2(CH_2)_7CH_3$", are thus obtained in the form of a white powder, the structure of which is confirmed by the infrared spectrum and the elemental analysis (found) of which is: C % = 12.6, H % = 2.44, N % = 1.05.

1080 g of "C_{11}-C_3-(silica)-O-$Si(CH_3)_2(CH_2)_7CH_3$" silica are suspended in 2500 cm^3 of N,N-dimethylformamide, which has been dried over 4Å molecular sieve, in a 6-dm^3, three-necked, round-bottomed flask. 108 g of N-(3,5-dinitrobenzoyl)-L-phenylalanine and 75 g of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline are added. The reaction mixture is stirred overnight. The silica is separated by filtration on sintered glass and is then washed with 2 times 2500 cm^3 of dichloromethane, 2 times 2500 cm^3 of tetrahydrofuran, 2500 cm^3 of N,N-dimethylformamide and 2500 cm^3 of dichloromethane. The silica, thus washed, is resuspended in 2500 cm^3 of N,N-dimethylformamide. 108 g

of N-(3,5-dinitrobenzoyl)-L-phenylalanine and 75 g of N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline are successively added and the reaction mixture is then stirred overnight at 20°C. The silica is separated by filtration on sintered glass and is washed successively with 2 times 2500 cm^3 of dichloromethane, 2 times 2500 cm^3 of tetrahydrofuran, 2 times 2500 cm^3 of methanol and 2 times 2500 cm^3 of diethyl ether. After drying at 60°C under reduced pressure (2.7 kPa), 1093.6 g of silica, denoted by the term "DNB-L-Phe-C_{11}-C_3(silica)-O-Si$(CH_3)_2(CH_2)_7CH_3$", are obtained in the form of a pale yellow powder, the structure of which is confirmed by its infrared spectrum and the elemental analysis (found) of which is: C % = 14.5, H % = 2.4, N % = 1.68.

519 g of "DNB-L-Phe-C_{11}-C_3(silica)-O-Si$(CH_3)_2(CH_2)_7CH_3$" silica are suspended in 3000 cm^3 of N,N-dimethylformamide, dried over 4Å molecular sieve, in a 4-dm^3, three-necked, round-bottomed flask. 450 cm^3 of trimethylsilylimidazole are added over 15 minutes and the reaction mixture is then stirred overnight. The silica is separated by filtration and is washed successively with 2 times 1500 cm^3 of tetrahydrofuran, 2 times 1500 cm^3 of methanol, 2 times 1500 cm^3 of acetone and 2 times 1500 cm^3 of dichloromethane. After drying at a temperature of 60°C under reduced pressure (2.7 kPa), 519 g of silica, denoted by the term "DNB-L-Phe-C_{11}-C_3(silica)-[O-Si$(CH_3)_2(CH_2)_7CH_3$]-[O-Si$(CH_3)_3$]", are

obtained in the form of a pale yellow powder, the structure of which is confirmed by its infrared spectrum and the elemental analysis (found) of which is: C % = 15.3, H % = 1.8, N % = 2.6.

The anhydride of N-(*tert*-butoxycarbonyl)-11-aminoundecanoic acid can be prepared in the following way:

30.1 g of N-(*tert*-butoxycarbonyl)-11-aminoundecanoic acid are dissolved in 480 cm^3 of ethyl acetate. This solution is cooled to 5°C and then, while maintaining it at this temperature, a solution of 10.63 g of 1,3-dicyclohexylcarbodiimide in 120 cm^3 of ethyl acetate is added over 10 minutes. The reaction mixture is stirred for 1 hour at 5°C and then for 16 hours at a temperature in the region of 20°C. The precipitate formed is separated by filtration and washed with 30 cm^3 of ethyl acetate. The filtrate is concentrated to dryness under reduced pressure (2.7 kPa) at 30°C. The solid obtained is dried at 20°C under reduced pressure (2.7 kPa). 31 g of the anhydride of N-(*tert*-butoxycarbonyl)-11-aminoundecanoic acid are thus obtained, with a yield in the region of 100 %.

N-(*tert*-Butoxycarbonyl)-11-aminoundecanoic acid can be prepared according to J. Org. Chem., 41, 1350 (1976).

EXAMPLE 4

Isolation of the laevorotatory enantiomer of (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

500 mg of (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are resolved on a chiral silica column, carrying (3,5-dinitrobenzoyl)-S-phenylalanine grafts, elution being carried out with a dichloromethane/isopropanol/n-heptane (85/10/5 by volume) mixture. On collecting the first fraction eluted (retention time 47 minutes), 240 mg of the laevorotatory enantiomer are obtained after concentrating under reduced pressure, the characteristics of which enantiomer are as follows:

- melting point = 225°C
- mass spectrum (EI): M/Z = 493 (M^+) and 449 (M^+-CO_2)
- optical rotation: $[\alpha]_{365}^{20}$ = - 76.0 +/- 1.2° (c = 0.5, methanol).

EXAMPLE 5

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

362 mg (2.17 mmol) of 2-methoxyphenylacetic acid, 456 mg (2.38 mmol) of 1-ethyl-3-[(3-dimethyl-

amino)propyl]carbodiimide and 59 mg (0.43 mmol) of N-hydroxybenzotriazole hydrate are successively added to a solution of 755 mg (2.17 mmol) of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, obtained in Stage E of Example 1, in 20 cm^3 of dichloromethane. After stirring overnight at room temperature, 15 cm^3 of dichloromethane are added, washing is carried out with two times 15 cm^3 of water, drying is carried out over magnesium sulphate and the solvent is evaporated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (90/10 by volume) mixture, 820 mg (76%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after concentrating the solvent under reduced pressure, in the form of a white powder, the characteristics of which are as follows:

- melting point = 189°C
- mass spectrum (EI): M/Z = 495 (M^+)

Stage B

By carrying out the reaction as in Example 2, but from 819 mg (1.65 mmol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for 18 hours

in 17 cm^3 of a normal aqueous sodium hydroxide solution and 17 cm^3 of methanol, 720 mg (74%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 25 cm^3 of diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = 182°C
- ^1H N.M.R. spectrum (400 MHz, d6-DMSO, at a temperature of 423 K, δ in ppm): 1.40, 1.64, 1.95 and 2.10 (4 mts, each 1H, CH_2CH_2), 2.41 (s, 3H, $ArCH_3$), from 3.30 to 3.65 (mt, 6H, CH_2 at 1, $NCOCH_2Ar$, 1H of the CH_2 at 3 and H at 9a), 3.48 (mt, 1H, H at 4), 3.75 (s, 3H, OCH_3), 4.18 (d, J = 12.5 HJz, 1H, the other H of the CH_2 at 3), 6.46 (broad d, J = 7.5 Hz, 1H, H at 8), 6.90 (broad t, J = 7.5 Hz, 1H, aromatic H in the para position with respect to the OCH_3), 6.96 (broad d, J = 7.5 Hz, 1H, aromatic H in the ortho position with respect to the OCH_3), from 7.00 to 7.35 (mt, 5H, H at 5, H at 6, H at 7 and aromatic H at the meta position with respect to the OCH_3), 7.30 (limit AB, 4H, aromatic H at the ortho and meta positions of the aromatic at 9).

EXAMPLE 6

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

2.07 cm^3 (16.5 mmol) of 4-bromoanisole and 402 mg (16.5 mmol) of magnesium turnings in 20 cm^3 of diethyl ether are heated at reflux under an argon atmosphere for three hours. After cooling to 0°C, 1.36 g (5.5 mmol) of anhydrous cerium chloride are added and then a solution of 2 g (5.5 mmol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydro-isoindole-3a-carboxylate, obtained in Stage B of Example 1, in 5 cm^3 of dry diethyl ether is run in dropwise at a temperature in the region of 5°C and under an argon atmosphere. The reaction mixture is stirred for one hour at a temperature in the region of 0°C and then overnight at room temperature. After cooling to 0°C, the reaction mixture is hydrolysed by 15 cm^3 of a saturated aqueous ammonium chloride solution. The aqueous phase is separated by settling and extracted with two times 50 cm^3 of ethyl acetate. The organic phases are combined, washed successively with 25 cm^3 of distilled water and 25 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica

gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (60/40 by volume) mixture, 1.345 g (51%) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(4-methoxyphenyl)-4-phenyloctahydroisoindole-3a-carboxylate are obtained in the form of a white solid, the characteristic of which is as follows:

- melting point = 136°C

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 1.343 g (2.85 mmol) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(4-methoxyphenyl)-4-phenyloctahydroisoindole-3a-carboxylate and from 4.56 cm^3 of trifluoromethanesulphonic acid in 65 cm^3 of dichloromethane for 30 minutes at a temperature in the region of 0°C and then overnight at room temperature, 863 mg (67%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 127°C

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 839 mg (1.85 mmol) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methoxy-

phenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 0.35 g (5.5 mmol) of ammonium formate in the presence of 0.27 g of 10% (w/w) palladium-on-charcoal in 20 cm^3 of methanol, heating being carried out at reflux for 3 hours, 559 mg (83%) of methyl (3aRs,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate are obtained, after stirring the foam obtained in 30 cm^3 of pentane, in the form of a white solid, the characteristic of which is as follows:

- melting point = 112°C

Stage D

By carrying out the reaction as in Stage A of Example 5, but from 548 mg (1.51 mmol) of methyl (3aRs,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 251 mg (1.51 mmol) of 2-methoxyphenylacetic acid, from 318 mg (1.66 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide and from 41 mg (0.3 mmol) of N-hydroxybenzotriazole hydrate in 15 cm^3 of dichloromethane, 575 mg (75%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a white powder, the characteristics of

which are as follows:

- melting point = 169°
- mass spectrum (EI): M/Z = 511 (M^+)

Stage E

By carrying out the reaction as in Example 2, but from 566 mg (1.1 mmol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for eighteen hours in 11.5 cm^3 of a normal aqueous sodium hydroxide solution and 7.5 cm^3 of methanol, 385 mg (70%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 10 cm^3 of diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = 163°C
- ^1H N.M.R. spectrum (400 MHz, d6-DMSO, at a temperature of 393 K, δ in ppm): 1.36, 1.61, 1.90 and 2.07 (4 mts, each 1H, CH_2CH_2), from 3.30 to 3.65 (mt, 6H, CH_2 at 1, $NCOCH_2Ar$, 1H of the CH_2 at 3 and H at 9a), 3.46 (mt, 1H, H at 4), 3.73 (broad s, 3H, OCH_3), 3.80 (s, 3H, OCH_3 of the aromatic at 9), 4.15 (d, J = 12.5 Hz, 1H, the other H of the CH_2 at 3), 6.45 (broad d, J = 7.5 Hz, 1H, H at 8), 6.90 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to OCH_3), 6.96 (broad d, J = 7.5 Hz, 1H,

aromatic H at the ortho position with respect to the OCH_3), 7.06 (d, J = 8 Hz, 2H, aromatic H at the ortho positions with respect to the OCH_3 for the aromatic at 9), from 7.00 to 7.30 (mt, 5H, H at 5, H at 6, H at 7 and aromatic H at the meta positions with respect to the OCH_3), 7.30 (d, J = 8 Hz, 2H, aromatic H at the meta positions with respect to the OCH_3 for the aromatic at 9).

EXAMPLE 7

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage A of Example 6, but from 1.34 g (6.6 mmol) of 4-bromothioanisole and 161 mg (6.6 mmol) of magnesium turnings at reflux for three hours in 4 cm^3 of diethyl ether and then, successively, from 543 mg (2.2 mmol) of anhydrous cerium chloride and from a solution of 800 mg (2.2 mmol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, obtained in Stage B of Example 1, in 2 cm^3 of diethyl ether, 679 g (63%) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(4-methylsulphanylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then

with a cyclohexane/ethyl acetate (80/20 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 124-6°C

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 676 mg (1.39 mmol) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(4-methylsulphanylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate and from 2.22 cm^3 of trifluoromethanesulphonic acid in 34 cm^3 of dichloromethane for thirty minutes at a temperature in the region of 0°C and then seventy hours at room temperature, 366 mg (56%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 105-7°C

Stage C

A solution of 246 mg (0.52 mmol) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in 10 cm^3 of dichloromethane is cooled to 0°C under an argon

atmosphere. 115 mg (0.79 mmol) of 2-chloroethyl chloroformate are then added and then the reaction mixture is stirred overnight at room temperature. After concentrating the solvent under reduced pressure, the residue is heated at reflux for four hours in 10 cm^3 of methanol containing 1.5 cm^3 of a 1M solution of hydrochloric acid in methanol. The crystals formed are filtered off, washed with two times 1 cm^3 of ice-cold methanol and then neutralized by stirring in 10 cm^3 of a decinormal solution of sodium hydroxide. After extracting with dichloromethane and concentrating to dryness, 145 mg (62%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a white foam, the characteristic of which is as follows:

- melting point = 90-4°C

Stage D

By carrying out the reaction as in Stage A of Example 5, but from 145 mg (0.38 mmol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methylsulphanyl-phenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 64 mg (0.38 mmol) of 2-methoxy-phenylacetic acid, from 91 mg (0.42 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 10 mg (0.076 mmol) of N-hydroxybenzotriazole hydrate in 5 cm^3 of dichloromethane, 182 mg (90%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxy-

phenyl)acetyl]-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane/ethyl acetate (80/20, then 70/30, by volume) mixtures, in the form of a white powder, the characteristics of which are as follows:

- melting point = 137°C
- mass spectrum (EI): M/Z = 527 (M^+)

Stage E

By carrying out the reaction as in Example 2, but from 180 mg (0.34 mmol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for eighteen hours in 3.7 cm^3 of a normal aqueous sodium hydroxide solution and 3.7 cm^3 of methanol, 144 mg (81%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 5 cm^3 of diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = 145°C
- ^1H N.M.R. spectrum (250 MHz, d6-DMSO, at a temperature of 393 K, δ in ppm): 1.40, 1.63, 1.92 and 2.10 (4 mts, each 1H, CH_2CH_2), 2.59 (s, 3H, SCH_3), from

3.30 to 3.70 (mt, 6H, CH_2 at 1, $NCOCH_2Ar$, 1H of the CH_2 at 3 and H at 9a), 3.50 (mt, 1H, H at 4), 3.73 (broad s, 3H, OCH_3), 4.18 (d, J = 12.5 Hz, 1H, the other H of the CH_2 at 3), 6.48 (broad d, J = 7.5 Hz, 1H, H at 8), 6.92 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to OCH_3), 7.00 (broad d, J = 7.5 Hz, 1H, aromatic H at the ortho position with respect to the OCH_3), from 7.05 to 7.35 (mt, 5H, H at 5, H at 6, H at 7 and aromatic H at the meta positions with respect to the OCH_3), 7.35 and 7.45 (2 broad d, J = 8 Hz, each 2H, aromatic H at the ortho and meta positions of the aromatic at 9).

EXAMPLE 8

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage A of Example 6, from 6.1 cm^3 of a 1M solution of 4-fluorophenylmagnesium bromide in diethyl ether and then, successively, from 1.36 g (5.5 mmol) of anhydrous cerium chloride and from a solution of 2 g (5.5 mmol) of methyl (3aRs,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, obtained in Stage B of Example 1, in 20 cm^3 of diethyl ether, 507 g (20%) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(4-fluorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate are

obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (60/40 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 163°C

Stage B

By carrying out the reaction as in Stage D of Example 1, from 433 mg (0.94 mmol) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(4-fluorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate and from 1.51 cm^3 of trifluoromethanesulphonic acid in 20 cm^3 of dichloromethane for thirty minutes at a temperature in the region of 0°C and then 70 hours at room temperature, 360 mg (86%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 157°C

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 358 mg (0.81 mmol) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-fluoro-

phenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 153 mg (2.43 mmol) of ammonium formate in the presence of 120 mg of 10% (w/w) palladium-on-charcoal in 20 cm^3 of methanol, heating being carried out at reflux for 3 hours, 236 mg (83%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after stirring the foam obtained in 15 cm^3 of pentane, in the form of a white solid, the characteristic of which is as follows:

- melting point = 163°C

Stage D

By carrying out the reaction as in Stage A of Example 5, from 235 mg (0.67 mmol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 112 mg (0.67 mmol) of 2-methoxyphenylacetic acid, from 142 mg (0.74 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 19 mg (0.076 mmol) of N-hydroxybenzotriazole hydrate in 10 cm^3 of dichloromethane, 230 mg (68%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane/ethyl acetate (90/10, then 80/20, by volume) mixtures, in the form of a white powder, the

characteristics of which are as follows:

- melting point = 216°C
- mass spectrum (EI): M/Z = 499 (M^+)

Stage E

By carrying out the reaction as in Example 2, but from 228 mg (0.45 mmol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for eighteen hours in 4.7 cm^3 of a normal aqueous sodium hydroxide solution and 5 cm^3 of methanol, 171 mg (77%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 5 cm^3 of diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = 250°C
- ^1H N.M.R. spectrum (400 MHz, d6-DMSO, at a temperature of 423 K, d in ppm): 1.40, 1.64, 1.95 and 2.10 (4 mts, each 1H, CH_2CH_2), 2.41 (s, 3H, $ArCH_3$), from 3.30 to 3.65 (mt, 6H, CH_2 at 1, $NCOCH_2Ar$, 1H of the CH_2 at 3 and H at 9a), 3.48 (mt, 1H, H at 4), 3.75 (s, 3H, OCH_3), 4.18 (d, J = 12.5 Hz, 1H, the other H of the CH_2 at 3), 6.46 (broad d, J = 7.5 Hz, 1H, H at 8), 6.90 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to the OCH_3), 6.96 (broad d, J = 7.5 Hz, 1H, aromatic H at the ortho position with

respect to the OCH_3), from 7.00 to 7.35 (mt, 5H, H at 5, H at 6, H at 7 and aromatic H at the meta positions with respect to the OCH_3), 7.30 (limit AB, 4H, aromatic H at the ortho and meta positions of the aromatic at 9).

EXAMPLE 9

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage A of Example 6, but from 2.42 cm^3 of a 1M solution of meta-tolylmagnesium bromide in tetrahydrofuran and then, successively, from 543 mg (2.2 mmol) of anhydrous cerium chloride and from a solution of 800 mg (2.2 mmol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, obtained in Stage B of Example 1, in 10 cm^3 of diethyl ether, 505 mg (50%) of methyl (3aRS,4SR,7Rs,7aRS)-2-benzyl-7-hydroxy-7-(3-methylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (80/20 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 117-9°C

Stage B

By carrying out the reaction as in Stage D according to Example 1, but from 669 mg (1.47 mmol) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(3-methylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate and from 2.35 cm^3 of trifluoromethanesulphonic acid in 33 cm^3 of dichloromethane for thirty minutes at a temperature in the region of 0°C and then forty-eight hours at room temperature, 582 mg (90%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 113-5°C

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 578 mg (1.27 mmol) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 241 mg (3.82 mmol) of ammonium formate in the presence of 185 mg of 10% (w/w) palladium-on-charcoal in 20 cm^3 of methanol, heating being carried out at reflux for 3 hours, 412 mg (93%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-

isoindole-3a-carboxylate are obtained, after stirring the foam obtained in 10 cm^3 of pentane, in the form of a white solid, the characteristic of which is as follows:

- melting point = 103°C

Stage D

By carrying out the reaction as in Stage A of Example 6, but from 409 mg (1.18 mmol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 196 mg (1.18 mmol) of 2-methoxyphenylacetic acid, from 248 mg (1.29 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 32 mg (0.076 mmol) of N-hydroxybenzotriazole hydrate in 12 cm^3 of dichloromethane, 509 mg (86%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a white powder, the characteristics of which are as follows:

- melting point = 132°C
- mass spectrum (EI): M/Z = 495 (M^+)

Stage E

By carrying out the reaction as in Example 2, but from 506 mg (1.02 mmol) of methyl

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for eighteen hours in 10.3 cm^3 of a normal aqueous sodium hydroxide solution and 7 cm^3 of methanol, 424 mg (87%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 5 cm^3 of diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = 138°C
- ^1H N.M.R. spectrum (250 MHz, d6-DMSO, at a temperature of 393 K, d in ppm): 1.40, 1.66, 1.95 and 2.10 (4 mts, each 1H, CH_2CH_2), 2.43 (s, 3H, $ArCH_3$), from 3.30 to 3.65 (mt, 6H, CH_2 at 1, $NCOCH_2Ar$, 1H of the CH_2 at 3 and H at 9a), 3.48 (mt, 1H, H at 4), 3.73 (broad s, 3H, OCH_3), 4.18 (d, J = 12.5 Hz, 1H, the other H of the CH_2 at 3), 6.45 (broad d, J = 7.5 Hz, 1H, H at 8), 6.92 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to the OCH_3), 6.98 (broad d, J = 7.5 Hz, 1H, aromatic H at the ortho position with respect to the OCH_3), from 7.00 to 7.35 (mt, 8H, H at 5, H at 6, H at 7, aromatic H at the meta position with respect to the OCH_3 and aromatic H at the ortho and para positions with respect to the CH_3 for the aromatic at 9), 7.40 (t, J = 8 Hz, 1H, aromatic H at the meta position with respect to the CH_3 for the aromatic at 9).

EXAMPLE 10

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage A of Example 6, but from 1.56 cm^3 (12.4 mmol) of 3-bromoanisole and from 302 mg (12.4 mmol) of magnesium turnings at reflux for one hour in 5 cm^3 of dry diethyl ether, followed successively by 1.02 g (4.13 mmol) of anhydrous cerium chloride and by a solution of 1.5 g (4.13 mmol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, obtained in Stage B of Example 1, in 8 cm^3 of diethyl ether, 945 mg (48%) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(3-methoxyphenyl)-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (80/20 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 118°C

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 941 mg (1.99 mmol) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(3-methoxy-

phenyl)-4-phenyloctahydroisoindole-3a-carboxylate and from 3.19 cm^3 of trifluoromethanesulphonic acid in 45 cm^3 of dichloromethane for 30 minutes at a temperature in the region of 0°C and then forty-eight hours at room temperature, 755 mg (83%) of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-4,9-ethano-9-(3-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 117°C

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 747 mg (1.65 mmol) of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-4,9-ethano-9-(3-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 311 mg (4.94 mmol) of ammonium formate in the presence of 240 mg of 10% (w/w) palladium-on-charcoal in 18 cm^3 of methanol, heating being carried out at reflux for three hours, 501 mg (83%) of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate are obtained, after stirring the foam obtained in 10 cm^3 of pentane, in the form of a white solid, the characteristic of which is as follows:

- melting point = 96-8°C

Stage D

By carrying out the reaction as in Stage A of Example 5, but from 500 mg (1.38 mmol) of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 229 mg (1.38 mmol) of 2-methoxyphenylacetic acid, from 291 mg (1.52 mmol) of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 37 mg (0.27 mmol) of N-hydroxybenzotriazole hydrate in 14 cm^3 of dichloromethane, 451 mg (64%) of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with cyclohexane and then with a cyclohexane/ethyl acetate (80/20 by volume) mixture, in the form of a white powder, the characteristics of which are as follows:

- melting point = 128°C
- mass spectrum (EI): M/Z = 511 (M^+)

Stage E

By carrying out the reaction as in Example 2, from 450 mg (0.88 mmol) of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2-[(2-methoxyphenyl)-acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for 18 hours in 4.7 cm^3 of a

normal aqueous sodium hydroxide solution and 5 cm^3 of methanol, 391 mg (89%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 10 cm^3 of diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = 135°C
- ^1H N.M.R. spectrum (250 MHz, d6-DMSO, at a temperature of 393 K, d in ppm): 1.40, 1.63, 1.94 and 2.10 (4 mts, each 1H, CH_2CH_2), from 3.35 to 3.70 (mt, 6H, CH_2 at 1, $NCOCH_2Ar$, 1H of the CH_2 at 3 and H at 9a), 3.50 (mt, 1H, H at 4), 3.73 (broad s, 3H, OCH_3), 3.87 (s, 3H, OCH_3 of the aromatic at 9), 4.18 (d, J = 12.5 Hz, 1H, the other H of the CH_2 at 3), 6.48 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.85 to 7.35 (mt, 10H, H at 5, H at 6, H at 7, aromatic H at the ortho, meta and para position with respect to the OCH_3 and aromatic H at the ortho and para positions with respect to the OCH_3 for the aromatic at 9), 7.43 (t, J = 8 Hz, 1H, aromatic H at the meta position with respect to the OCH_3 for the aromatic at 9).

EXAMPLE 11

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate acid

Stage A

2.3 cm^3 of 4-bromo-ortho-xylene and 0.42 g of magnesium turnings in a mixture of 20 cm^3 of diethyl ether and 20 cm^3 of tetrahydrofuran are heated at reflux for one hour. After cooling to a temperature in the region of -7°C, a solution of 3.11 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydro-isoindole-3a-carboxylate in 20 cm^3 of diethyl ether is added over 25 minutes. The reaction mixture is stirred for four hours at a temperature in the region of 25°C and then hydrolysed by 50 cm^3 of a saturated aqueous ammonium chloride solution. The aqueous phase is separated by settling and extracted with 25 cm^3 of ethyl acetate. The organic phases are combined, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture, 1.995 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(3,4-dimethylphenyl)-4-phenyl-octahydroisoindole-3a-carboxylate are obtained, the characteristic of which compound, used as is in the following stage, is as follows:

- mass spectrum (EI): M/Z = 469 (M^+) and 410 (M^+-CO_2).

Stage B

By carrying out the reaction as in Stage D of Example 1, but starting from 1.99 g of the mixture obtained in the preceding stage, in solution in 100 cm^3 of dichloromethane, maintained at a temperature in the region of -5°C, and from 3.7 cm^3 of trifluoromethanesulphonic acid, stirring being carried out for 72 hours at a temperature in the region of 25°C, 1.63 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-9-(3,4-dimethylphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a brown oil, the characteristic of which compound, used as is in the following stage, is as follows:

- mass spectrum (EI): M/Z = 451 (M^+).

Stage C

The reaction is carried out as in Stage E of Example 1, but starting from 1.63 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-9-(3,4-dimethylphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate in 40 cm^3 of methanol and from 0.68 g of ammonium formate in the presence of 0.41 g of 10% (w/w) palladium-on-charcoal, heating being carried out at reflux for two hours, 0.79 g of methyl (3aRS,4SR,9RS,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-

carboxylate is obtained in the form of a white solid, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 361 (M^+).

Stage D

By carrying out the reaction as in Stage A of Example 5, but from 0.79 g of methyl (3aRS,4SR,9RS,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.44 g of 2-methoxyphenylacetic acid, from 0.5 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 0.35 g of N-hydroxybenzotriazole hydrate in 35 cm^3 of dichloromethane, 0.7 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on 37 g of silica gel (230-400 mesh), elution being carried out with pure dichloromethane and then with a dichloromethane/ethanol (99/1 by volume) mixture, in the form of a foam which is recrystallized in the following way: this foam is dissolved in 5 cm^3 of absolute ethanol, water is added until the solution becomes cloudy and then the mixture is cooled for one hour at a temperature in the region of 0°C. 0.61 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is thus obtained in the form of a yellow powder, the

characteristics of which are as follows:

- melting point = 88°C
- mass spectrum (EI): M/Z = 509 (M^+)

EXAMPLE 12

Preparation of (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, from 637 mg of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for 18 hours in 1.9 cm^3 of a normal aqueous sodium hydroxide solution and 60 cm^3 of ethanol, 176 mg of (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 5 cm^3 of diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = 257°C
- mass spectrum (EI): M/Z = 495 (M^+) and 451 (M^+-CO_2)

EXAMPLE 13

Preparation of (3aRS,4SR,9SR,9aRS)-3a-N-benzylcarbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

A solution of 0.19 cm^3 of oxalyl chloride in

5 cm^3 of dichloromethane is added dropwise to a solution of 1 g of (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 10 cm^3 of dichloromethane containing 1 drop of N,N-dimethylformamide. The reaction mixture is stirred for a further 2 hours at a temperature in the region of 20°C, then cooled to a temperature in the region of 0°C and run dropwise into a solution of 0.22 cm^3 of benzylamine in 10 cm^3 of dichloromethane and 0.57 cm^3 of triethylamine, the temperature being maintained in the region of 0°C. The reaction mixture is stirred for a further 15 minutes at a temperature in the region of 0°C and then for two hours at a temperature in the region of 20°C, and poured into 50 cm^3 of distilled water. The organic phase is separated by settling, washed with 50 cm^3 of distilled water and then 50 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture, 0.8 g of (3aRS,4SR,9SR,9aRS)-3a-N-benzylcarbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole is obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 227°C

- ^{1}H N.M.R. spectrum (300 MHz, d6-DMSO, at a temperature of 413 K, d in ppm): 1.40, 1.64, 2.02 and 2.15 (4 mts, each 1H, CH_2CH_2), 2.39 (s, 3H, $ArCH_3$), 3.31 and 3.40 (respectively mt and d (broad), J = 13 Hz, each 1H, CH_2 at 1), 3.50 and 4.20 (respectively d and d (broad), J = 13 Hz, each 1H, CH_2 at 3), 3.59 (mt, 1H, H at 9a), 3.61 (broad s, 1H, H at 4), 3.71 (s, 3H, $ArOCH_3$), 4.22 (limit AB, 2H, CH_2NAr), 5.52 and 5.67 (2s, each 1H, $=CH_2$), 6.44 (broad d, J = 7.5 Hz, 1H, H at 8), 6.95 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to the OCH_3), 7.01 (broad d, J = 7.5 Hz, 1H, aromatic H at the ortho position with respect to the OCH_3), from 6.95 to 7.35 (mt, 14H, H at 5, H at 6, H at 7, aromatic H at the meta positions with respect to the OCH_3, H at the ortho and meta positions of the aromatic at 9 and aromatic H of the benzyl), 7.75 (unresolved peak, 1H, CONH).

EXAMPLE 14

Preparation of benzyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate

By carrying out the reaction as in Example 13, but from 2.49 g of (3aRS,4SR,9RS,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 20 cm^3 of dichloromethane containing

2 drops of N,N-dimethylformamide, from a solution of 0.48 cm^3 of oxalyl chloride in 5 cm^3 of dichloromethane and from a solution of 0.8 g of O-benzylhydroxylamine hydrochloride in a mixture of 2.1 cm^3 of triethylamine and of 20 cm^3 of dichloromethane, 2.4 g of benzyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate are obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 227°C
- ^1H N.M.R. spectrum (300 MHz, d6-DMSO, at a temperature of 413 K, d in ppm): 1.38, 1.61, 1.98 and 2.10 (4 mts, each 1H, CH_2CH_2), 2.39 (s, 3H, $ArCH_3$), 3.26 and 3.38 (respectively dd and d (very broad), J = 13 and 9 Hz and J = 13 Hz, each 1H, CH_2 at 1), 3.46 and 4.14 (respectively d and d (broad), J = 13 Hz, each 1H, CH_2 at 3), 3.50 (mt, 1H, H at 4), 3.52 (dt, J = 9 and 3 Hz, 1H, H at 9a), 3.72 (s, 3H, $ArOCH_3$), 4.63 and 4.70 (2 d, J = 11 Hz, each 1H, OCH_2Ar), 5.52 and 5.68 (respectively s and s (broad), each 1H, $=CH_2$), 6.44 (broad d, J = 7.5 Hz, 1H, H at 8), 6.95 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to the OCH_3), from 7.00 to 7.40 (mt, 15H, H at 5, H at 6, H at 7, aromatic H at the meta and ortho positions with respect to the OCH_3, H at the ortho and meta positions of the aromatic at 9 and aromatic H of the benzyl), 10.83 (unresolved peak, 1H, CONH).

EXAMPLE 15

Preparation of (3aRS,4SR,9SR,9aRS)-3a-carbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

A solution of 0.24 cm^3 of oxalyl chloride in 5 cm^3 of dichloromethane is added dropwise to a solution of 1.24 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 10 cm^3 of dichloromethane containing 1 drop of N,N-dimethylformamide. The reaction mixture is stirred for a further two hours at a temperature in the region of 20°C and then concentrated under reduced pressure. The residue is dissolved in 10 cm^3 of dioxane and run dropwise into 10 cm^3 of a 2.5N aqueous ammonia solution, the temperature being maintained in the region of 0°C. The reaction mixture is stirred for a further one hour at a temperature in the region of 0°C and then filtered. The precipitate is washed successively with three times 50 cm^3 of distilled water and 50 cm^3 of diisopropyl ether and then dried under reduced pressure at a temperature in the region of 40°C. 0.85 g of (3aRS,4SR,9SR,9aRS)-3a-carbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole is thus obtained, after recrystallization from methanol, in the form of a white solid, the characteristics of which are as follows:

- melting point: >260°C

- ^{1}H N.M.R. spectrum (300 MHz, d6-DMSO, at a temperature of 413 K, d in ppm): 1.38, 1.60, 1.98 and 2.12 (4 mts, each 1H, CH_2CH_2), 2.39 (s, 3H, $ArCH_3$), 3.26 and 3.36 (respectively dd and d (very broad), J = 13 and 9 Hz and J = 13 Hz, each 1H, CH_2 at 1), 3.48 and 4.16 (respective d and d (broad), J = 13 Hz, each 1H, CH_2 at 3), 3.50 (dt, J = 9 and 3 Hz, 1H, H at 9a), 3.56 (mt, 1H, H at 4), 3.72 (s, 3H, $ArOCH_3$), 5;52 and 5;68 (respectively s and s (broad), each 1H, $=CH_2$), 6.42 (broad d, J = 7.5 Hz, 1H, H at 8), 6.70 (unresolved peak, 2H, $CONH_2$), 6.95 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to the OCH_3), 7.03 (broad d, J = 7.5 Hz, 1H, aromatic H at the ortho position with respect to OCH_3); from 7.00 to 7.40 (mt, 9H, H at 5, H at 6, H at 7, aromatic H at the meta positions with respect to the OCH_3 and H at the ortho and meta positions of the aromatic at 9).

EXAMPLE 16

<u>Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid</u>

0.61 cm^3 of anisole and then 0.72 g of aluminium chloride are added to a solution of 1.3 g of benzyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate in a

mixture of 10 cm^3 of nitromethane and 10 cm^3 of dichloromethane cooled to a temperature in the region of -15°C. The reaction mixture is stirred for one hour at a temperature in the region of 20°C and then concentrated under reduced pressure. The residue is taken up in 50 cm^3 of a normal aqueous hydrochloric acid solution and extracted with two times 50 cm^3 of dichloromethane. The extracts are combined, washed successively with 50 cm^3 of distilled water and 50 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (90/10 by volume) mixture. 0.75 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid is thus obtained, after recrystallization from acetonitrile, in the form of a cream solid, the characteristics of which are as follows:

- melting point = 252°C
- ^1H N.M.R. spectrum (300 MHz, d6-$(CD_3)_2SO$, at a temperature of 413 K, d in ppm): 1.36, 1.60, 1.98 and 2.08 (4 mts, each 1H, CH_2CH_2), 2.39 (s, 3H, $ArCH_3$), 3.26 and from 3.30 to 3.45 (respectively dd and mt, J = 13 and 9 Hz, each 1H, CH_2 at 1), 3.43 and 4.12 (respectively d and d (broad), J = 13 Hz, each 1H, CH_2

at 3), 3.50 (dt, J = 9 and 3 Hz, 1H, H at 9a), 3.56 (mt, 1H, H at 4), 3.72 (s, 3H, $ArOCH_3$), 5;52 and 5;68 (respectively s and s (broad), each 1H, $=CH_2$), 6.42 (broad d, J = 7.5 Hz, 1H, H at 8), 6.95 (broad t, J = 7.5 Hz, 1H, aromatic H at the para position with respect to the OCH_3), 7.03 (broad d, J = 7.5 Hz, 1H, aromatic H at the ortho position with respect to the OCH_3), from 7.00 to 7.40 (mt, 9H, H at 5, H at 6, H at 7, aromatic H at the meta positions with respect to the OCH_3 and H at the ortho and meta positions of the aromatic at 9). At room temperature, the signals are observed corresponding to the exchangeables: 8.70 (unresolved peak, 1H, CONH), 10.65 (unresolved peak, 1H, OH).

EXAMPLE 17

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

A solution of 0.24 cm^3 of oxalyl chloride in 5 cm^3 of dichloromethane is added dropwise to a solution of 1.24 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 10 cm^3 of dichloromethane and one drop of N,N-dimethylformamide. The reaction mixture is stirred for two hours at a temperature in the region of 20°C, then cooled to a temperature in the region of 0°C

and run onto a solution of 0.26 cm^3 of 3-(aminomethyl)-pyridine and of 0.7 cm^3 of triethylamine in 10 cm^3 of dichloromethane cooled to a temperature in the region of 0°C. The reaction mixture is stirred at a temperature in the region of 0°C for fifteen minutes and then in the region of 20°C for two hours, and then run into 100 cm^3 of distilled water. The aqueous phase is separated by settling and extracted with two times 50 cm^3 of dichloromethane. The organic phases are combined, washed with 50 cm^3 of distilled water and then 50 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (95/5 by volume) mixture, and crystallization by reflux in isopropanol, 1.0 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide is obtained, the characteristics of which compound are as follows:

- melting point: 234°C.
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 393 K, d in ppm): 1.40, 1.62 and from 1.90 to 2.20 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.39 (s, 3H, $ArCH_3$), from 3.20 to 3.40 (limit AB, 2H, CH_2 at 1), 3.44 (d, J = 12.5 Hz, 1H, 1H of the CH_2 at 3), from 3.55 to 3.65 (mt, 2H, CH at 4 and CH at

9a), 3.68 (s, 3H, $ArOCH_3$), from 4.10 to 4.35 (mt, 3H, the other H of the CH_2 at 3 and NCH_2Ar), 5;51 and 5;68 (2 s, each 1H, $=CH_2$), 6.42 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.50 (mt, 13H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl, aromatic H of the 4-methylphenyl, H at 4 of the pyridyl and H at 5 of the pyridyl), 8.05 (unresolved peak, 1H, CONH), 8.39 (broad s, 1H, H at 2 of the pyridyl), 8.44 (broad d, J = 5 Hz, 1H, H at 6 of the pyridyl).

EXAMPLE 18

Isolation of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

12 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide, obtained in Example 17, are resolved, in 12 injections of 1 g, on a Whelk 01 (SS) chiral silica column, elution being carried out with an n-heptane/dichloromethane/propanol (50/50/2 by volume) mixture. On collecting the first fraction eluted (retention time 42 min), 4.78 g of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide are obtained, after concentrating the solvent under reduced

pressure, the characteristics of this product being as follows:

- melting point = 210°C
- mass spectrum (EI): M/Z = 583 (M^+)
- optical rotation: $[a]_{365}^{20}$ = + 104.6 +/- 1.6° (c = 0.5, methanol)

EXAMPLE 19

Isolation of the levorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

12 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide, obtained in Example 17, are resolved, in 12 injections of 1 g, on a Whelk 01 (SS) chiral silica column, elution being carried out with an n-heptane/dichloromethane/propanol (50/50/2 by volume) mixture. On collecting the second fraction eluted (retention time 65 min), 4.86 g of the levorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide are obtained, after concentrating the solvent under reduced pressure, the characteristics of this product being as follows:

- melting point = 210°C

- mass spectrum (EI): M/Z = 583 (M^+)
- optical rotation: $[a]_{365}^{20}$ = - 102.2 +/- 1.5°

(c = 0.5, methanol)

EXAMPLE 20

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(4-pyridylmethyl)carboxamide

By carrying out the reaction as in Example 17, but from 1.24 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, from one drop of N,N-dimethylformamide, from 0.24 cm^3 of oxalyl chloride, [lacuna] 0.26 cm^3 of 4-(aminomethyl)pyridine and from 0.7 cm^3 of triethylamine, 0.7 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(4-pyridylmethyl)carboxamide is obtained, after crystallization from a mixture of equal volumes of isopropanol and of diisopropyl ether, the characteristic of which product is as follows:

- melting point = 202°C.

EXAMPLE 21

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate

A solution of 0.24 cm^3 of oxalyl chloride in 5 cm^3 of dichloromethane is added dropwise to a solution of 1.24 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 10 cm^3 of dichloromethane and one drop of N,N-dimethylformamide. The reaction mixture is stirred for two hours at a temperature in the region of 20°C and then run onto a solution of 0.21 g of O-methylhydroxylamine hydrochloride in a mixture of 1.05 cm^3 of triethylamine and of 10 cm^3 of dichloromethane cooled to a temperature in the region of 0°C. The reaction mixture is stirred at a temperature in the region of 0°C for thirty minutes and then at a temperature in the region of 20°C for one hour, [lacuna] run into 50 cm^3 of distilled water. The organic phase is separated by settling, washed with two times 50 cm^3 of distilled water, two times 20 cm^3 of a normal aqueous sodium hydroxide solution, 50 cm^3 of distilled water and 50 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After recrystallization from 20 cm^3 of refluxing isopropanol,

0.95 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate is obtained, the characteristics of which product are as follows:

- melting point = 256°C
- ^{1}H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.38, 1.62 and 1.90 to 2.20 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.40 (s, 3H, $ArCH_3$), from 3.15 to 3.45 (respectively dd and mt, J = 12 and 9 Hz, 2H, CH_2 at 1), from 3.30 to 3.60 (mt, 3H, CH at 9a, CH at 4 and 1H of the CH_2 at 3), 3.48 (s, 3H, $NOCH_3$); 3.71 (s, 3H, $ArOCH_3$), 4.14 (broad d, J = 12.5 Hz, 1H, the other H of the CH_2 at 3), 5.52 and 5.69 (2 s, each 1H, $=CH_2$), 6.43 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.40 (mt, 11H, H at 5, H at 6, H at 7 and aromatic H of the 2-methoxyphenyl and aromatic H of the 4-methylphenyl).

EXAMPLE 22

<u>Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N',N'-dimethylcarbohydrazide</u>

A solution of 0.24 cm^3 of oxalyl chloride in 5 cm^3 of dichloromethane is added dropwise to a solution of 1.24 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-

3a-carboxylic acid in 10 cm^3 of dichloromethane and one drop of N,N-dimethylformamide. The reaction mixture is stirred for two hours at a temperature in the region of 20°C and then run onto a solution of 0.2 cm^3 of N,N-dimethylhydrazine and of 0.7 cm^3 of triethylamine in 10 cm^3 of dichloromethane cooled to a temperature in the region of 0°C. The reaction mixture is stirred at a temperature in the region of 0°C for thirty minutes and then at a temperature in the region of 20°C for one hour and then run into 50 cm^3 of distilled water. The organic phase is separated by settling, washed with 50 cm^3 of distilled water, two times 25 cm^3 of a normal aqueous sodium hydroxide solution, 50 cm^3 of distilled water and 50 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (97.5/2.5 by volume) mixture, and recrystallization from 50 cm^3 of an isopropanol/diisopropyl ether (1/9 by volume) mixture, 0.95 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N',N'-dimethylcarbohydrazide is obtained, the characteristics of which compound are as follows:

- melting point: 230°C
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a

temperature of 383 K, d in ppm): 1.38, 1.60 and from 1.90 to 2.20 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.40 (s, 3H, $ArCH_3$), 2.47 (s, 6H, $N(CH_3)_2$), 3.21 and 3.35 (respectively dd and mt, J = 12 and 9 Hz, each 1H, CH_2 at 1), 3.40 and 4.19 (respectively d and d (broad), J = 13 Hz, each 1H, CH_2 at 3), from 3.50 to 3.65 (mt, 2H, CH at 9a and CH at 4), 3.71 (s, 3H, $ArOCH_3$), 5.51 and 5.69 (2 s, each 1H, $=CH_2$), 6.42 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.40 (mt, 11H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl and aromatic H [lacuna] 4-methylphenyl), 8.41 (unresolved peak, 1H, CONH).

EXAMPLE 23

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide

By carrying out the reaction as in Example 22, but from 0.5 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, from one drop of N,N-dimethylformamide, from 0.095 cm^3 of oxalyl chloride, [lacuna] 0.098 cm^3 of N-phenylhydrazine and from 0.28 cm^3 of triethylamine, 0.22 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide is

obtained, after crystallization from 10 cm^3 of diisopropyl ether, the characteristics of which compound are as follows:

- melting point: 220°C.

EXAMPLE 24

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N',N'-pentamethylenecarbohydrazide

By carrying out the reaction as in Example 22, but from 0.5 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, from one drop of N,N-dimethylformamide, from 0.095 cm^3 of oxalyl chloride, [lacuna] 0.095 cm^3 of 1-aminopiperidine and from 0.28 cm^3 of triethylamine, 0.06 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N',N'-pentamethylenecarbo-hydrazide is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with ethyl acetate, and after crystallization from diisopropyl ether, the characteristics of which compound are as follows:

- melting point: 220°C.

EXAMPLE 25

[lacuna] (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(methoxyphenyl)propenoyl]-9-(4-methylphenyl)-3a-phenylsulphonylaminocarbonyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

A solution of 0.096 cm^3 of oxalyl chloride in 0.5 cm^3 of dichloromethane is added dropwise to a solution of 0.5 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 5 cm^3 of dichloromethane and one drop of N,N-dimethylformamide. The reaction mixture is stirred for two hours at a temperature in the region of 20°C and then run into a mixture of 0.12 g of a 60% suspension of sodium hydride in petroleum jelly and 0.31 g of benzenesulphonamide in 5 cm^3 of N,N-dimethylformamide. The reaction mixture is stirred at a temperature in the region of 20°C for three days. 10 cm^3 of distilled water are subsequently added and the mixture is extracted with two times 20 cm^3 of dichloromethane. The organic extracts are combined, washed with 20 cm^3 of distilled water and then 20 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (98/2 by volume) mixture, and crystallization from diisopropyl ether,

0.005 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(methoxyphenyl)propenoyl]-9-(4-methylphenyl)-3a-phenylsulphonylaminocarbonyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole is obtained, the characteristics of which compound are as follows:

- melting point: approximately 166°C.
- ^{1}H N.M.R. spectrum (400 MHz, d6-$(CD_3)_2SO$, at a temperature of 393 K, d in ppm): 1.35, 1.58, 1.97 and 2.09 (4 mts, each 1H, CH_2CH_2), 2.39 (s, 3H, $ArCH_3$), 3.20 and 3.31 (respectively dd and d (broad), J = 12.5 and 9 Hz and J = 12.5 Hz, each 1H, CH_2 at 1), from 3.40 to 3.50 (mt, 1H, CH at 9a), 3.45 and 4.14 (respectively dd and d (broad), J = 13 Hz, each 1H, CH_2 at 3), 3.59 (mt, 1H, CH at 4), 3.66 (s, 3H, $ArOCH_3$), 5.45 and 5.65 (2 s, each 1H, $=CH_2$), 6.35 (mt, 1H, H at 8), from 6.85 to 7.60 (mt, 14H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl, aromatic H of the 4-methylphenyl, aromatic H at the meta positions of the phenylsulphonyl and aromatic H at the para position of the phenylsulphonyl), 7.77 (d, J = 8 Hz, 2H, aromatic H at the ortho positions of the phenylsulphonyl), 8.00 (broad s, 1H, CONH).

EXAMPLE 26

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(N-oxo-3-pyridyl)methylcarboxamide

0.20 g of sodium carbonate and 6 cm^3 of

distilled water are added to a solution of 0.29 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide in 8 cm^3 of chloroform. The mixture is cooled to a temperature in the region of 0°C and 0.11 g of meta-chloroperbenzoic acid is added. The reaction mixture is stirred for one hour at 2°C and then for twenty-two hours at a temperature in the region of 20°C. 0.22 g of meta-chloroperbenzoic acid is again added and the mixture is stirred for four hours at a temperature in the region of 20°C and then diluted with 10 cm^3 of dichloromethane. The organic phase is separated by settling, washed with three times 5 cm^3 of a 10% aqueous sodium sulphite solution, three times 5 cm^3 of a saturated aqueous sodium hydrogencarbonate solution and 5 cm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. The residue is purified by recrystallization from 8 cm^3 of isopropyl acetate to give 0.25 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(N-oxo-3-pyridyl)methyl-carboxamide, the characteristics of which are as follows:

- melting point = 250°C.
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.40, 1.62 and from

1.90 to 2.25 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.40 (s, 3H, $ArCH_3$), from 3.20 to 3.50 (limit AB, 2H, CH_2 at 1), 3.44 (d, J = 12.5 Hz, 1H, 1H of the CH_2 at 3), from 3.50 to 3.65 (mt, 1H, CH at 9a), 3.57 (mt, 1H, CH at 4), 3.70 (s, 3H, $ArOCH_3$), from 4.00 to 4.30 (mt, 3H, the other H of the CH_2 at 3 and NCH_2Ar), 5.51 and 5.68 (2 s, each 1H, $=CH_2$), 6.41 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.40 (mt, 13H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl, H at 4 of the N-oxopyridyl, H at 5 of the N-oxopyridyl and aromatic H of the 4-methylphenyl), 8.00 (broad s, 1H, H at 2 of the N-oxopyridyl), 8.05 (broad d, J = 5 Hz, 1H, H at 6 of the N-oxopyridyl), 8.11 (broad t, J = 5 Hz, 1H, CONH).

EXAMPLE 27

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(4-methoxyphenyl)carbohydrazide

0.21 g of 4-methoxyphenylhydrazine hydrochloride, 0.23 g of 1-ethyl-3-[(dimethylamino)-propyl]carbodiimide hydrochloride, 0.08 g of N-1-hydroxybenzotriazole hydrate and 0.17 cm^3 of triethylamine are successively added to a solution of 0.49 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 10 cm^3 of dichloromethane. The

reaction mixture is stirred for twenty hours at a temperature in the region of 20°C and then diluted with 15 cm^3 of dichloromethane. The organic phase is washed with three times 10 cm^3 of distilled water, dried over magnesium sulphate in the presence of 3S charcoal and concentrated under reduced pressure. By crystallization from 10 cm^3 of isopropyl acetate, 0.36 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(4-methoxyphenyl)carbohydrazide is obtained, the characteristics of which are as follows:

- melting point = 180°C.
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.40, 1.62 and from 1.90 to 2.25 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.38 (s, 3H, $ArCH_3$), 3.25 (dd, J = 12 and 9 Hz, 1H, 1H of the CH_2 at 1), 3.39 (broad d, J = 12 Hz, 1H, the other H of the CH_2 at 1), 3.48 and 4.22 (respectively d and d (broad), J = 12.5 Hz, each 1H, CH_2 at 3), 3.56 (mt, 1H, CH at 9a), from 3.60 to 3.75 (mt, 1H, CH at 4), 3.68 (s, 6H, the 2 $ArOCH_3$), 5.52 and 5.69 (2 s, each 1H, $=CH_2$), 6.42 (broad d, J = 7.5 Hz, 1H, H at 8), 6.56 and 6.69 (2 d, J = 8 Hz, each 2H, aromatic H at the ortho and meta positions with respect to the OCH_3), 6.80 (broad s, 1H, ArNH), from 6.90 to 7.40 (mt, 11H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl and aromatic H of the 4-methylphenyl),

9.46 (broad s, 1H, -CONH).

EXAMPLE 28

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-methyl-N'-phenylcarbohydrazide

By carrying out the reaction as in Example 27, but from 0.49 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, 0.14 cm^3 of N-methyl-N-phenylhydrazine, 0.23 g of 1-ethyl-3-[(dimethylamino)propyl]carbodiimide hydrochloride, 80 mg of N-1-hydroxybenzotriazole hydrate and 0.17 cm^3 of triethylamine, 0.22 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-methyl-N'-phenylcarbohydrazide is obtained, after crystallization from 5 cm^3 of isopropanol, the characteristic of which compound is as follows:

- melting point = 240°C.

EXAMPLE 29

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(2-methylphenyl)carbohydrazide

By carrying out the reaction as in

Example 27, but from 0.4 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, 0.16 g of N-(2-methylphenyl)hydrazine, 0.19 g of 1-ethyl-3-[(dimethylamino)propyl]carbodiimide hydrochloride, 60 mg of N-1-hydroxybenzotriazole hydrate and 0.14 cm^3 of triethylamine, 0.28 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(2-methylphenyl)carbohydrazide is obtained, after crystallization from 7.5 cm^3 of isopropyl acetate, the characteristic of which compound is as follows:

- melting point = 235°C.

EXAMPLE 30

<u>Isolation of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid</u>

(3aRS,4SR,9SR,9aRS)-4,9-Ethano-2-[2-(2-methoxyphenyl)acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, obtained in Example 5, can be resolved, on a chiral silica column carrying N-(3,5-dinitrobenzoyl)-(S)-phenylalanine grafts, by carrying out the resolution as in Example 3. On collecting the second fraction eluted by a mixture of

dichloromethane, of isopropanol and of n-heptane (85/10/5 by volume), 70 mg of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after concentrating under reduced pressure, the characteristics of which compound are as follows:

- melting point = 205°C.
- mass spectrum (EI): M/Z = 481 (M^+)
- optical rotation: $[a]_{365}^{20}$ = + 59.5 +/- 0.9° (c = 0.5, methanol)

EXAMPLE 31

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

7.1 cm^3 of 1,4-benzodioxane are added, under an argon atmosphere, to a solution of 6.3 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydro-isoindole-3a-carboxylate in 60 cm^3 of dichloromethane stabilized over amylene; this solution is cooled by a bath of ice-cold water and 10.7 cm^3 of 99% trifluoromethanesulphonic acid are run in over 5 minutes. After stirring in the cold bath, the temperature is allowed to rise to a temperature in the region of 20°C and reaction is allowed to take place at

this temperature for twenty-one hours, under an argon atmosphere. 200 cm^3 of distilled water are then run in, followed by 300 cm^3 of ethyl acetate. The organic phase is separated by settling and washed successively three times with 180 cm^3 of a 1N aqueous sodium hydroxide solution and then 240 cm^3 of a saturated aqueous sodium chloride solution, and then dried over magnesium sulphate. After filtration, the organic phase is evaporated under reduced pressure to give 10.8 g of an oil. This oil is purified by flash chromatography on an 8-cm diameter column containing 430 g of silica gel (230-400 mesh), elution being carried out successively with 1 dm^3 of the cyclohexane/ethyl acetate (98/2 by volume) mixture, then 2 dm^3 of the cyclohexane/ethyl acetate (95/5 by volume) mixture and then the cyclohexane/ethyl acetate (90/10 by volume) mixture, 50-cm^3 fractions being collected. After concentrating the solvent under reduced pressure, 5.41 g of impure methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a white foam, which can be used as is in the following stage, the characteristics of which compound are as follows:

- mass spectrum (EI): M/Z = 481 (M^+)
- ^1H N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): 1.45, 1.65 and from 2.40 to 2.55 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.31 and 3.20 (2 d, J = 10 Hz,

each 1H, CH_2 at 3), from 2.35 to 2.45 (mt, 1H, 1H of the CH_2 at 1), 2.81 (d, J = 10 Hz, 1H, the other H of the CH_2 at 1), from 3.00 to 3.20 (mt, 1H, CH at 9a), from 3.30 to 3.45 and 3.71 (respectively mt and d (broad), J = 13 Hz, each 1H, NCH_2Ar), 3.39 (broad s, 1H, CH at 4), 3.55 (s, 3H, $COOCH_3$), 4.31 (s, 4H, OCH_2CH_2O), 6.63 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.85 to 7.40 (mt, 11H, H at 5, H at 6, H at 7, aromatic H of the benzyl and aromatic H of the 1,4-benzodioxanyl).

Stage B

By carrying out the reaction as in Example 1, Stage E, starting from 5.4 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-carboxylate, from 2.16 g of ammonium formate and from 1.35 g of 10% (w/w) palladium hydroxide-on-charcoal in 80 cm^3 of refluxing methanol for five hours, 4 g of impure methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate are obtained in the form of an off-white foam, which can be used as is in the following stage, the characteristic of which compound is as follows:

- mass spectrum (DCI):M/Z = 392 ($M+H^+$)

Stage C

By carrying out the reaction as in Example 1, Stage G, starting from a solution of 0.275 g of 2-(2-

methoxyphenyl)propenoic acid in 5 cm^3 of dichloromethane containing 4 drops of N,N-dimethylformamide, a solution of 0.2 cm^3 of oxalyl chloride in 7 cm^3 of dichloromethane is added dropwise. The reaction mixture is stirred for a further two hours at a temperature in the region of 20°C and then cooled to a temperature in the region of 0°C; the introduction is then carried out, over twenty minutes, of a solution of 0.73 g of impure methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in 15 cm^3 of dichloromethane, followed by 0.4 cm^3 of triethylamine. The reaction mixture is stirred at the same temperature for one hour and 100 cm^3 of distilled water are run in; dilution is carried out with dichloromethane, so as to bring the organic phase to approximately 200 cm^3. The pH is brought to 11 by running in 10 cm^3 of a 32% aqueous ammonia solution, the aqueous phase is separated by settling and then the organic phase is washed with successively 100 cm^3 of a 1N aqueous hydrochloric acid solution, then 100 cm^3 of distilled water and then 100 cm^3 of a saturated aqueous sodium chloride solution. After drying over magnesium sulphate, the organic phase is evaporated to give 0.75 g of an oil, which is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and ethyl acetate (60/40 by volume), 10-cm^3 fractions being

collected. The fractions containing the good product (140 to 650 cm^3) are combined and evaporated without going to dryness to give an oil, which is taken up in diisopropyl ether; 465 mg of methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are thus obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 184°C.
- mass spectrum (EI): M/Z = 551 (M^+)
- ^1H N.M.R. spectrum (400 MHz, d6-$(CD_3)_2SO$, at a temperature of 403 K, d in ppm): 1.40, 1.58, 1.96 and 2.12 (4 mts, each 1H, CH_2CH_2), from 3.25 to 3.45 (mt, 3H, CH_2 at 1 and CH at 9a), 3.42 (mt, 1H, CH at 4), 3.52 (s, 3H, $COOCH_3$), 3.60 and 4.06 (respectively d and d (broad), J = 13 Hz, each 1H, CH_2 at 3), 3.73 (s, 3H, $ArOCH_3$), 4.31 (s, 4H, OCH_2CH_2O), 5.54 and 5.68 (2 s, each 1H, $=CH_2$), 6.51 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.75 to 7.35 (mt, 10H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl and aromatic H of the 1,4-benzodioxanyl).

EXAMPLE 32

<u>Preparation of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid</u>

By carrying out the reaction as in Example 2,

but from 5.43 g of methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, obtained in the preceding example, and from 40 cm^3 of a normal aqueous sodium hydroxide solution in 150 cm^3 of refluxing dioxane for sixteen hours, then addition of 50 cm^3 of a normal aqueous sodium hydroxide solution, at reflux for four hours, and then 3.5 cm^3 of a 10N aqueous sodium hydroxide solution, at reflux for sixteen hours, 3.76 g of a beige-coloured solid are obtained after taking up in diisopropyl ether. By dissolving in 50 cm^3 of absolute ethanol and then diluting with 12.5 cm^3 of distilled water, 2.64 g of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 78°C.
- mass spectrum (EI): M/Z = 537 (M^+)
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.38, 1.57, 1.94 and 2.11 (4 mts, each 1H, CH_2CH_2), from 3.20 to 3.45 (mt, 3H, CH_2 at 1 and CH at 9a), 3.42 (mt, 1H, CH at 4), 3.59 and 4.06 (respectively d and d (broad), J = 13 Hz, each 1H, CH_2 at 3), 3.73 (s, 3H, $ArOCH_3$), 4.31 (s, 4H, OCH_2CH_2O), 5.54 and 5.69 (2 s, each 1H, $=CH_2$), 6.50

(broad d, J = 7.5 Hz, 1H, H at 8), from 6.75 to 7.40 (mt, 10H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl and aromatic H of the 1,4-benzodioxanyl).

EXAMPLE 33

Preparation of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

By carrying out the reaction as in Example 13, and by starting from 0.5 g of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, from 0.24 cm^3 of oxalyl chloride and from 0.5 cm^3 of N,N-dimethylformamide, in 20 cm^3 of dichloromethane, for 2 hours, then evaporation to dryness, taken up in 20 cm^3 of dichloromethane and addition of 0.09 cm^3 of 3-aminomethylpyridine and of 0.26 cm^3 of triethylamine in 15 cm^3 of dichloromethane; then, after stirring for eighteen hours at a temperature in the region of 20°C, successively running in 50 cm^3 of distilled water and 40 cm^3 of a normal aqueous sodium hydroxide solution; dilution with 200 cm^3 of dichloromethane; separation by settling and washing of the organic phase with two times 100 cm^3 of a normal aqueous hydrochloric acid solution, then 200 cm^3 of a saturated aqueous sodium chloride solution and finally

drying over magnesium sulphate, 0.38 g of a green-yellow foam is obtained, which foam is recrystallized from diisopropyl ether to produce 249 mg of a yellow solid, which is then purified on a Merck 60F254 preparative silica plate, elution being carried out with the dichloromethane/methanol (90/10 by volume) mixture. An orange-coloured oil is thus obtained which, taken up in diisopropyl ether, gives 165 mg of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide in the form of a white powder, the characteristics of which are as follows:

- melting point = 228°C.
- mass spectrum (EI): M/Z = 627 (M^+)
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 373 K, d in ppm): 1.38, 1.56, 1.93 and 2.10 (4 mts, each 1H, CH_2CH_2), from 3.20 to 3.55 (mt, 3H, CH_2 at 1 and CH at 9a), 3.43 (d, J = 12.5 Hz, 1H, 1H of the CH_2 at 3), 3.57 (broad s, 1H, CH at 4), 3.71 (s, 3H, $ArOCH_3$), from 4.05 to 4.30 (mt, 3H, the other H of the CH_2 at 3 and NCH_2Ar), 4.31 (s, 4H, OCH_2CH_2O), 5.52 and 5.70 (2s, each 1H, $=CH_2$), 6.48 (mt, 1H, H at 8), from 6.75 to 7.45 (mt, 12H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl, aromatic H of the 1,4-benzodioxanyl, H at 4 of the pyridyl and H at 5 of the pyridyl), 8.10 (mt, 1H, CONH), 8.38 (broad s, 1H, H at 2 of the pyridyl), 8.45 (broad d, J = 5 Hz, 1H, H at

6 of the pyridyl).

EXAMPLE 34

Isolation of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

By carrying out the reaction as in Example 18, but from 17 g of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide, in 10 successive injections, on a Whelk 01 (SS) chiral silica column, elution being carried out with an n-heptane/ethanol/triethylamine (70/30/0.05 by volume) mixture and the first product eluted (retention time = 45 min) being isolated, 8.4 g of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide are obtained, after concentrating the solvent under reduced pressure, in the form of a white powder, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 627 (M^+)
- optical rotation: $[a]_{365}^{20}$ = + 103.2 +/- 1.5°

(c = 0.5, methanol)

EXAMPLE 35

Isolation of the levorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

By carrying out the reaction as in Example 19, but from 17 g of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide, in 10 successive injections, on a Whelk 01 (SS) chiral silica column, elution being carried out with a mixture of n-heptane, of ethanol and of triethylamine (70/30/0.05 by volume) and the second product eluted (retention time = 67 min) being isolated, 6.6 g of the levorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide are obtained, after concentrating the solvent under reduced pressure, in the form of a white powder, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 627 (M^+)
- optical rotation: $[a]_{365}^{20}$ = - 102 +/- 1.5° (c = 0.5, methanol)

EXAMPLE 36

Preparation of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(2-thienylmethyl)carboxamide

By carrying out the reaction as in Example 33, and by starting from 0.5 g of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, from 0.24 cm^3 of oxalyl chloride, from 0.1 cm^3 of N,N-dimethylformamide, in 20 cm^3 of dichloromethane, and then from 0.1 cm^3 of 2-(aminomethyl)thiophene and from 0.26 cm^3 of triethylamine in 15 cm^3 of dichloromethane, 29 mg of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(2-thienylmethyl)carboxamide are obtained, after lyophilization, in the form of a powder, the characteristics of which are as follows:

- melting point = 134°C
- mass spectrum (EI): M/Z = 632 (M^+)

EXAMPLE 37

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(3,4,5-trimethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Example 31, Stage A, starting from 3.49 g of methyl (3aRS,4SR,7aRS)-2-[(2-methoxyphenyl)acetyl]-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 40 cm^3 of dichloromethane stabilized over amylene, from 3.34 cm^3 of 1,2,3-trimethylbenzene and from 5.1 cm^3 of trifluoromethanesulphonic acid; after stirring for eighteen hours at a temperature in the region of 20°C, 2.8 cm^3 of trifluoromethanesulphonic anhydride are added and the reaction mixture is stirred for a further 18 hours. 263 mg of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(3,4,5-trimethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are thus obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 159°C.
- mass spectrum (EI): M/Z = 523 (M^+)

Stage B

By carrying out the reaction as in Example 2, from 192 mg of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(3,4,5-trimethylphenyl)-

2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for eighteen hours in 0.55 cm^3 of 1N aqueous sodium hydroxide solution and 20 cm^3 of ethanol, 69.3 mg of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-9-(3,4,5-trimethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 5 cm^3 of diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = > 260°C.
- mass spectrum (EI): M/Z = 509 (M^+)

EXAMPLE 38

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage C of Example 1, but from 1.33 cm^3 of 2-bromotoluene, from 0.27 g of magnesium turnings and from 2 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydro-isoindole-3a-carboxylate, 2.2 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(2-methyl-phenyl)-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a pale-yellow foam, used as is

in the subsequent syntheses.

Stage B

A mixture of 3.2 cm^3 of trifluoromethanesulphonic acid and of 3 cm^3 of dichloromethane is added dropwise to a solution of 2.2 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(2-methylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate in 20 cm^3 of dichloromethane maintained at a temperature in the region of 0°C. The reaction mixture is stirred for thirty minutes at a temperature in the region of 0°C and twenty hours at a temperature in the region of 20°C and then cooled to a temperature in the region of 0°C. The pH is then brought to 8 by addition of a normal aqueous sodium hydroxide solution. The aqueous phase is separated by settling and extracted with three times 50 cm^3 of dichloromethane. The organic phases are combined, washed with three times 100 cm^3 of distilled water and 100 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. 1.9 g of methyl (3aRS,4SR)-2-benzyl-7-(2-methylphenyl)-4-phenyl-1,3,3a,4,5,6-hexahydroisoindole-3a-carboxylate are thus obtained in the form of an oil, used as is in the subsequent syntheses, the characteristics of which are as follows:

- ^1H N.M.R. spectrum (250 MHz, $CDCl_3$ with addition of a few drops of d4-CD_3COOD, d in ppm): 1.90 (mt, 1H, 1H of the CH_2 at 5), 2.17 (s, 3H, $ArCH_3$), from 2.40 to 2.55

(mt, 2H, the other H of the CH_2 at 5 and 1H of the CH_2 at 6), 2.66 (mt, 1H, the other H of the CH_2 at 6), 3.08 (dd, J = 11 and 2.5 Hz, 1H, CH at 4), 3.32 (mt, 1H, 1H of the CH_2 at 1), 3.63 (s, 3H, $COOCH_3$), from 3.60 to 3.70 (mt, 1H, 1H of the CH_3 at 3), 3.75 (d, J = 11.5 Hz, the other H of the CH_2 at 1), 3.92 (d, J = 10 Hz, the other H of the CH_2 at 3), 3.98 and 4.32 (2 d, J = 11 Hz, each 1H, NCH_2Ar), from 6.90 to 7.40 (mt, 14H, aromatic H of the phenyl, aromatic H of the benzyl and aromatic H of the 2-methylphenyl).

Stage C

A mixture of 5.8 cm^3 of trifluoromethanesulphonic acid and of 5 cm^3 of dichloromethane is added dropwise to a solution of 1.9 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-7-(2-methylphenyl)-4-phenyl-1,3,3a,4,5,6-hexahydroisoindole-3a-carboxylate in 50 cm^3 of dichloromethane maintained at a temperature in the region of 0°C. The reaction mixture is stirred for one hour at a temperature in the region of 0°C and ninety-six hours at a temperature in the region of 20°C and then cooled to a temperature in the region of 0°C. The pH is then brought to 8 by addition of a normal aqueous sodium hydroxide solution. The organic phase is separated by settling, washed with 100 cm^3 of distilled water and 100 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (230-

400 mesh), elution being carried out with a cyclohexane/ethyl acetate (95/5 by volume) mixture. 0.85 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained in the form of an oil, used as is in the subsequent syntheses.

Stage D

By carrying out the reaction as in Stage E of Example 1, but from 0.85 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.37 g of ammonium formate and from 0.15 g of 10% (w/w) palladium-on-charcoal, 0.6 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture, in the form of a colourless oil, used as is in the subsequent syntheses.

Stage E

By carrying out the reaction as in Stage G of Example 1, but from 0.6 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.31 g of 2-(2-methoxyphenyl)-propenoic acid and from 0.15 cm^3 of oxalyl chloride, 0.51 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-

2-[2-(2-methoxyphenyl)propenoyl]-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture, in the form of an off-white foam, used as is in the subsequent syntheses.

Stage F

By carrying out the reaction as in Example 2, but from 0.51 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in 1.5 cm^3 of a normal aqueous sodium hydroxide solution and 15 cm^3 of ethanol, 0.22 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid is obtained, after recrystallization from isopropanol, the characteristic of which compound is as follows:

- melting point: above 260°C
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 393 K, d in ppm): from 1.15 to 1.50 and from 2.05 to 2.35 (2 mts, each 2H, CH_2CH_2), 2.25 (s, 3H, $ArCH_3$), 3.13 (dd, J = 12 and 9 Hz, 1H, 1H of the CH_2 at 1), 3.31 (broad d, J = 12 Hz, 1H, the other H of the CH_2 at 1), 3.44 (mt, 1H, CH at 4), 3.60 and 4.05 (respectively d and d (broad), J = 12.5 Hz, each 1H, CH_2 at 3), 3.75 (s, 3H, $ArOCH_3$), 5.54 and 5.69 (2 s, each

1H, $=CH_2$), 6.62 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.45 (mt, 11H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl and aromatic H of the 2-methylphenyl).

EXAMPLE 39

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate

Stage A

0.8 g of magnesium turnings is added to a solution of 7.2 g of 4-(trifluoromethyl)bromobenzene in 40 cm^3 of dry diethyl ether. The reaction mixture is spontaneously brought to reflux for ten minutes and is then heated at reflux for twenty minutes. The reaction mixture is subsequently cooled and a solution of 5.6 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 40 cm^3 of dry diethyl ether is added over fifteen minutes at a temperature in the region of 10°C. The reaction mixture is stirred for ten minutes at a temperature in the region of 10°C and then poured into 150 cm^3 of a saturated aqueous ammonium chloride solution. The aqueous phase is separated by settling and extracted with three times 75 cm^3 of diethyl ether. The organic phases are combined, washed successively with three times 75 cm^3 of distilled water, dried over magnesium sulphate in the presence of 3S charcoal and concentrated under reduced pressure. After

crystallization from 25 cm^3 of pentane, 5.2 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-[(4-trifluoromethyl)phenyl]-4-phenyloctahydroisoindole-3a-carboxylate are obtained in the form of a beige solid, the characteristic of which is as follows:

- melting point = 164°C.

Stage B

4 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-[(4-trifluoromethyl)phenyl]-4-phenyloctahydroisoindole-3a-carboxylate are added to 20 cm^3 of trifluoromethanesulphonic acid cooled to a temperature in the region of 0°C. The reaction mixture is stirred for 3 hours at a temperature in the region of 20°C and then cooled to a temperature in the region of 10°C. 50 cm^3 of distilled water are then added and then the pH of the aqueous phase is brought to between 8 and 9 by addition of a 30% aqueous sodium hydroxide solution, the temperature always being maintained in the region of 10 to 15°C with a bath containing an ethanol/dry ice mixture. The aqueous phase is separated by settling and extracted with three times 75 cm^3 of ethyl acetate. The organic extracts are combined, washed with three times 75 cm^3 of distilled water, dried over magnesium sulphate in the presence of 3S charcoal and concentrated under reduced pressure. 3.4 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are thus obtained in

two crops, after crystallization from petroleum ether, in the form of a white solid, the characteristic of which is as follows:

- melting point: 132°C.

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 3.4 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 1.3 g of ammonium formate and from 0.4 g of 10% (w/w) palladium-on-charcoal, 2.2 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a white solid, a characteristic of which is as follows:

- melting point = 172°C.

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 1.4 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-[(4-trifluoromethyl)-phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.62 g of 2-(2-methoxyphenyl)-propenoic acid, from 0.94 cm^3 of triethylamine and from 0.3 cm^3 of oxalyl chloride, 1.3 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are

obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture, and crystallization from diisopropyl ether, the characteristics of which compound are as follows:

- melting point = 163°C.
- ^{1}H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 373 K, d in ppm): 1.45, 1.72 and from 1.95 to 2.25 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), from 3.20 to 3.45 (mt, 3H, CH_2 at 1 and CH at 9a), 3.48 (mt, 1H, CH at 4), 3.55 (s, 3H, $COOCH_3$), 3.61 and 4.11 (respectively d and d (broad), J = 12.5 Hz, each 1H, CH_2 at 3), 3.70 (s, 3H, $ArOCH_3$), 5.55 and 5.68 (2 s, each 1H, $=CH_2$), 6.36 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.40 (mt, 7H, H at 5, H at 6, H at 7 and aromatic H of the 2-methoxyphenyl), 7.59 and 7.83 (2 broad d, J = 8 Hz, each 2H, aromatic H of the 4-trifluoromethylphenyl).

EXAMPLE 40

<u>Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid</u>

By carrying out the reaction as in Example 2, but from 1.1 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 9.8 cm^3 of a

normal aqueous sodium hydroxide solution and 20 cm^3 of methanol, 0.65 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid is obtained, after crystallization from diisopropyl ether, base/acid passage and recrystallization from 8 cm^3 of isopropyl acetate, the characteristic of which compound is as follows:

- melting point = 153°C.

EXAMPLE 41

Isolation of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

11 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid, obtained in Example 40, are resolved on a chiral silica column carrying N-(3,5-dinitrobenzoyl)-(R)-phenylalanine grafts, in 4 successive injections and by eluting with a mixture of n-heptane, of dichloromethane and of ethanol (50/50/1 by volume). On collecting the first fractions eluted (retention time 31 min), 5 g of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-

benzo[f]isoindole-3a-carboxylic acid are obtained, after concentrating under reduced pressure, in the form of a white powder, the characteristics of which are as follows:

- melting point = 228°C
- mass spectrum (EI): M/Z = 547 (M^+)
- optical rotation: $[a]_{365}^{20}$ = + 63.1 +/- 1.2°

(c = 0.5, methanol)

The chiral stationary phase carrying N-(3,5-dinitrobenzoyl)-(R)-phenylalanine grafts can be prepared according to the synthesis described in Example 3, by replacing N-(3,5-dinitrobenzoyl)-(S)-phenylalanine by N-(3,5-dinitrobenzoyl)-(R)-phenylalanine.

EXAMPLE 42

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

0.24 cm^3 of 3-(aminomethyl)pyridine, 0.46 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and 0.16 g of N-1-hydroxybenzotriazole hydrate are successively added to a solution of 1.1 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 20 cm^3 of dichloromethane. The reaction mixture is stirred for forty-eight hours at a

temperature in the region of 20°C. The organic phase is washed with three times 10 cm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. After recrystallizing from 15 cm^3 of isopropanol, 0.95 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-N-(3-pyridylmethyl)carboxamide is obtained, the characteristic of which is as follows:

- melting point = 214°C.

EXAMPLE 43

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-N'-benzoylcarbohydrazide

0.16 g of benzoylhydrazine, 0.23 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and 81 mg of N-1-hydroxybenzotriazole hydrate are successively added to a solution of 0.55 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 10 cm^3 of dichloromethane. The reaction mixture is stirred for twenty hours at a temperature in the region of 20°C and then filtered through sintered glass. The precipitate is washed successively with three times 1.5 cm^3 of dichloromethane and then three times 2.5 cm^3 of distilled water. 0.34 g

of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-[(4-trifluoromethyl)phenyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-benzoylcarbohydrazide is thus obtained, the characteristics of which are as follows:

- melting point = 275°C.
- ^{1}H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.44, 1.70, 2.01 and 2.18 (4 mts, each 1H, CH_2CH_2), from 3.20 to 3.40 (limit AB, 2H, CH_2 at 1), from 3.55 to 3.85 (mt, 3H, 1H of the CH_2 at 3, CH at 9a and CH at 4), 3.72 (s, 3H, $ArOCH_3$), 4.36 (broad d, J = 12.5 Hz, 1H, the other H of the CH_2 at 3), 5.57 and 5.70 (2 s, each 1H, $=CH_2$), 6.34 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.85 to 7.60 (mt, 10H, H at 5, H at 6, H at 7, aromatic H at the meta positions of the benzoylcarbohydrazide, aromatic H at the para position of the benzoylcarbohydrazide and aromatic H of the 2-methoxyphenyl), 7.60 and 7.85 (2d, J = 8 Hz, each 2H, aromatic H of the 4-trifluoromethylphenyl), 7.81 (d, J = 8 Hz, 2H, aromatic H at the ortho positions of the benzoylcarbohydrazide), 9.66 and 9.91 (2 broad s, each 1H, CONHNHCO).

EXAMPLE 44

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide

0.12 cm^3 of phenylhydrazine, 0.23 g of

1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and 81 mg of N-1-hydroxybenzotriazole hydrate are successively added to a solution of 0.55 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid in 10 cm^3 of dichloromethane. The reaction mixture is stirred for twenty hours at a temperature in the region of 20°C. The reaction mixture is diluted with 15 cm^3 of dichloromethane, washed with three times 10 cm^3 of distilled water, dried over magnesium sulphate in the presence of 3S charcoal and concentrated under reduced pressure. After recrystallizing from 10 cm^3 of isopropanol, 0.21 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide is obtained, the characteristics of which compound are as follows:

- melting point: 226°C.
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.44, 1.69 and from 1.95 to 2.25 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), from 3.20 to 3.45 (limit AB, 2H, CH_2 at 1), 3.52 and 4.26 (respectively d and d (broad), J = 12.5 Hz, each 1H, CH_2 at 3), 3.63 (mt, 1H, CH at 9a), 3.69 (s, 3H, $ArOCH_3$), 3.75 (mt, 1H, CH at 4), 5.55 and 5.68 (2 s, each 1H, $=CH_2$), 6.35 (broad d,

J = 7.5 Hz, 1H, H at 8), 6.60 (d, J = 7.5 Hz, 2H, aromatic H at the ortho positions of the phenylcarbohydrazide), 6.70 (t, J = 7.5 Hz, 1H, aromatic H at the para position of the phenylcarbohydrazide), from 6.90 to 7.45 (mt, 10H, H at 5, H at 6, H at 7, aromatic H at the meta positions of the phenylcarbohydrazide, aromatic H of the 2-methoxyphenyl and ArNH), 7.61 and 7.82 (2d, J = 8 Hz, each 2H, aromatic H of the 4-trifluoromethylphenyl), 9.52 (broad s, 1H, CONH).

EXAMPLE 45

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

21.4 g of hydrazine hydrate are added to a solution of 40 g of methyl 2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, obtained in Stage B of Example 1, in 300 cm^3 of ethanol and then the reaction mixture is brought to reflux for two hours thirty minutes. After concentrating the solvent under reduced pressure, the residue is taken up in water and extracted with dichloromethane. The organic phase is separated by settling, washed with water and dried over magnesium sulphate. After concentrating under reduced pressure, 38.73 g (93%) of methyl (3aRs,4SR,7aRS)-2-benzyl-7-hydrazono-4-phenyloctahydroisoindole-3a-

carboxylate are obtained in the form of a brown oil, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 377 (M^+)
- IR spectrum (in solution in dichloromethane):

3400 cm^{-1}	n NH
3080, 3060, 3045, 3030 cm^{-1}	n CH, aromatic
2950, 2800 cm^{-1}	n CH, aliphatic
2730 cm^{-1}	n CH, $N(CH_2)_3$
1720 cm^{-1}	n C=O, methyl ester
1605, 1495, 1455, 1435 cm^{-1}	respiration of the aromatic nuclei
1435 cm^{-1}	d_s CH_3, methyl ester
1220 cm^{-1}	n O-C=O, methyl ester

Stage B

52.07 g of iodine, in solution in 250 cm^3 of tetrahydrofuran, are added dropwise to a solution of 37.75 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-hydrazono-4-phenyloctahydroisoindole-3a-carboxylate in 200 cm^3 of tetrahydrofuran and 43 cm^3 of triethylamine. Stirring is maintained at room temperature for one hour after the end of the addition. 1 dm^3 of water and 1 dm^3 of ethyl acetate are then added. The organic phase is separated by settling, washed successively with a saturated sodium hydrosulphite solution and then with a saturated sodium chloride solution, and dried over magnesium sulphate. After concentrating the solvent under reduced pressure, the residue is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (95/5 by volume). 22.25 g (47 %) of

methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate are thus obtained in the form of a yellow pasty solid, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 473 (M^+)
- IR spectrum (in solution in carbon tetrachloride):

3080, 3060, 3030 cm^{-1}	n CH, aromatic
2925, 2800 cm^{-1}	n CH, aliphatic
2730 cm^{-1}	n CH, $N(CH_2)_3$
1730 cm^{-1}	n C=O, methyl ester
1600, 1495, 1455, 1435 cm^{-1}	respiration of the aromatic nuclei
1435 cm^{-1}	d_s CH_3, methyl ester
1210 cm^{-1}	n O-C=O, methyl ester
700 cm^{-1}	g CH, aromatic

Stage C

240 mg of tetrakis(triphenylphosphine)-palladium and then a solution of 0.69 g of 2-naphthylboronic acid, isolated in the trimer anhydride form, in 20 cm^3 of methanol are added to a solution of 2 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-phenyl-2,3,a,4,5,7a-hexahydroisoindole-3a-carboxylate in 40 cm^3 of toluene. 45 cm^3 of a 2N aqueous sodium carbonate solution are added dropwise and the reaction mixture is brought to reflux for four hours. After cooling, 80 cm^3 of water and 60 cm^3 of ethyl acetate are added. The organic phase is separated by settling, washing with water to neutrality and dried over magnesium sulphate. After concentrating the solvent under reduced pressure, the residue is purified by flash chromatography on

silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (90/10 by volume). 1.33 g (67 %) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(2-naphthyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate are thus obtained in the form of a white foam, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 473 (M^+).

Stage D

By carrying out the reaction as in Stage C of Example 38, but from 1.66 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(2-naphthyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate and from 1.9 cm^3 of trifluoromethanesulphonic acid in solution in 20 cm^3 of dry dichloromethane for four hours at room temperature, 1.22 g (51 %) of a white foam are isolated after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (95/5 by volume), the white foam mainly containing (approximately 90 % by NMR quantitative determination) methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, which foam, used as is in the continuation of the synthesis, has the following characteristics:

- ^1H N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): from 1.40 to 2.00 and 2.52 (2 mts, each 2H, CH_2CH_2), from

2.20 to 2.40 (mt, 2H, 1H of the CH_2 at 1 and 1H of the CH_2 at 3), 2.68 (broad d, J = 10 Hz, 1H, the other H of the CH_2 at 1), 3.21 (broad d, J = 10 Hz, the other H of the CH_2 at 3), 3.31 and 3.67 (d, J = 12.5 Hz, 2H, NCH_2Ar), 3.36 (mt, 1H, CH at 9a), 3.45 (broad s, 1H, CH at 4), 3.58 (s, 3H, $COOCH_3$), 6.61 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.91 to 8.00 (mt, 15H, H at 5, H at 6, H at 7, aromatic H of the naphthyl and aromatic H of the benzyl).

Stage E

1.2 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, in solution in 50 cm^3 of methanol and 2 cm^3 of a 2M solution of hydrochloric acid in methanol, are stirred, in the presence of 115 mg of 10 % (w/w) palladium-on-charcoal, for five hours at 50°C under hydrogen at atmospheric pressure. After filtering off the catalyst, the solvent is concentrated under reduced pressure. 0.96 g (91 %) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride is thus obtained in the form of a beige powder, the characteristics of which are as follows:

- melting point > 260°C
- mass spectrum (EI): M/Z = 383 (M^+).

Stage F

By carrying out the reaction as in Stage G of

Example 1, but from 0.96 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, from 0.41 g of 2-(2-methoxyphenyl)propenoic acid, from 0.2 cm^3 of oxalyl chloride and from 0.64 cm^3 of triethylamine in solution in 60 cm^3 of dichloromethane for twenty hours at room temperature, 1.15 g (78 %) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (70/30 by volume), in the form of a white powder, the characteristics of which are as follows:

- melting point = 140-2°C
- mass spectrum (EI): M/Z = 473 (M^+).

EXAMPLE 46

<u>Preparation of the sodium salt of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid</u>

By carrying out the reaction as in Example 2, but from 1.15 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for five hours in 6.3 cm^3 of a

normal aqueous sodium hydroxide solution and of 40 cm^3 of ethanol, 50 mg (4.8 %) of the sodium salt of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of dichloromethane and of methanol (95/5 by volume), and then by high performance liquid chromatography on C18 Waters grafted silica, elution being carried out with a mixture of water and of acetonitrile (70/30 by volume), in the form of a white solid, the characteristics of which are as follows:

- melting point > 260°C
- mass spectrum (EI): M/Z = 529 (M^+).

EXAMPLE 47

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage A of Example 31, but from 2 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, from 0.8 cm^3 of 2-methylthiophene and from 3 cm^3 of trifluoromethanesulphonic acid in 30 cm^3 of dichloromethane for five hours at room temperature, 0.49 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-

ethano-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification on silica gel (230-400 mesh), elution being carried out with mixtures of cyclohexane and ethyl acetate (95/5, then 90/10, by volume), in the form of a white powder, the characteristics of which are as follows:

- ^{1}H N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): 1.14, 1.66 and from 2.35 to 2.55 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.29 and 3.18 (d, J = 10 Hz, each 1H, CH_2 at 3), from 2.35 to 2.55 and 3.00 (respectively mt and d, J = 10 Hz, each 1H, CH_2 at 1), 2.52 (s, 3H, $ArCH_3$), 3.10 (broad d, J = 8 Hz, 1H, CH at 9a), from 3.30 to 3.40 (mt, 2H, H at 4 and 1H of the NCH_2Ar), 3.54 (s, 3H, $COOCH_3$), 3.74 (d, J = 12.5 Hz, 1H, the other H of the NCH_2Ar), 6.71 (mt, 1H, H at 8), 6.71 and 6.74 (respectively mt and d, J = 4 Hz, each 1H, aromatic H of the thienyl), from 6.95 to 7.45 (mt, 8H, H at 5, H at 6, H at 7 and aromatic H of the benzyl).

Stage B

A solution of 0.48 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and of 0.17 cm^3 of vinyl chloroformate in 5 cm^3 of dichloromethane is stirred at room temperature for eighteen hours. After concentrating the solvent under reduced pressure, the residue is purified by flash chromatography on silica gel, elution being

carried out with a mixture of cyclohexane and of ethyl acetate (85/15 by volume), to give 0.37 g of a foam, which is redissolved in 7 cm^3 of methanol. 1.65 cm^3 of a normal aqueous hydrochloric acid solution are then added and the mixture is brought to reflux for three hours. After concentrating the solvent, the residue is recrystallized from a mixture of isopropanol and of isopropyl ether (50/50 by volume). 0.3 g (70 %) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride is then obtained in the form of a pale-green solid, the characteristics of which are as follows:

- melting point = 226-30°C
- mass spectrum (EI): M/Z = 353 (M^+).

Stage C

By carrying out the reaction as in Stage G of Example 1, but from 0.58 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, from 0.27 g of 2-(2-methoxyphenyl)propenoic acid, from 0.13 cm^3 of oxalyl chloride and from 0.42 cm^3 of triethylamine in solution in 35 cm^3 of dichloromethane for twenty hours at room temperature, 0.53 g (69 %) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-

carboxylate is obtained, after purification on silica gel (230-400 mesh), elution being carried out with mixtures of cyclohexane and of ethyl acetate (80/20, then 60/40, by volume), in the form of a light-beige powder, the characteristics of which are as follows:

- melting point = 112-5°C
- mass spectrum (EI): M/Z = 513 (M^+).

EXAMPLE 48

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 0.45 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for five hours in 2.6 cm^3 of a normal aqueous sodium hydroxide solution and of 15 cm^3 of ethanol, 285 mg of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by recrystallization from diisopropyl ether, in the form of a light-beige solid, the characteristics of which are as follows:

- melting point = 164-6°C
- mass spectrum (EI): M/Z = 499 (M^+).

EXAMPLE 49

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 45, but from 1 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-phenyl-2,3,a,4,5,7a-hexahydroisoindole-3a-carboxylate in 20 cm^3 of toluene, from 120 mg of tetrakis(triphenylphosphine)palladium, from 0.46 g of 4-bromophenylboronic acid in 10 cm^3 of methanol and from 15 cm^3 of a 2N aqueous sodium carbonate solution at reflux for eighteen hours, 0.77 g (73%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(4-bromophenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (90/10 by volume), in the form of a white foam, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 502 (M^+).

Stage B

By carrying out the reaction as in Stage C of Example 38, but from 0.77 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(4-bromophenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate and from 1.18 cm^3 of trifluoromethanesulphonic acid in 20 cm^3 of

dichloromethane for eighteen hours at room temperature, 0.71 g (92%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained in the form of a beige powder, used as is in the continuation of the synthesis, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 502 (M^+).

Stage C

By carrying out the reaction as in Stage B of Example 47, but from 0.71 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate and from 0.4 cm^3 of vinyl chloroformate for seventy-two hours at room temperature in 20 cm^3 of dichloromethane, and by then taking the concentrate up in 40 cm^3 of methanol and 5 cm^3 of a 6M solution of hydrochloric acid in dioxane at reflux for three hours, 0.45 g (77%) of methyl (3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate hydrochloride is obtained, after crystallizing from diisopropyl ether, in the form of white crystals, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 412 (M^+).

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 0.45 g of methyl

(3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, from 0.21 g of 2-(2-methoxyphenyl)propenoic acid, from 0.10 cm^3 of oxalyl chloride and from 0.33 cm^3 of triethylamine in solution in 30 cm^3 of dichloromethane for twenty hours at room temperature, 0.25 g (40%) of methyl (3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and ethyl acetate (70/30 by volume), in the form of a light-beige powder, the characteristics of which are as follows:

- melting point = 190-2°C
- mass spectrum (EI): M/Z = 572 (M^+).

EXAMPLE 50

<u>Preparation of (3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid</u>

By carrying out the reaction as in Example 2, but from 0.19 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for three hours in 0.44 cm^3 of a normal aqueous sodium hydroxide

solution and of 10 cm^3 of ethanol, 120 mg (66%) of (3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by recrystallizing from diisopropyl ether, in the form of a white solid, the characteristics of which are as follows:

- melting point = 169°C
- mass spectrum (EI): M/Z = 558 (M^+).

EXAMPLE 51

Preparation of (3aRS,4SR,9SR,9aRS)-9-(3,4-dichlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage A of Example 39, but from 3.6 g of 3,4-dichloro-bromobenzene, from 0.4 g of magnesium turnings in 20 cm^3 of diethyl ether and from 2.9 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 20 cm^3 of diethyl ether, 1.8 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(3,4-dichlorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after recrystallization from 35 cm^3 of isopropanol, in the form of a white solid, the characteristic of which is as follows:

- melting point = 144°C.

Crystallization by diisopropyl ether of the filtrate, brought to dryness, makes it possible to obtain an additional 0.6 g. The purification of this second filtrate by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture, makes it possible to obtain, after crystallization from diisopropyl ether, an additional 0.25 g.

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 1.2 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(3,4-dichlorophenyl)-7-hydroxy-4-phenyl-1,3,3a,4,5,6-hexahydroisoindole-3a-carboxylate, from 3 cm^3 of trifluoromethanesulphonic acid and from 45 cm^3 of dichloromethane, 1.1 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3,4-dichlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a white foam, used as is in the subsequent syntheses.

Stage C

0.18 cm^3 of vinyl chloroformate is added to a solution of 0.7 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3,4-dichlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in 7.5 cm^3 of dichloromethane. The reaction mixture is stirred for twenty hours at a temperature in the region of 20°C and then concentrated under reduced pressure. The residue

is diluted with 7.5 cm^3 of methanol. 14 cm^3 of a normal solution of hydrogen chloride gas in diethyl ether are added to this solution. The reaction mixture is stirred for twenty hours at a temperature in the region of 20°C and then concentrated under reduced pressure. The residue is taken up in a mixture of 25 cm^3 of dichloromethane and 20 cm^3 of a saturated aqueous sodium hydrogencarbonate solution. The aqueous phase is separated by settling and extracted with two times 15 cm^3 of diethyl ether. The organic phases are combined, washed with three times 15 cm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. After flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture, and crystallization from 5 cm^3 of diisopropyl ether, 0.21 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dichlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is thus obtained in the form of a white solid, the characteristic of which is as follows:

- melting point = 185°C.

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 0.2 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dichlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.1 g of 2-(2-methoxyphenyl)propenoic

acid, from 0.04 cm^3 of oxalyl chloride and from 0.14 cm^3 of triethylamine, 0.19 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dichlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after crystallization from diisopropyl ether, in the form of a white solid, the characteristic of which is as follows:

- melting point = 150°C.

Stage E

By carrying out the reaction as in Example 2, but from 0.16 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dichlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 1.4 cm^3 of a normal aqueous sodium hydroxide solution and [lacuna] 3 cm^3 of methanol, 0.1 g of (3aRS,4SR,9SR,9aRS)-9-(3,4-dichlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid is obtained, after recrystallization from 2.5 cm^3 of isopropyl acetate, the characteristic of which is as follows:

- melting point = 168°C.

EXAMPLE 52

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 1, but from 9.58 g of 4-chlorobromobenzene, from 1.2 g of magnesium turnings and from 9.1 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, 7.9 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(4-chlorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after recrystallization from 25 cm^3 of isopropanol, in the form of a white solid, the characteristic of which is as follows:

- melting point = 189°C.

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 7.5 g of methyl (3aRS,4SR,7RS,7aSR)-2-benzyl-7-(4-chlorophenyl)-7-hydroxy-4-phenyl-2,3,3a,4,5,6-hexahydroisoindole-3a-carboxylate, from 25 cm^3 of trifluoromethanesulphonic acid and from 80 cm^3 of dichloromethane, 6.35 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-chlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after crystallization from 100 cm^3 of isopropanol, in the form

of a white solid, the characteristic of which is as follows:

- melting point = 142°C.

Stage C

By carrying out the reaction as in Stage C of Example 51, but from 2.29 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-chlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 0.98 cm^3 of vinyl chloroformate in 7.5 cm^3 of dichloromethane, and by then treating the intermediate, diluted in 25 cm^3 of methanol, with 8.5 cm^3 of a hexanormal solution of hydrogen chloride gas in dioxane, 0.8 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (98/2 by volume) mixture, in the form of a light-coloured foam, used as is in the subsequent syntheses.

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 0.75 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.36 g of 2-(2-methoxyphenyl)propenoic acid, from 0.17 cm^3 of oxalyl chloride and from 0.57 cm^3 of triethylamine, 0.8 g of

methyl (3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, the characteristic of which is as follows:

- melting point = 90°C.

EXAMPLE 53

Preparation of (3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 0.7 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 2 cm^3 of a normal aqueous sodium hydroxide solution and [lacuna] 30 cm^3 of ethanol, 0.45 g of (3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid is obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (98/2 by volume) mixture, the characteristic of which is as follows:

- melting point: approximately 160°C.

EXAMPLE 54

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage A of Example 31, but from 2 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, from 2 g of 2-methylanisole and from 2.9 cm^3 of trifluoromethanesulphonic acid in 30 cm^3 of dichloromethane, 2.3 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of an off-white foam, used as is in the subsequent syntheses.

Stage B

By carrying out the reaction as in Stage E of Example 1, but from 2.3 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.93 g of ammonium formate and from 0.5 g of 10% (w/w) palladium-on-charcoal, 0.5 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-

hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after [lacuna] by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (99/1 by volume) mixture, and recrystallization from 20 cm^3 of isopropanol, in the form of a white solid, the characteristic of which is as follows:

- melting point = 123°C.

Stage C

By carrying out the reaction as in Stage G of Example 1, but from 1.1 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.52 g of 2-(2-methoxyphenyl)propenoic acid, from 0.25 cm^3 of oxalyl chloride and from 0.82 cm^3 of triethylamine, 0.85 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (99/1 by volume) mixture, and recrystallization from 5 cm^3 of isopropanol, the characteristic of which compound is as follows:

- melting point = 125°C.

Stage D

By carrying out the reaction as in Example 2,

but from 0.8 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 2.25 cm^3 of a normal aqueous sodium hydroxide solution and [lacuna] 40 cm^3 of ethanol, 0.45 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid is obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (97.5/2.5 by volume) mixture, in the form of an amorphous white solid.

- mass spectrum (EI): M/Z = 523 (M^+)

EXAMPLE 55

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-indolyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage A of Example 31, but from 3.63 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, from 3.85 g of 1-phenylsulphonylindole and from 5.3 cm^3 of trifluoromethanesulphonic acid in 30 cm^3 of dichloromethane, 2.1 g of a crude product are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out

with a cyclohexane/ethyl acetate (80/20 by volume) mixture, which crude product is combined with a second batch originating from an experiment carried out with respect to the same amounts. The purification of this mixture by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (95/5 by volume) mixture, provides 1 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-indolyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in the form of an off-white foam, used as is in the subsequent syntheses, the characteristics of which are as follows:

- ^{1}H N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): from 1.30 to 1.60 and 2.55 (2 mts, each 2H, CH_2CH_2), 2.11 and 2.65 (respectively dd and d, J = 10 and 9 Hz and J = 10 Hz, each 1H, CH_2 at 1), 2.31 and 3.21 (2d, J = 10 Hz, each 1H, CH_2 at 3), 3.37 and 3.51 (2 d, J = 12.5 Hz, each 1H, NCH_2Ar), 3.42 (broad s, 1H, CH at 4), from 3.50 to 3.70 (mt, 1H, CH at 9a), 3.59 (s, 3H, $COOCH_3$), 6.81 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.60 (mt, 13H, H at 5, H at 6, H at 7, aromatic H of the indole and aromatic H of the benzyl), 8.11 (broad s, 1H, NH).

Stage B

By carrying out the reaction as in Stage C of Example 51, but from 1 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-indolyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from

0.285 cm^3 of vinyl chloroformate in 20 cm^3 of dichloromethane, and by then treating the intermediate, dissolved in 20 cm^3 of methanol, with 21.4 cm^3 of a normal solution of hydrogen chloride gas in diethyl ether, 0.3 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-indolyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (97.5/2.5 by volume) mixture, in the form of an orange-coloured foam, used as is in the subsequent syntheses.

Stage C

By carrying out the reaction as in Stage G of Example 1 but from 0.3 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-indolyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.145 g of 2-(2-methoxyphenyl)propenoic acid and from 0.07 cm^3 of oxalyl chloride, 0.16 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-indolyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture, and crystallization from diisopropyl ether, the characteristics of which compound are as follows:

- mass spectrum (EI): M/Z = 532 (M^+)

- ^{1}H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.46 and 2.16 (2 mts, each 2H, CH_2CH_2), from 3.30 to 3.80 (mt, 4H, CH_2 at 1, CH at 9a and 1H of the CH_2 at 3), 3.47 (mt, 1H, CH at 4), 3.57 (s, 3H, $COOCH_3$), 3.71 (s, 3H, $ArOCH_3$), 4.10 (broad d, J = 12.5 Hz, 1H, the other H of the CH_2 at 3), 5.52 and 5.67 (2 s, each 1H, $=CH_2$), 6.65 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.88 (mt, 12H, H at 5, H at 6, H at 7, aromatic H of the indole and aromatic H of the 2-methoxyphenyl).

EXAMPLE 56

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage A of Example 1, but from 6 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 60 cm^3 of dry diethyl ether and from a solution of 4-isopropylphenylmagnesium bromide, prepared at the time of use from 4 g of 4-bromoisopropylbenzene and 0.52 g of magnesium turnings in 7 cm^3 of dry diethyl ether, for eighteen hours at room temperature, 3.3 g (41%) of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(4-isopropylphenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh),

elution being carried out with a gradient of mixtures of cyclohexane and of ethyl acetate (from 98/2 to 80/20 by volume), in the form of a yellow oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 483 (M^+).

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 1.7 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(4-isopropylphenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate and from 2.3 cm^3 of trifluoromethanesulphonic acid in 22 cm^3 of dichloromethane for three hours at room temperature, 1.44 g (90%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-isopropylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a brown viscous oil, used as is in the continuation of the synthesis, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 465 (M^+).

Stage C

By carrying out the reaction as in Stage C of Example 45, but from 1.4 g (3 mmol) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-isopropylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 140 mg of 10% (w/w) palladium-on-charcoal in 125 cm^3 of methanol and 3.3 cm^3 of a normal aqueous hydrochloric acid solution for four hours at room temperature under hydrogen at

atmospheric pressure, 1.03 g (86%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride are obtained, after crystallization from diisopropyl ether, in the form of a beige powder, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 375 (M^+).

Stage D

By carrying out the reaction as in Stage A of Example 5, but from 500 mg of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, from 240 mg of 2-methoxyphenylacetic acid, from 280 mg of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, from 16 mg of N-1-hydroxybenzotriazole hydrate and from 0.2 cm^3 of triethylamine in 55 cm^3 of dichloromethane, 460 mg (76%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[2-(methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (240-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture, in the form of a white powder, the characteristics of which are as follows:

- melting point = 85-7°
- mass spectrum (EI): M/Z = 523 (M^+).

Stage E

By carrying out the reaction as in Example 2, but from 0.379 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[2-(methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for three hours in 0.85 cm^3 of a normal aqueous sodium hydroxide solution and 15 cm^3 of ethanol, 170 mg (47%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by stirring in ethyl acetate in the presence of silica gel (230-400 mesh) and then recrystallization from pentane, in the form of a white solid, the characteristics of which are as follows:

- melting point = 135-6°C
- mass spectrum (EI): M/Z = 509 (M^+).

EXAMPLE 57

<u>Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid</u>

By carrying out the reaction as in Stage G of Example 1, but from 0.53 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, obtained in Stage C of Example 56, from 0.25 g of 2-(2-methoxyphenyl)propenoic

acid, from 0.12 cm^3 of oxalyl chloride and from 0.4 cm^3 of triethylamine in solution of 30 cm^3 of dichloromethane for twenty hours at room temperature, 0.375 g (54%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification on silica gel (230-400 mesh), elution being carried out with a gradient of mixtures of cyclohexane and of ethyl acetate (from 98/2 to 70/30 by volume), in the form of a white powder, the characteristics of which are as follows:

- melting point = 98-100°C
- mass spectrum (EI): M/Z = 535 (M^+).

By carrying out the reaction as in Example 2, but from 0.32 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for two hours in 0.71 cm^3 of a normal aqueous sodium hydroxide solution and 15 cm^3 of ethanol, 190 mg (59%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by stirring in ethyl acetate in the presence of silica gel (230-400 mesh) and then recrystallization from pentane, in the form of a white solid, the characteristics of which are as follows:

- melting point = 168-70°C
- mass spectrum (EI): M/Z = 521 (M^+).

EXAMPLE 58

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 45, but from 1.2 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-phenyl-2,3,a,4,5,7a-hexahydroisoindole-3a-carboxylate in 30 cm^3 of toluene, from 150 mg of tetrakis(triphenylphosphine)palladium, from 0.35 g of 3-thienylboronic acid in 15 cm^3 of methanol and from 28 cm^3 of a 2N aqueous sodium carbonate solution at reflux for three hours, 0.99 g (93%) of methyl (3aRS,4SR,7aRS)-2-benzyl-4-phenyl-7-(3-thienyl)-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and ethyl acetate (85/15 by volume), in the form of a yellow oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 429 (M^+).

Stage B

By carrying out the reaction as in Stage C of Example 38, but from 1.1 g of methyl (3aRS,4SR,7aRS)-2-benzyl-4-phenyl-7-(3-thienyl)-2,3,3a,4,5,7a-hexahydro-

1H-isoindole-3a-carboxylate and from 1.4 cm^3 of trifluoromethanesulphonic acid in 15 cm^3 of dichloromethane for eighteen hours at room temperature, 0.62 g (56%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained in the form of a beige powder, used as is in the continuation of the synthesis, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 429 (M^+).

Stage C

By carrying out the reaction as in Stage B of Example 47, but from 0.62 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 0.19 cm^3 of vinyl chloroformate for seventy-two hours at room temperature in 10 cm^3 of dichloromethane, and by then taking the concentrate up in 20 cm^3 of methanol and 2.7 cm^3 of a 5M solution of hydrochloric acid in isopropanol at reflux for two hours, 0.48 g (89%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride is obtained, after crystallization from diisopropyl ether, in the form of a white solid, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 339 (M^+).

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 0.48 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, from 0.27 g of 2-(2-methoxyphenyl)propenoic acid, from 0.12 cm^3 of oxalyl chloride and from 0.36 cm^3 of triethylamine in solution of 35 cm^3 of dichloromethane for twenty hours at room temperature, 0.40 g (63%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (60/40 by volume), followed by recrystallization from diisopropyl ether, in the form of a white solid, the characteristics of which are as follows:

- melting point = 174°C
- mass spectrum (EI): M/Z = 499 (M^+).

Stage E

By carrying out the reaction as in Example 2, but from 0.35 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for three hours in 2.1 cm^3 of a normal aqueous sodium hydroxide solution and 12 cm^3 of ethanol, 340 mg (88%) of (3aRS,4SR,9SR,9aRS)-4,9-

ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by recrystallization from petroleum ether (40-65°C), in the form of a white solid, the characteristics of which are as follows:

- melting point = 170°C
- mass spectrum (EI): M/Z = 485 (M^+).

EXAMPLE 59

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 45, but from 1.35 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-phenyl-2,3,a,4,5,7a-hexahydroisoindole-3a-carboxylate in 20 cm^3 of toluene, from 340 mg of tetrakis(triphenylphosphine)palladium, from 0.38 g of trimer anhydride of 4-ethylphenylboronic acid in 10 cm^3 of methanol and from 15 cm^3 of a 2N aqueous sodium carbonate solution at reflux for eighteen hours, 0.92 g (72%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(4-ethylphenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (90/10 by

volume), in the form of a viscous yellow oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 451 (M^+).

Stage B

By carrying out the reaction as in Stage C of Example 38, but from 0.92 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(4-ethylphenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate and from 1.18 cm^3 of trifluoromethanesulphonic acid in 18 cm^3 of dichloromethane for six hours at room temperature, 0.68 g (74%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-ethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (95/5 by volume), in the form of a viscous yellow oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 451 (M^+).

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 0.68 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-ethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 0.27 g of ammonium formate in 40 cm^3 of methanol in the presence of 200 mg of 3% (w/w) palladium-on-charcoal at reflux for four hours, 0.47 g (87%) of methyl

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained in the form of a yellow pasty solid, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 461 (M^+).

Stage D

By carrying out the reaction as in Stage A of Example 5, but from 0.47 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.23 g of 2-(2-methoxyphenyl)-propenoic acid, from 0.3 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 20 mg of N-1-hydroxybenzotriazole hydrate in 30 cm^3 of dichloromethane for six hours at room temperature, 0.26 g (38%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (70/30 by volume), in the form of a white powder, the characteristics of which are as follows:

- melting point = 90-2°C
- mass spectrum (EI): M/Z = 521 (M^+).

EXAMPLE 60

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but starting from 0.18 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for three hours in 0.43 cm^3 of a normal aqueous sodium hydroxide solution and of 10 cm^3 of methanol, 59 mg (34%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by recrystallization from petroleum ether, in the form of a white solid, the characteristics of which are as follows:

- melting point = 141°C
- mass spectrum (EI): M/Z = 507 (M^+).

EXAMPLE 61

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Example

31, Stage A, but starting from 2.5 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 250 cm^3 of dichloromethane, from 2.4 cm^3 of 2,3-dihydrobenzofuran and from 4.25 cm^3 of trifluoromethanesulphonic acid; after stirring for 18 hours at a temperature in the region of 20°C, 1.56 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of an orangey-yellow oil, used as in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 465 (M^+)

Stage B

By carrying out the reaction as in Stage E of Example 1, but from 1.56 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.63 g of ammonium formate and from 0.2 g of 10% (w/w) palladium-on-charcoal in 30 cm^3 of methanol at reflux for 5 hours, 0.995 g of impure methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained in the form of an orange-coloured lacquer, which can be used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (DCI): M/Z = 376 ($M+H^+$)

Stage C

By carrying out the reaction as in Stage G of Example 1, but from a solution of 0.45 g of 2-(2-methoxyphenyl)propenoic acid in 20 cm^3 of dichloromethane containing 4 drops of N,N-dimethylformamide and from 0.54 cm^3 of oxalyl chloride, after one night at a temperature in the region of 20°C, by evaporating to dryness and by taking up the residue in 20 cm^3 of dichloromethane; by then pouring this solution onto the solution of 0.99 g of methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, obtained in the preceding stage, with 0.31 cm^3 of triethylamine added, in 20 cm^3 of dichloromethane, 39 mg of methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a beige solid, the characteristics of which are as follows:

- melting point = 200°C (dec)
- mass spectrum (EI): M/Z = 535 (M^+)

EXAMPLE 62

<u>Preparation of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid</u>

By carrying out the reaction as in Example 2,

but from 7.21 g of methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, prepared in the preceding example, from 50 cm^3 of a normal aqueous sodium hydroxide solution and from 100 cm^3 of dioxane for three hours at reflux, 3.44 g of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after crystallization from 80 cm^3 of an ethanol/water (75/25 by volume) mixture, in the form of a white crystalline powder, the characteristics of which are as follows:

- melting point = 241°C
- mass spectrum (EI): M/Z = 521 (M^+)

EXAMPLE 63

<u>Preparation of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide</u>

By carrying out the reaction as in Example 42, but from 522 mg of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, from 0.122 cm^3 of 3-(aminomethyl)pyridine, from 0.23 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and

from 80 mg of N-1-hydroxybenzotriazole hydrate in 15 cm^3 of dichloromethane, 462 mg of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide are obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 238°C (dec)
- mass spectrum (EI): M/Z = 611 (M^+)
- ^1H N.M.R. spectrum (400 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.40, 1.60, 199 and 2.14 (4 mts, each 1H, CH_2CH_2), 3.29 and 3.41 (respectively dd and d (broad), J = 12 and 9 Hz and J = 12 Hz, each 1H, CH_2 at 1), 3.26 (broad t, J = 8.5 Hz, 2H, $ArCH_2$ of the 2,3-dihydrobenzofuran), 3.47 and 4.17 (2d, J = 12.5 Hz, each 1H, CH_2 at 3), 3.53 (mt, 1H, CH at 9a), 3.56 (broad s, 1H, CH at 4), 3.70 (s, 3H, $ArOCH_3$), 4.22 (AB, J = 15 and 6 Hz, 2H, NCH_2Ar), 4.60 (t, J = 8.5 Hz, 2H, CH_2O of the 2,3-dihydrobenzofuran), 5.52 and 5.68 (2 s, each 1H, $=CH_2$), 6.48 (mt, 1H, H at 8), from 6.75 to 7.50 (mt, 12H, H at 5, H at 6, H at 7, aromatic H of the 2-methoxyphenyl, aromatic H of the 2,3-dihydrobenzofuran, H at the 4 position of the pyridyl and H at the 3 position of the pyridyl), 7.96 (mt, 1H, CONH), 8.38 (broad s, 1H, H at 2 of the pyridyl), 8.44 (broad d, J = 5 and 1.5 Hz, 1H, H at 6 of the pyridyl).

EXAMPLE 64

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage A of Example 39, but from 2.8 g of 4-fluorobromobenzene, from 0.4 g of magnesium turnings in 20 cm^3 of diethylether and from 2.9 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 20 cm^3 of diethyl ether, 1.2 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(4-fluorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after crystallization from 40 cm^3 of an isopropanol/diisopropyl ether (50/50 by volume) mixture, in the form of a white solid, the characteristic of which is as follows:

- melting point = 130°C.

The purification of this filtrate by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (80/20 by volume) mixture, makes it possible to obtain an additional 1.2 g.

Stage B

By carrying out the reaction as in Stage C of Example 38, but from 2.2 g of methyl (3aRS,4SR)-2-

benzyl-7-(4-fluorophenyl)-7-hydroxy-4-phenyl-2,3,3a,4,5,6-hexahydroisoindole-3a-carboxylate, from 6.3 cm^3 of trifluoromethanesulphonic acid and from 21 cm^3 of dichloromethane, 1.0 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after recrystallization from 24 cm^3 of diisopropyl ether, in the form of a white solid, the characteristic of which is as follows:

- melting point = 135°C.

By concentrating the filtrate and crystallization from 25 cm^3 of petroleum ether, an additional 0.75 g is obtained.

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 1.5 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.64 g of ammonium formate and from 0.2 g of 10% (w/w) palladium-on-charcoal, 1.0 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained in the form of a white solid, the characteristic of which is as follows:

- melting point = 145°C.

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 1.0 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.51 g of 2-(2-methoxyphenyl)propenoic acid, from 0.24 cm^3 of oxalyl chloride and from 0.79 cm^3 of triethylamine, 0.7 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after crystallization from 16 cm^3 of isopropanol, in the form of a white solid, the characteristic of which is as follows:

- melting point = 165°C

EXAMPLE 65

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 0.85 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 8.5 cm^3 of a normal aqueous sodium hydroxide solution and from 15 cm^3 of methanol, 0.65 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-

carboxylic acid is obtained, after crystallization from aqueous acidic medium, the characteristic of which compound is as follows:

- melting point = 170°C.

EXAMPLE 66

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 1, but from 6.3 g of 4-chloro-3-fluorobromobenzene, from 0.73 g of magnesium turnings and from 5.45 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, 4.8 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(4-chloro-3-fluorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (95/5 by volume) mixture, and recrystallization from 75 cm^3 of isopropanol, in the form of a white solid, the characteristic of which is as follows:

- melting point = 175°C.

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 4.6 g of methyl (3aRS,4SR,7RS,7aSR)-2-benzyl-7-(4-chloro-3-

fluorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate, from 12.4 cm^3 of trifluoromethanesulphonic acid and from 50 cm^3 of dichloromethane, 3 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after crystallization from 25 cm^3 of isopropanol, in the form of a white solid, the characteristic of which is as follows:

- melting point = 136°C.

Stage C

By carrying out the reaction as in Stage C of Example 51, but from 2.8 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and from 1.95 cm^3 of vinyl chloroformate in 40 cm^3 of dichloromethane, and by then treating the intermediate, dissolved in 40 cm^3 of methanol, with 59 cm^3 of a normal solution of hydrogen chloride gas in diethyl ether, 1 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (97.5/2.5 by volume) mixture, in the form of a yellow foam, used as is in the subsequent syntheses.

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 1.4 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.67 g of 2-(2-methoxyphenyl)propenoic acid, from 0.33 cm^3 of oxalyl chloride and from 1.06 cm^3 of triethylamine, 1.5 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture, and recrystallization from an isopropanol/diisopropyl ether (1/1 by volume) mixture, the characteristic of which compound is as follows:

- melting point = 173°C.

EXAMPLE 67

Preparation of (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 1.2 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 3.3 cm^3 of a normal aqueous sodium hydroxide solution and [lacuna]

20 cm^3 of ethanol, 1.15 g of (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 5 cm^3 of isopropanol, the characteristic of which compound is as follows:

- melting point = 170°C.

EXAMPLE 68

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 1, but from 3.68 cm^3 of 3-bromotoluene, from 0.73 g of magnesium turnings and from 5.45 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, 4.2 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(3-methylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate are obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (95/5 by volume) mixture, and recrystallization from 75 cm^3 of isopropanol, in the form of an orangey-yellow foam, used as is in the subsequent syntheses.

Stage B

By carrying out the reaction as in Stage C of

Example 38, but from 4.2 g of methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-hydroxy-7-(3-methylphenyl)-4-phenyloctahydroisoindole-3a-carboxylate, from 12.4 cm^3 of trifluoromethanesulphonic acid and from 42 cm^3 of dichloromethane, 4 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of an orange-coloured foam, used as is in the subsequent syntheses.

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 4 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 1.73 g of ammonium formate and from 0.75 g of 10% (w/w) palladium-on-charcoal, 3 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a yellow oil, used as is in the subsequent syntheses.

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 3 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 1.54 g of 2-(2-methoxyphenyl)propenoic acid, from 0.74 cm^3 of oxalyl chloride and from 2.45 cm^3 of triethylamine,

2.5 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture, and recrystallization from 10 cm^3 of isopropanol, the characteristic of which compound is as follows:

- melting point = 142°C.

EXAMPLE 69

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 2.2 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 8.7 cm^3 of a normal aqueous sodium hydroxide solution and [lacuna] 22 cm^3 of ethanol, 1.75 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after recrystallization from 50 cm^3 of isopropanol, the characteristic of which compound is as follows:

- melting point = 252°C.

EXAMPLE 70

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage A of Example 31, but from 5.9 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, from 2.5 cm^3 of veratrole and from 6.3 cm^3 of trifluoromethanesulfonic acid in 26 cm^3 of dichloromethane, 1.8 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3,4-dimethoxyphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (90/10 by volume) mixture, in the form of a colourless oil, used as is in the subsequent syntheses.

Stage B

A solution of 1.8 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3,4-dimethoxyphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in 20 cm^3 of dichloromethane is added to 22.3 cm^3 of boron tribromide cooled to a temperature in the region of -50°C. The reaction mixture is stirred for one hour at a temperature in the region of -50°C and then 75 cm^3 of a

saturated aqueous sodium hydrogencarbonate solution are added. The aqueous phase is separated by settling and extracted with two times 25 cm^3 of dichloromethane. The organic phases are combined, washed with three times 15 cm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (97.5/2.5 by volume) mixture. 0.8 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3,4-dihydroxyphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, in the form of an orange oil used as is in the subsequent syntheses, and 1.0 g of a mixture of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-hydroxy-4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-hydroxy-3-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, in the form of an orange oil used as is in the subsequent syntheses, are thus obtained.

Stage C

A solution of 1.8 g of potassium carbonate in 4 cm^3 of distilled water and then 60 mg of Adogen 464 are added to a solution of 0.58 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3,4-dihydroxyphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in 4 cm^3 of

dibromomethane. The reaction mixture is heated at reflux with stirring for 90 minutes, then cooled to a temperature in the region of 20°C and diluted with 25 cm^3 of dichloromethane. The aqueous phase is separated by settling and extracted with two times 15 cm^3 of dichloromethane. The organic phases are combined, washed with three times 15 cm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. 0.8 g of a crude product is thus obtained, which product is combined with a second batch of 0.4 g originating from another experiment. The purification of this mixture by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (90/10 by volume) mixture, provides 0.45 g of methyl (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-2-benzyl-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in the form of a white foam, used as is in the subsequent syntheses, the characteristics of which are as follows:

- ^1H N.M.R. spectrum (400 MHz, $CDCl_3$, at a temperature of 333K, δ in ppm): 1.43, 1.65 and 2.47 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), from 2.25 to 2.40 (mt, 1H, 1H of the CH_2 at 1), 2.36 (d, J = 10 Hz, 1H, 1H of the CH_2 at 3), 2.77 (broad d, J = 9.5 Hz, 1H, the other H of the CH_2 at 1), from 3.15 to 3.25 (mt, 1H, CH at 9a), 3.21 (d, J = 10 Hz, 1H, the other H of the CH_2 at 3), 3.39 (broad s, 1H, CH at 4), 3.43 and 3.67 (2 d,

J = 13 Hz, each 1H, NCH_2Ar), 3.55 (s, 3H, $COOCH_3$), 5.98 (limit AB, 2H, OCH_2O), 6.63 (broad d, J = 7.5 Hz, 1H, H at 8), 6.85 and 6.91 (2 broad d, J = 8.5 Hz, each 1H, H at 6 and H at 7 of the 1,3-benzodioxol), 6.96 (broad s, 1H, H at 4 of the 1,3-benzodioxol), from 7.00 to 7.35 (mt, 8H, H at 5, H at 6, H at 7 and aromatic H of the benzyl).

Stage D

By carrying out the reaction as in Stage E of Example 1 but from 0.5 g of methyl (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-2-benzyl-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.21 g of ammonium formate and from 70 mg of 10% (w/w) palladium-on-charcoal, 0.25 g of methyl (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained in the form of a white solid, used as is in the subsequent syntheses.

Stage E

By carrying out the reaction as in Stage G of Example 1, but from 0.25 g of methyl (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.12 g of 2-(2-methoxyphenyl)-propenoic acid, from 0.06 cm^3 of oxalyl chloride and from 0.19 cm^3 of triethylamine, 0.26 g of methyl (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-4,9-

ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (97.5/2.5 by volume) mixture, in the form of a white foam, used as is in the subsequent syntheses.

Stage F

By carrying out the reaction as in Example 2, but from 0.26 g of (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 2.4 cm^3 of a normal aqueous sodium hydroxide solution and [lacuna] 5 cm^3 of methanol, 80 mg of (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (97.5/2.5 by volume) mixture, and crystallization from 2.5 cm^3 of diisopropyl ether, the characteristic of which compound is as follows:

- melting point = 204°C.

EXAMPLE 71

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage A of Example 31, but from 10.34 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 40 cm^3 of dichloromethane, from 50 cm^3 of ortho-xylene, from 24 cm^3 of 99% trifluoromethanesulphonic acid and from 6.5 cm^3 of trifluoromethanesulphonic anhydride under an argon atmosphere for 23 hours at a temperature in the region of 20°C, 7.27 g of impure methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3,4-dimethylphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a colourless oil, which can be used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (DCI): M/Z = 452 ($M+H^+$).

Stage B

By carrying out the reaction as in Stage E of Example 1, but from 9.51 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3,4-dimethylphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, obtained as in the preceding stage, from 4 g of ammonium formate, from

0.5 g of 10% (w/w) palladium-on-charcoal in 150 cm^3 of methanol and from 100 cm^3 of dioxane at a temperature in the region of 50°C for six hours, after flash chromatography on 500 g of silica gel, elution being carried out successively with one dm^3 of pure dichloromethane, then one dm^3 of the dichloromethane/ethanol (98/2 by volume) mixture, then one dm^3 of the dichloromethane/ethanol (95/5 by volume) mixture, then dm^3 litres of the dichloromethane/ ethanol (90/10 by volume) mixture and then the dichloromethane/ethanol (80/20 by volume) mixture, 5.79 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a slightly foamy colourless lacquer, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (DCI): M/Z = 361 (M^+).

Stage C

By carrying out the reaction as in Stage G of Example 1, but from a solution of 2.67 g of 2-(2-methoxyphenyl)propenoic acid in 50 cm^3 of dichloromethane containing 2 drops of N,N-dimethylformamide, from 1.31 cm^3 of oxalyl chloride, for 2 hours, and from a solution of 5.075 g of (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, obtained in the preceding stage, and from

4.4 cm^3 of triethylamine in 100 cm^3 of dichloromethane, and then running in 100 cm^3 of water after 1 hour, 3.4 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 163°C (dec)
- mass spectrum (EI): M/Z = 521 (M^+).

EXAMPLE 72

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3,4-dimethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 4.736 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate, obtained in the preceding stage, and from 36 cm^3 of a normal aqueous sodium hydroxide solution in 50 cm^3 of ethanol and 100 cm^3 of dioxane for sixteen hours at a temperature in the region of 70°C, 3.375 g of (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid are obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 200°C, then 245°C.
- N.M.R. spectrum No. 127748
- mass spectrum (EI): M/Z = 507 (M^+).

EXAMPLE 73

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage A of Example 31, but from 11.5 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate, from 13.1 cm^3 of anisole and from 21.2 cm^3 of trifluoromethanesulphonic acid in 120 cm^3 of dichloromethane, 12 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture, the characteristic of which compound is as follows:

- melting point = 150°C.

Stage B

By carrying out the reaction as in Stage E of Example 1, but from 11.4 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-

3a-carboxylate, from 4.76 g of ammonium formate and from 1 g of 10% (w/w) palladium-on-charcoal, 9 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, which product is used as is in the subsequent syntheses.

Stage C

By carrying out the reaction as in Stage G of Example 1, but from 8.9 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 4.36 g of 2-(2-methoxyphenyl)-propanoic acid, from 2.1 cm^3 of oxalyl chloride and from 6.9 cm^3 of triethylamine, 0.47 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), eluting being carried out with a cyclohexane/ethyl acetate (50/50 by volume) mixture, in the form of a white foam, the characteristic of which is as follows:

- melting point = 90°C.

EXAMPLE 74

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 11 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 42 cm^3 of a normal aqueous sodium hydroxide solution and [lacuna] 100 cm^3 of methanol, 2.15 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with dichloromethane/methanol (100/0 to 98/2 by volume) mixtures, the characteristic of which compound is as follows:

- melting point = 165°C.

EXAMPLE 75

Isolation of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

9.2 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-

carboxylic acid, obtained in Example 74, are resolved, on a chiral silica column carrying N-(3,5-dinitrobenzoyl)-(R)-phenylalanine grafts, in 5 successive injections and by eluting with an n-heptane/dichloromethane/methanol (50/50/3 by volume) mixture. On collecting the first fractions eluted (retention time 42 min), 3.51 g of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after concentrating the solvent under reduced pressure, in the form of a white powder, the characteristics of which are as follows:

- melting point = 203°C
- mass spectrum (EI): M/Z = 509 (M^+)
- optical rotation: $[a]_{365}^{20}$ = + 71.7 +/- 1.2° (c = 0.5, methanol)

EXAMPLE 76

<u>Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide</u>

By carrying out the reaction as in Example 42, but from 1 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid, 0.24 cm^3 of 3-(aminomethyl)pyridine, 0.46 g of 1-ethyl-3-[3-

(dimethylamino)propyl]carbodiimide hydrochloride and 0.16 g of N-1-hydroxybenzotriazole hydrate, 0.72 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide is obtained, after crystallization from 11 cm^3 of an isopropanol/diisopropyl ether (10/90 by volume) mixture, the characteristic of which compound is as follows:

- melting point = 121°C.

EXAMPLE 77

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide

By carrying out the reaction as in Example 27, but from 1 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid, 0.25 cm^3 of N-phenylhydrazine, 0.45 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and 0.16 g of N-1-hydroxybenzotriazole hydrate, 0.9 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide is obtained, after crystallization from 11 cm^3 of an isopropanol/diisopropyl ether (10/90 by volume)

mixture, the characteristic of which compound is as follows:

- melting point = 180°C.

EXAMPLE 78

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid

Stage A

A solution of 0.83 g of O-benzylhydroxylamine and of 0.73 cm^3 of triethylamine in 10 cm^3 of dichloromethane is added to a solution of 2.2 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, of 1 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide [lacuna] and of 0.35 g of N-1-hydroxybenzotriazole hydrate in 10 cm^3 of dichloromethane. The reaction mixture is stirred for twenty-four hours at a temperature in the region of 20°C and then 15 cm^3 of distilled water are added. The organic phase is separated by settling, washed with 20 cm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. The residue is crystallized from 25 cm^3 of an isopropanol/diisopropyl ether (20/80 by volume) mixture. 2.03 g of benzyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-

1H-benzo[f]isoindole-3-hydroxamate are thus obtained in [lacuna] of a white solid, the characteristic of which is as follows:

- melting point = 201°C.

Stage B

By carrying out the reaction as in Example 16, but from 1.84 g of benzyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3-hydroxamate, from 1 g of aluminium chloride and from 0.98 cm^3 of anisole, 0.5 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid is obtained, after flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (90/10 by volume) mixture, in the form of an ecru solid, the characteristic of which is as follows:

- melting point = 165°C.

EXAMPLE 79

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(3-pyridyl)carbohydrazide

By carrying out the reaction as in Example 27, but from 1 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)-

propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid, 0.26 g of N-(3-pyridyl)-hydrazine, 0.45 g of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride and from 0.16 g of N-1-hydroxybenzotriazole hydrate, 0.6 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(3-pyridyl)carbohydrazide is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with dichloromethane/methanol (95/5, then 90/10, by volume) mixtures, and recrystallization from isopropanol, the characteristic of which compound is as follows:

- melting point = 180°C.

EXAMPLE 80

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-thienylmethyl)carboxamide

By carrying out the reaction as in Example 42, but from 1 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid, 0.2 g of 3-aminomethyl-thiophene, 0.45 g of 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride and 0.16 g of N-1-hydroxybenzotriazole hydrate, 1 g of

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-thienylmethyl)carboxamide is obtained, after recrystallization from 11 cm^3 of an isopropanol/diisopropyl ether (10/90 by volume) mixture, the characteristic of which compound is as follows:

- melting point = 130°C.

EXAMPLE 81

Preparation of (RS)- and (SR)-2-{(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carbonylamino}phenylacetic acids

Stage A

By carrying out the reaction as in Example 42, but from 1.27 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid, 0.61 g of methyl phenylglycinate hydrochloride, 0.59 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, 0.42 cm^3 of triethylamine and 0.2 g of N-1-hydroxy-benzotriazole hydrate, 1 g of a mixture of methyl (RS)- and (SR)-2-{(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carbonylamino}phenylacetates is obtained, after flash chromatography on silica gel (230-400 mesh), elution

being carried out with a dichloromethane/methanol (99/1 by volume) mixture, in the form of a foam, used as is in the subsequent syntheses.

Stage B

By carrying out the reaction as in Example 2, but from 0.6 g of a mixture of methyl (RS)- and (SR)-2-{(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carbonylamino}phenylacetates in 1.83 cm^3 of a normal aqueous sodium hydroxide solution and 20 cm^3 of ethanol, 0.5 g of crude product is obtained, which is combined with a second batch of 0.65 g originating from another experiment. The purification of this mixture, by recrystallization from 50 cm^3 of an isopropanol/diisopropyl ether (50/50 by volume) mixture, provides 1.05 g of an equimolar mixture of (RS)- and (SR)-2-{(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carbonylamino}phenylacetic acids, the characteristics of which are as follows:

- melting point = 196°C
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm). The mixture of the two diastereoisomers is observed in the proportions 50/50. * 1.38, 1.60, 1.98 and 2.14 (4 mts, each 1H, CH_2CH_2), from 3.15 to 3.80 (mt, 5H, CH_2 at 1, 1H of the CH_2 at 3, CH at 9a and CH at 4), 3.64, 3.71 and 3.84 (3 s, 6H in

all, the 2 $ArOCH_3$), from 4.20 to 4.45 (mt, 1H, the other H of the CH_2 at 3), 5.19 (mt, 1H, NCHAr), 5.47, 5.51, 5.66 and 5.69 (4 broad s, 2H in all, $=CH_2$), 6.42 (mt, 1H, H at 8), from 6.80 to 7.50 (mt, 16H, H at 5, H at 6, H at 7, aromatic H of the 4-methoxyphenyl, aromatic H at the 2-methoxyphenyl and aromatic H of the phenyl), 7.98 and 8.02 (2 broad s, 1H in all, CONH).

EXAMPLE 82

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage C of Example 45, but from 1.51 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-phenyl-2,3,a,4,5,7a-hexahydroisoindole-3a-carboxylate, from 0.17 g of tetrakis(triphenylphosphine)palladium, from 0.73 g of 4-trifluoromethoxyphenylboronic acid, obtained in trimeric anhydride form by carrying out the reaction as in Patent D.E. 4,218,614, and [lacuna] 1.5 g of sodium carbonate at reflux for two hours in 15 cm^3 of toluene and 13 cm^3 of methanol, 1.2 g (79%) of methyl (3aRS,4SR,7aRS)-2-benzyl-4-phenyl-7-(4-trifluoromethoxyphenyl)-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and

ethyl acetate (80/20 by volume), in the form of a pale-yellow oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 507 (M^+).

Stage B

By carrying out the reaction as in Stage C of Example 38, but from 0.48 g of methyl (3aRS,4SR,7aRS)-2-benzyl-4-phenyl-7-(4-trifluoromethoxyphenyl)-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate and from 1.18 cm^3 of trifluoromethanesulphonic acid in 2 cm^3 of dichloromethane for two hours at room temperature, 0.43 g (89%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-40 mesh), elution being carried out with a mixture of cyclohexane and ethyl acetate (90/10 by volume), in the form of a beige paste, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 507 (M^+).

Stage C

By carrying out the reaction as in Stage B of Example 47, but from 0.83 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-4,9-ethano-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate and from 0.29 cm^3 of vinyl chloroformate for eighteen hours at room temperature in 10 cm^3 of dichloromethane, and by then taking the concentrate up

in 20 cm^3 of a normal solution of hydrogen chloride gas in isopropanol at reflux for one hour, 0.59 g (75%) of methyl (3aRS,4SR,9RS,9aRS)-4,9-ethano-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after neutralization with a normal aqueous sodium hydroxide solution and then extraction with dichloromethane and concentration of the solvent under reduced pressure, in the form of a white foam, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 417 (M^+).

Stage D

By carrying out the reaction as in Stage E of Example 5, but from 0.59 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 0.25 g of 2-(2-methoxyphenyl)-propanoic acid, from 0.2 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 27 mg of N-1-hydroxybenzotriazole hydrate in 15 cm^3 of dichloromethane for eighteen hours at room temperature, 0.41 g (53%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (60/40 by volume), in the form of a

light-beige powder, the characteristics of which are as follows:

- melting point = 86°C
- mass spectrum (EI): M/Z = 577 (M^+)

Stage E

By carrying out the reaction as in Example 2, but from 0.38 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate at reflux for four hours in 13 cm^3 of a decinormal aqueous sodium hydroxide solution and 13 cm^3 of methanol, 200 mg (54%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by recrystallization from pentane, in the form of a white solid, the characteristics of which are as follows:

- melting point = 160°C
- mass spectrum (EI): M/Z = 563 (M^+).

EXAMPLE 83

<u>Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate</u>

Stage A

By carrying out the reaction as in Stage C of Example 45, but from 11.61 g of methyl (3aRS,4SR,7aRS)-

2-benzyl-7-iodo-4-phenyl-2,3,a,4,5,7a-hexahydroisoindole-3a-carboxylate, from 1.33 g of tetrakis(triphenylphosphine)palladium, from 5.46 g of 3-bromophenylboronic acid, obtained in the trimeric anhydride form, and from 11.5 g of sodium carbonate at reflux for two hours in 70 cm^3 of toluene and 50 cm^3 of methanol, 8.5 g (75%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(3-bromophenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (80/20 by volume), in the form of a pale-yellow oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 502 (M^+).

Stage B

By carrying out the reaction as in Stage C of Example 38, but from 8.6 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(3-bromophenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate and from 25 cm^3 of trifluoromethanesulphonic acid in 25 cm^3 of dichloromethane for two hours at room temperature, 4.58 g (64%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (90/10 by

volume), in the form of a beige powder, the characteristics of which are as follows:

- melting point = 74°C
- mass spectrum (EI): M/Z = 502 (M^+).

Stage C

By carrying out the reaction as in Stage B of Example 47, but from 1.88 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate and from 0.6 cm^3 of vinyl chloroformate for two hours at room temperature in 15 cm^3 of dichloromethane, and by then taking the concentrate up in 30 cm^3 of a 2M solution of hydrogen chloride gas in methanol at reflux for three hours, 1.72 g (76%) of methyl (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride are obtained, after crystallization from diisopropyl ether, in the form of white crystals, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 412 (M^+).

Stage D

By carrying out the reaction as in Stage E of Example 5, but from 1.72 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, from 0.68 g of 2-(2-methoxyphenyl)propenoic acid, from 0.73 g of

1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, from 50 mg of N-1-hydroxybenzotriazole hydrate and from 0.54 cm^3 of triethylamine in 15 cm^3 of dichloromethane for eighteen hours at room temperature, 0.58 g (27%) of methyl (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (70/30 by volume), in the form of a light-beige powder, the characteristics of which are as follows:

- melting point = 184-5°C
- mass spectrum (EI): M/Z = 572 (M^+).

EXAMPLE 84

<u>Preparation of (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid</u>

By carrying out the reaction as in Example 2, but from 0.50 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate at reflux for four hours in 70 cm^3 of a decinormal aqueous sodium hydroxide solution and 70 cm^3 of methanol, 170 mg (35%) of (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-

1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by recrystallization from a mixture of water and of ethanol (90/10 by volume), in the form of a white solid, the characteristics of which are as follows:

- melting point: 164°C
- mass spectrum (EI): M/Z = 558 (M^+).

EXAMPLE 85

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 1, but from 2 g of magnesium turnings, from 9.1 cm^3 of 3-fluorobromobenzene, in 60 cm^3 of diethyl ether, then in 20 cm^3 of toluene, and then from 15 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 60 cm^3 of toluene, 21.29 g of impure methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-7-(3-fluorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate are obtained in the form of a brown oil, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (DCI): M/Z = 460 ($M+H^+$).

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 21.29 g of methyl

(3aRS,4SR,9RS,9aRS)-2-benzyl-7-(3-fluorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-3a-carboxylate and from 40 cm^3 of 99% trifluoromethanesulphonic acid in 300 cm^3 of dichloromethane under an argon atmosphere for forty-three hours at a temperature in the region of 20°C, 14.38 g of impure methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a brown oil, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 441 (M^+).

Stage C

By carrying out the reaction as in Stage E of Example 1, but from 14.38 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 5.53 g of ammonium formate and from 1.8 g of 10% (w/w) palladium-on-charcoal in 200 cm^3 of methanol for sixteen hours at reflux, 10.36 g of impure methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a brown oil, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 351 (M^+).

Stage D

By carrying out the reaction as in Stage G of

Example 1, but from a solution of 5.66 g of 2-(2-methoxyphenyl)propenoic acid in 50 cm^3 of dichloromethane containing 2 drops of N,N-dimethylformamide, from 2.75 cm^3 of oxalyl chloride, for two hours, from a solution of 10.36 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, obtained in the preceding stage, and from 7.3 cm^3 of triethylamine in 100 cm^3 of dichloromethane, 3.59 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are then obtained, after crystallization from petroleum ether (40-60°C), in the form of a beige powder, the characteristics of which are as follows:

- melting point = 151°C.
- ^1H N.M.R. spectrum (250 MHz, $(CD_3)_2SO$, d in ppm): 1.43, 1.67, 2.00 and 2.14 (4 mts, 1H: CH_2CH_2), from 3.30 to 3.45 (mt, 3H, CH_2 at 1 and CH at 9a), 3.46 (mt, 1H, CH at 4), 3.54 (s, 3H, $COOCH_3$), 3.61 and 4.09 (respectively d and d (broad), J = 12.5 Hz, each 1H, CH_2 at 3), 3.71 (s, 3H, $ArOCH_3$), 5.5 and 5.68 (2s, each 1H, CH_2 [lacuna], 6.41 (broad d, J = 7.5 Hz, 1H, H at 8), from 6.90 to 7.40 (mt, 10H, H at 6, at 7 and aromatic H of the 3-fluorophenyl), 7.54 (broad q, J = 7.5 Hz, 1H, H at 5 of the 3-fluorophenyl)
- mass spectrum (EI): M/Z = 511 (M^+).

EXAMPLE 86

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 1.02 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate, obtained as in the preceding stage, and from 24 cm^3 of a normal aqueous sodium hydroxide solution in 30 cm^3 of dioxane for eighteen hours at reflux, 0.71 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid is obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 161°C.
- mass spectrum (EI): M/Z = 497 (M^+).

EXAMPLE 87

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

By carrying out the reaction as in Example 42, but from 0.52 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)-

propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid, from 0.128 cm^3 of 3-(aminomethyl)pyridine, from 0.24 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 85 mg of N-1-hydroxybenzotriazole hydrate in 30 cm^3 of dichloromethane, 183.6 mg of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-N-(3-pyridylmethyl)carboxamide are obtained, after sixteen hours at a temperature in the region of 20°C, in the form of an ecru powder, the characteristics of which are as follows:

- melting point = 223°C.
- mass spectrum (EI): M/Z = 587 (M^+).

EXAMPLE 88

<u>Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(3-chloro-phenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate</u>

Stage A

By carrying out the reaction as in Stage C of Example 1, but from 2 g of magnesium turnings, from 9.75 cm^3 of 3-chlorobromobenzene, in 60 cm^3 of diethyl ether, then in 20 cm^3 of toluene, and then from 15 g of methyl (3aRs,4SR,7aRS)-2-benzyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate in 60 cm^3 of toluene, 31.2 g of impure methyl (3aRS,4SR,7RS,7aRS)-2-benzyl-7-(3-chlorophenyl)-7-hydroxy-4-phenyloctahydroisoindole-

3a-carboxylate, which are used as is in the following stage, are obtained in the form of an orange-coloured oil, the characteristic of which is as follows:

- mass spectrum (DCI): M/Z = 476 ($M+H^+$).

Stage B

By carrying out the reaction as in Stage D of Example 1, but from 31.2 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(3-chlorophenyl)-7-hydroxy-4-phenyloctahydro-isoindole-3a-carboxylate, obtained in the preceding stage, and from 40 cm^3 of 99% trifluoromethanesulphonic acid in 300 cm^3 of dichloromethane under an argon atmosphere for four days at a temperature in the region of 20°C, 23.88 g of impure methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3-chlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of an oil, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 457 (M^+).

Stage C

By carrying out the reaction as in Stage B of Example 47, but from 23.88 g of impure methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3-chlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 5.4 cm^3 of vinyl chloroformate and from 11.5 g of potassium carbonate in 200 cm^3 of dichloromethane for sixteen hours at a temperature in the region of 20°C, 24.4 g of impure methyl

(3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-vinyloxycarbonyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a brown oil, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 437 (M^+).

After taking this oil up again for eighteen hours in a 6N solution of hydrogen chloride gas in dioxane, 18.28 g of impure methyl (3aRS,4SR,9SR,9aRS)-7-(3-chlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride are obtained in the form of a thick brown oil, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 368 (M^+).

Stage D

By carrying out the reaction as in Stage G of Example 1, but from a solution of 8.76 g of 2-(2-methoxyphenyl)propenoic acid in 50 cm^3 of dichloromethane containing 2 drops of N,N-dimethylformamide, from 4.21 cm^3 of oxalyl chloride, for two hours thirty minutes, then from a solution of 18.5 g of methyl (3aRS,4SR,9SR,9aRS)-7-(3-chlorophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, obtained in the preceding stage, and from 11.5 cm^3 of triethylamine in 100 cm^3 of dichloromethane, then running in 100 cm^3 of water after forty-two hours, 0.95 g of methyl (3aRS,4SR,9SR,9aRS)-

9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate is obtained in the form of a beige powder, the characteristics of which are as follows, the characteristics of which are as follows:

- melting point = 159°C.
- mass spectrum (EI): M/Z = 527 (M^+).

EXAMPLE 89

Preparation of (3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 795 mg of methyl (3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate, obtained as in the preceding stage, and from 30 cm^3 of a normal aqueous sodium hydroxide solution in 30 cm^3 of dioxane for eighteen hours at reflux, 0.77 g of (3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid is obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 170°C
- mass spectrum (EI): M/Z = 513 (M^+).

EXAMPLE 90

Preparation of (3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

By carrying out the reaction as in Example 42, but from 0.46 g of (3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid, from 0.11 cm^3 of 3-(aminomethyl)pyridine, from 0.21 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride and from 70 mg of N-1-hydroxybenzotriazole hydrate in 30 cm^3 of dichloromethane, 269.8 mg of (3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-N-(3-pyridylmethyl)carboxamide are obtained, after sixteen hours at a temperature in the region of 20°C, in the form of an off-white powder, the characteristics of which are as follows:

- melting point = 244°C.
- mass spectrum (EI): M/Z = 603 (M^+).

EXAMPLE 91

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 45, but from 2.5 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-phenyl-2,3,3a,4,5,7a-hexahydroisoindole-3a-carboxylate, from 0.30 g of tetrakis(triphenylphosphine)palladium, from 0.77 g of 3-N,N-dimethylaminophenylboronic acid, obtained in the trimeric anhydride form, and [lacuna] 20 cm^3 of a 2M aqueous sodium carbonate solution at reflux for seven hours in 20 cm^3 of toluene and 10 cm^3 of methanol, 2.09 g (85%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(3-N,N-dimethylaminophenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (90/10 by volume), in the form of an orange-coloured pasty solid, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 466 (M^+)

Stage B

The reaction is carried out as in Stage B of Example 39, but from 2.09 g of methyl (3aRS,4SR,7aRS)-

2-benzyl-7-(3-N,N-dimethylaminophenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate and from 20 cm^3 of pure trifluoromethanesulphonic acid for four days at room temperature. After neutralization with a 30% aqueous sodium hydroxide solution in the presence of dichloromethane, the organic phase is separated by settling, then washed with water and dried over magnesium sulphate, and then stirred for one hour with 20 g of silica gel (230-400 mesh). After concentrating the solvent under reduced pressure, 1.74 g (83 %) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are then obtained in the form of a yellow pasty solid, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 466 (M^+).

Stage C

The reaction is carried out as in Stage B of Example 47, but from 2.21 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3-N,N-dimethylamino-phenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 3 cm^3 of vinyl chloroformate and from 4.6 cm^3 of triethylamine for seven hours at room temperature in 20 cm^3 of dichloromethane. After hydrolysis, the organic phase is separated by settling and then concentrated under reduced pressure. After purification by flash

chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (85/15 by volume), 0.27 g (27 %) of methyl (3aRS,4SR,7aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2-vinyloxycarbonyl-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate is then obtained, which product is dissolved in [lacuna] cm^3 of methanol and heated at reflux for five hours in the presence of 5 cm^3 of a 5M solution of hydrogen chloride gas in dioxane. After crystallization from diisopropyl ether, 0.68 g (98 %) of methyl (3aRS,4SR,7aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate dihydrochloride is thus obtained in the form of a white solid, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 376 (M^+).

Stage D

By carrying out the reaction as in Stage E of Example 5, but from 0.68 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate dihydrochloride, from 0.29 g of 2-(2-methoxyphenyl)propenoic acid, from 0.38 g of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, from 20 mg of N-1-hydroxybenzotriazole hydrate and from 0.42 cm^3 of triethylamine in 15 cm^3 of dichloromethane for twenty-four hours at room temperature, 0.27 g (33%) of methyl

(3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (70/30 by volume), and then recrystallization from pentane, in the form of a white powder, the characteristics of which are as follows:

- melting point = 95°C
- mass spectrum (EI): M/Z = 536 (M^+).

EXAMPLE 92

Preparation of (3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid

By carrying out the reaction as in Example 2, but from 0.23 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate at reflux for five hours in 2 cm^3 of a normal aqueous sodium hydroxide solution and 5 cm^3 of ethanol, 120 mg (55%) of (3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid are obtained, after purification by recrystallization from a mixture of dichloromethane and of pentane (50/50 by volume), in

the form of a white solid, the characteristics of which are as follows:

- melting point = 194°C
- mass spectrum (EI): M/Z = 522 (M^+).

EXAMPLE 93

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(3-aminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride

Stage A

By carrying out the reaction as in Stage C of Example 45, but from 2.5 g of methyl (3aRS,4SR,7RS)-2-benzyl-7-iodo-4-phenyl-2,3,3a,4,5,7a-hexahydroisoindole-3a-carboxylate, from 0.30 g of tetrakis(triphenylphosphine)palladium, from 0.72 g of 3-aminophenylboronic acid and from 20 cm^3 of a 2M aqueous sodium carbonate solution at reflux for seven hours in 20 cm^3 of toluene and 10 cm^3 of methanol, 1.60 g (70%) of methyl (3aRS,4SR,7aRS)-7-(3-aminophenyl)-2-benzyl-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and ethyl acetate (80/20 by volume), in the form of an orange-coloured solid, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 438 (M^+).

Stage B

The reaction is carried out as in Stage B of Example 39, but from 0.20 g (0.4 mmol) of methyl (3aRS,4SR,7aRS)-7-(3-aminophenyl)-2-benzyl-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate and from 5 cm^3 of pure trifluoromethanesulphonic acid for three days at room temperature. After neutralization with a 30% aqueous sodium hydroxide solution in the presence of dichloromethane, the organic phase is separated by settling, then washed with water and dried over magnesium sulphate, and then stirred for one hour with 20 g of silica gel (230-400 mesh). After concentrating the solvent under reduced pressure, 0.16 g (80%) of methyl (3aRS,4SR,9SR,9aRS)-9-(3-aminophenyl)-2-benzyl-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is then obtained in the form of a brown oil, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 438 (M^+).

Stage C

By carrying out the reaction as in Stage E of Example 45, but from 1.5 g of methyl (3aRS,4SR,9RS,9aRS)-9-(3-aminophenyl)-2-benzyl-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate and from 0.6 g of 10% (w/w) palladium-on-charcoal in 100 cm^3 of methanol and 3.5 cm^3 of hydrogen chloride gas as a 1M solution in methanol for eight hours at 50°C under a hydrogen atmosphere, 1.27 g

(79%) of methyl (3aRS,4SR,9RS,9aRS)-9-(3-aminophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate dihydrochloride are obtained, after crystallization from diisopropyl ether, in the form of a white solid, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 348 (M^+).

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 0.74 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3-aminophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate dihydrochloride, from 0.41 g of 2-(2-methoxyphenyl)propenoic acid, from 0.22 cm^3 of oxalyl chloride and from 0.76 cm^3 of triethylamine in 10 cm^3 of dichloromethane for twenty hours at room temperature, 0.20 g (21%) of methyl (3aRS,4SR,9SR,9aRS)-9-(3-aminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (50/50 by volume), and then recrystallization from diisopropyl ether, in the form of a white powder, the characteristics of which are as follows:

- melting point = 186°C
- mass spectrum (EI): M/Z = 508 (M^+).

EXAMPLE 94

Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(4-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate

Stage A

By carrying out the reaction as in Stage C of Example 45, but from 1.15 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-phenyl-2,3,a,4,5,7a-hexahydroisoindole-3a-carboxylate, from 0.12 g of tetrakis(triphenylphosphine)palladium, from 0.44 g of 4-N,N-dimethylaminophenylboronic acid and from 15 cm^3 of a 2M aqueous sodium carbonate solution at reflux for four hours in 20 cm^3 of toluene and 10 cm^3 of methanol, 0.93 g (82%) of methyl (3aRs,4SR,7aRS)-2-benzyl-7-(4-N,N-dimethylaminophenyl)-4-phenyl-2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate is obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (80/20 by volume), in the form of an orange-coloured oil, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 466 (M^+).

Stage B

The reaction is carried out as in Stage B of Example 39, but from 0.53 g of methyl (3aRs,4SR,7aRS)-2-benzyl-7-(4-N,N-dimethylaminophenyl)-4-phenyl-

2,3,3a,4,5,7a-hexahydro-1H-isoindole-3a-carboxylate and from 10 cm^3 of pure trifluoromethanesulphonic acid for two days at room temperature. After neutralization with a 30% aqueous sodium hydroxide solution in the presence of dichloromethane, the organic phase is separated by settling, then washed with water and dried over magnesium sulphate. After concentrating the solvent under reduced pressure, the residue is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (90/10 by volume). 0.34 g (64%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-N,N-dimethylaminophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is then obtained in the form of a colourless oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 466 (M^+).

Stage C

By carrying out the reaction as in Stage E of Example 45, but from 0.34 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-9-(4-N,N-dimethylaminophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate and from 0.15 g of 10% (w/w) palladium-on-charcoal in 20 cm^3 of methanol, 10 cm^3 of chloroform and 1.5 cm^3 of a 1M solution of hydrogen chloride gas in methanol for 5 hours at 40°C under a hydrogen atmosphere, 0.31 g (96%) of methyl (3aRS,4SR,9RS,9aRS)-9-(4-N,N-dimethylaminophenyl)-4,9-

ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate dihydrochloride is obtained, after crystallization from diisopropyl ether, in the form of a light-green solid, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 376 (M^+).

Stage D

By carrying out the reaction as in Stage G of Example 1, but from 0.30 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-N,N-dimethylaminophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate dihydrochloride, from 0.13 g of 2-(2-methoxyphenyl)propenoic acid, from 0.07 cm^3 of oxalyl chloride and from 0.3 cm^3 of triethylamine in 5 cm^3 of dichloromethane for eighteen hours at room temperature, 0.18 g (50%) of methyl (3aRS,4SR,9SR,9aRS)-9-(4-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate and of a 28% ammonia solution (60/40/0.2 by volume), in the form of a white powder, the characteristics of which are as follows:

- melting point = 86-90°C
- mass spectrum (EI): M/Z = 536 (M^+).

EXAMPLE 95

Preparation of (3aRS,4SR,9SR,9aRS)-9-(4-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

1.15 g of tetrakis(triphenylphosphine)-palladium and 5.84 g of zinc cyanide are added to a solution, maintained under an argon atmosphere, of 5.02 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, obtained in Stage B of Example 49, in 50 cm^3 of dimethylformamide, the mixture is brought to reflux for five hours and is then stirred for an additional eighteen hours at room temperature, still under an argon atmosphere. After addition of water and of ethyl acetate, the organic phase is separated by settling, washed with water, dried over magnesium sulphate and concentrated under reduced pressure. The residue is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (95/5 by volume). 3.09 g (69%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(4-cyanophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are thus obtained in the form of a white powder, the characteristics of which are as follows:

- melting point = 158°C

- ^{1}H N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): 1.46, 1.70 and 2.49 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), from 2.25 to 2.40 and 2.63 (respectively mt and d, J = 10 Hz, each 1H, CH_2 at 1), 2.31 and 3.21 (2 d, J = 10 Hz, each 1H, CH_2 at 3), 3.23 (mt, 1H, CH at 9a), 3.41 and 3.63 (2 d, J = 12.5 Hz, each 1H, NCH_2Ar), 3.45 (broad s, 1H, CH at 4), 3.55 (s, 3H, $COOCH_3$), 6.43 (d, J = 7.5 Hz, 1H, H at 8), from 6.95 to 7.80 (mts, 12H, H at 5, H at 6, H at 7, aromatic H of the 4-cyanophenyl and aromatic H of the benzyl).
- mass spectrum (EI): M/Z = 448 (M^+).

Stage B

The reaction is carried out as in Stage B of Example 47, but from 0.80 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-9-(4-cyanophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate and from 1 cm^3 of vinyl chloroformate for twenty-four hours at room temperature in 20 cm^3 of dichloromethane. After hydrolysis, the organic phase is separated by settling and then concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (90/10 by volume), 0.69 g (91%) of methyl (3aRS,4SR,7aRS)-9-(4-cyanophenyl)-4,9-ethano-2-vinyloxycarbonyl-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate is then obtained, which compound is dissolved in 20 cm^3 of methanol and heated

at reflux for five hours in the presence of 5 cm^3 of a 5M solution of hydrogen chloride gas in dioxane. After crystallization from diisopropyl ether, 0.62 g (98%) of methyl (3aRS,4SR,9RS,9aRS)-9-(4-cyanophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate hydrochloride is thus obtained in the form of a white solid, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 358 (M^+).

Stage C

By carrying out the reaction as in Stage G of Example 1, but from 0.72 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-cyanophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, from 0.32 g of 2-(2-methoxyphenyl)propenoic acid, from 0.175 cm^3 of oxalyl chloride and from 0.55 cm^3 of triethylamine in 20 cm^3 of dichloromethane for eighteen hours at room temperature, 0.52 g (55%) of methyl (3aRS,4SR,9SR,9aRS)-9-(4-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and of ethyl acetate (70/30 by volume), in the form of a white powder, the characteristics of which are as follows:

- melting point = 90-2°C
- mass spectrum (EI): M/Z = 518 (M^+).

Stage D

By carrying out the reaction as in Example 2, but from 0.50 g of methyl (3aRS,4SR,9SR,9aRS)-9-(4-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate at reflux for five hours in 1.1 cm^3 of a normal aqueous sodium hydroxide solution and 20 cm^3 of ethanol, 220 mg (45%) of (3aRS,4SR,9SR,9aRS)-9-(4-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after purification by flash chromatography on silica gel, elution being carried out with a gradient of mixtures of cyclohexane and of ethyl acetate (from 95/5 to 50/50 by volume), in the form of a white solid, the characteristics of which are as follows:

- melting point = 182°C
- mass spectrum (EI): M/Z = 504 (M^+).

EXAMPLE 96

<u>Preparation of methyl (3aRS,4SR,9SR,9aRS)-9-(3-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate</u>

Stage A

By carrying out the reaction as in Stage A of Example 95, but from 2.69 g of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3-bromophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-

carboxylate, obtained in Stage B of Example 83, from 0.62 g of tetrakis(triphenylphosphine)palladium and [lacuna] 3.14 g of zinc cyanide in 50 cm^3 of dimethylformamide at reflux for five hours and then for an additional eighteen hours at room temperature under an argon atmosphere, 2.0 g (83%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-9-(3-cyanophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained, after purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a mixture of cyclohexane and ethyl acetate (90/10 by volume), in the form of a white powder, the characteristics of which are as follows:

- melting point = 88°C
- mass spectrum (EI): M/Z = 448 (M^+).

Stage B

By carrying out the reaction as in Stage B of Example 47, but from 2.0 g of methyl (3aRS,4SR,9RS,9aRS)-2-benzyl-9-(3-cyanophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate and from 0.6 cm^3 of vinyl chloroformate for 4 hours at room temperature in 20 cm^3 of dichloromethane, and by then taking the concentrate up in 20 cm^3 of methanol and 10 cm^3 of a normal solution of hydrogen chloride gas in isopropanol at reflux for 2 hours, 1.22 g (77%) of methyl (3aRS,4SR,9RS,9aRS)-9-(3-cyanophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-isoindole-3a-carboxylate are obtained, after

neutralization with a 5N aqueous sodium hydroxide solution and extraction with diethyl ether, in the form of a white foam, used as is in the following stage, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 358 (M^+).

Stage C

By carrying out the reaction as in Stage G of Example 1, but from 1.22 g of methyl (3aRS,4SR,9SR,9aRS)-9-(3-cyanophenyl)-4,9-ethano-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride, from 0.61 g of 2-(2-methoxyphenyl)propenoic acid, from 0.3 cm^3 of oxalyl chloride and from 0.96 cm^3 of triethylamine in 25 cm^3 of dichloromethane for 2 hours at room temperature, 0.75 g (48%) of methyl (3aRS,4SR,9SR,9aRS)-9-(3-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained, after purification on silica gel (230-400 mesh), elution being carried out with mixtures of cyclohexane and of ethyl acetate (95/5, then 80/20, by volume), in the form of a white powder, the characteristics of which are as follows:

- melting point = 176-8°C
- mass spectrum (EI): M/Z = 518 (M^+).

EXAMPLE 97

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-hydroxy-4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

By carrying out the reaction as in Stage E of Example 1, but from 3.1 g of a mixture of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(3-hydroxy-4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-hydroxy-3-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, obtained in Stage B of Example 70, from 1.25 g of ammonium formate and from 0.4 g of 10% (w/w) palladium-on-charcoal, 2.1 g of a mixture of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-hydroxy-4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-hydroxy-3-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of a colourless oil, used as is in the subsequent syntheses.

Stage B

By carrying out the reaction as in Stage G of Example 1, but from 2.1 g of a mixture of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-9-(3-hydroxy-4-

methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate and of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-hydroxy-3-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 1.0 g of 2-(2-methoxyphenyl)propenoic acid, from 0.47 cm^3 of oxalyl chloride and from 1.5 cm^3 of triethylamine, 0.4 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-hydroxy-4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, containing 5% of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-hydroxy-3-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, is obtained, after three flash chromatography operations on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol (96.5/3.5 by volume) mixture for the first, a dichloromethane/methanol (99/1 by volume) mixture for the second and a dichloromethane/methanol (99.5/0.5 by volume) mixture for the third, and after recrystallization from 25 cm^3 of acetonitrile, the characteristic of which compound is as follows:

- melting point = 242°C.

Stage C

By carrying out the reaction as in Example 2, but from 0.35 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-

ethano-9-(3-hydroxy-4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate, from 3.25 cm^3 of a normal aqueous sodium hydroxide solution and [lacuna] 5 cm^3 of methanol, 0.24 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-hydroxy-4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid is obtained, after recrystallization from 6 cm^3 of isopropanol, the characteristics of which compound are as follows:

- melting point = 278°C.
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.38, 1.56, 1.96 and 2.12 (4 mts, each 1H, CH_2CH_2), from 3.20 to 3.50 (mt, 3H, CH_2 at 1 and CH at 9a), 3.42 (mt, 1H: CH at 4), 3.59 and 4.06 (respectively d and d (broad), J = 12.5 Hz, each 1H, CH_2 at 3), 3.73 and 3.86 (2 s, each 3H, the two $ArOCH_3$, 5.54 and 5.69 (respectively d and s (broad), J = 1 Hz, each 1H, $=CH_2$), 6.52 (broad d, J = 7.5 Hz, 1H, H at 8), 6.73 (dd, J = 8 and 2 Hz, 1H, H at the 6 position of the 3-hydroxy-4-methoxyphenyl), 6.86 (d, J = 2 Hz, 1H, H at the 2 position of the 3-hydroxy-4-methoxyphenyl), from 6.90 to 7.40 (mt, 8H, H at 5, H at 6, H at 7, H at the 5 position of the 3-hydroxy-4-methoxyphenyl and aromatic H of the 2-methoxyphenyl), from 8.20 to 8.90 (broad unresolved peak, 1H, ArOH).

EXAMPLE 98

Preparation of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)-2-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

Stage A

77.5 g (1.1 mol) of methyl vinyl ketone and 1.1 dm^3 of a normal aqueous sodium hydroxide solution are successively added to a solution, cooled to 0°C, of 178 g (0.917 mol) of (2-methoxyphenyl)pyruvic acid, which can be obtained according to Org. Synth., 1939, 19, 1-3, in 970 cm^3 of methanol and then the mixture is stirred at a temperature in the region of 20°C for two hours. After neutralization with 1.1 dm^3 of a normal aqueous hydrochloric acid solution and concentration of the methanol, the precipitate formed is filtered off, washed with water and then dried at 20°C. 189.7 g (78%) of 6-(2-methoxyphenyl)-3-oxocyclohexan-1-ol-1-carboxylic acid are thus obtained in the form of a yellow powder, the characteristics of which are as follows:

- melting point = 204°C
- ^1H N.M.R. spectrum (250 MHz, $CDCl_3$, d in ppm): 1.20 (t, J = 7 Hz, 3H, CH_3 of the ethyl), 1.47 (d, J = 7 Hz, 3H, CH_3), 4.17 (q, J = 7 Hz, 2H, OCH_2 of the ethyl), 4.49 (q, J = 7 Hz, 1H, ArCH), from 7.15 to 7.45 (mt, 5H, aromatic H).

Stage B

396.7 g (1.5 mol) of 6-(2-methoxyphenyl)-3-oxocyclohexan-1-ol-1-carboxylic acid are heated at reflux for two hours in 13.3 dm^3 of toluene in the presence of 39.7 g of para-toluenesulphonic acid. The reaction mixture is subsequently concentrated under reduced pressure and the precipitate formed is filtered off, washed with isopropyl ether and then dried at 50°C. 288 g (78%) of (RS)-6-(2-methoxyphenyl)-3-oxocyclohexene-1-carboxylic acid are thus obtained in the form of a brown solid, the characteristics of which are as follows:

- melting point = 177°C
- mass spectrum (EI): M/Z = 246 (M^+).
- ^1H N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): from 2.10 to 2.50 (mt, 4H, CH_2CH_2), 3.70 (s, 3H, $COOCH_3$), 3.90 (s, 3H, $ArOCH_3$), 4.61 (mt, 1H, ArCH), from 6.80 to 7.00 and 7.25 (2 mts, 5H in whole, =CH and aromatic H).

Stage C

235 g (1.66 mol) of methyl iodide and 212 g (1.39 mol) of 1,8-diazabicyclo[5.4.0]undec-7-ene, dropwise, are successively added to a solution of 288 g (1.17 mol) of (RS)-6-(2-methoxyphenyl)-3-oxocyclohexene-1-carboxylic acid in 2.5 dm^3 of acetone and then the mixture is brought to reflux for one hour. The acetone is subsequently concentrated and then the residue is stirred with 1 dm^3 of water. After cooling to 10°C, the precipitate formed is filtered off, washed with petroleum ether and then dried at 50°C. 289 g

(95%) of methyl (RS)-6-(2-methoxyphenyl)-3-oxocyclohexene-1-carboxylate are thus obtained in the form of a mustard-coloured powder, the characteristics of which are as follows:

- melting point = 76°C
- mass spectrum (EI): M/Z = 260 (M^+).

Stage D

A solution of 6 g (0.023 mol) of methyl (RS)-6-(2-methoxyphenyl)-3-oxocyclohexene-1-carboxylate and of 0.3 cm^3 of trifluoroacetic acid in 185 cm^3 of dichloromethane is brought to reflux. 7.7 g (0.0275 mol) of N-n-butoxymethyl-N-(trimethylsilylmethyl)benzylamine, which can be obtained according to Chem. Pharm. Bull., 1985, 276, are then added dropwise and the mixture is brought to reflux for three hours. The reaction mixture is then cooled to 20°C. After stirring for one hour with approximately 5 g of potassium carbonate, the organic phase is concentrated and the yellow oil obtained is purified by chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (95/05 by volume) mixture. 6.1 g (68%) of methyl (3aRS,4SR,7aRS)-2-benzyl-4-(2-methoxyphenyl)-7-oxooctahydroisoindole-3a-carboxylate are then obtained in the form of a yellow oil, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 393 (M^+).

Stage E

A solution of 166.6 g (0.424 mol) of methyl (3aRS,4SR,7aRS)-2-benzyl-4-(2-methoxyphenyl)-7-oxo-octahydroisoindole-3a-carboxylate and of 84.5 g (1.69 mol) of hydrazine hydrate in 2.8 dm^3 of methanol is brought to reflux for two hours. After concentrating the methanol under reduced pressure, the residue is taken up in 2 dm^3 of dichloromethane, washed with four times 1 dm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. 175.2 g of methyl (3aRS,4SR,7aRS)-2-benzyl-7-hydrazono-4-(2-methoxyphenyl)octahydroisoindole-3a-carboxylate are thus obtained in the form of a yellow oil, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 407 (M^+).

Stage F

106.1 g (0.418 mol) of iodine in 1.1 dm^3 of tetrahydrofuran are added dropwise to a solution of 85 g (0.209 mol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-hydrazono-4-(2-methoxyphenyl)octahydroisoindole-3a-carboxylate in 2 dm^3 of tetrahydrofuran. After addition of 2 dm^3 of ethyl acetate, the organic phases are washed with two times 1 dm^3 of a saturated aqueous sodium hydrogencarbonate solution, washed with two times 1 dm^3 of a saturated aqueous sodium thiosulphate solution, then dried over magnesium sulphate and concentrated under reduced pressure. After purification by chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate

(95/05 by volume) mixture, 51 g (48%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-(2-methoxyphenyl)-1,2,3,4,5,7a-hexahydro-isoindole-3a-carboxylate are obtained in the form of a brown oil, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 503 (M^+).

Stage G

A solution of 0.41 g (2.99 mmol) of 4-methylphenylboronic acid in 13 cm^3 of methanol and 30 cm^3 of a 2N aqueous sodium carbonate solution are successively added to a solution of 1.37 g (2.7 mmol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-(2-methoxyphenyl)-1,2,3,4,5,7a-hexahydro-isoindole-3a-carboxylate and of 0.15 g (0.13 mmol) of tetrakis(triphenylphosphine)palladium in 30 cm^3 of toluene and then the mixture is brought to reflux for two hours. After returning to a temperature in the region of 20°C, the reaction mixture is extracted with 100 cm^3 of ethyl acetate, washed with two times 50 cm^3 of distilled water, dried over magnesium sulphate and then concentrated under reduced pressure. The brown residue obtained is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (95/05 by volume) mixture. 1.2 g (93%) of methyl (3aRS,4SR,7aRS)-2-benzyl-4-(2-methoxyphenyl)-7-(4-methylphenyl)-1,2,3,4,5,7a-hexahydro-isoindole-3a-carboxylate are thus obtained in the form of a yellow oil, the

characteristics of which are as follows:

- mass spectrum (EI): M/Z = 467 (M^+).

Stage H

94 cm^3 of trifluoromethanesulphonic acid are added dropwise to a solution of 66.4 g (0.142 mol) of methyl (3aRS,4SR,7aRS)-2-benzyl-4-(2-methoxyphenyl)-7-(4-methylphenyl)-1,2,3,4,5,7a-hexahydro-isoindole-3a-carboxylate in 750 cm^3 of dichloromethane maintained at a temperature in the region of 0°C. The reaction mixture is stirred for three hours at a temperature in the region of 20°C and then cooled to a temperature in the region of 0°C. 700 cm^3 of a saturated aqueous potassium carbonate solution are then added. The organic phase is separated by settling, washed successively with three times 150 cm^3 of distilled water and with two times 100 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After washing with diisopropyl ether, 54.9 g (82%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-5-methoxy-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are thus obtained in the form of an off-white solid, the characteristics of which are as follows:

- melting point = 129°C
- ^1H N.M.R. spectrum (250 MHz, $CDCl_3$, d in ppm): 1.41, 1.73 and from 2.40 to 2.60 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), from 2.30 to 2.40 (mt, 2H, 1H of

the CH_2 at 1 and 1H of the CH_2 at 3), 2.39 (s, 3H, $ArCH_3$), 2.75 (broad d, J = 10 Hz, 1H, the other H of the CH_2 at 1), 3.23 (d, J = 9.5 Hz, 1H, the other H of the CH_2 at 3), 3.26 (mt, 1H, CH at 9a), 3.41 and 3.65 (2 d, J = 12.5 Hz, each 1H, NCH_2Ar), 3.55 (s, 3H, $COOCH_3$), 3.81 (s, 3H, $ArOCH_3$), 3.96 (mt, 1H, CH at 4), 6.21 (d, J = 7.5 Hz, 1H, H at 8), 6.71 (d, J = 7.5 Hz, 1H, H at 6), 6.99 (t, J = 7.5 Hz, 1H, H at 7), from 7.15 to 7.40 (mt, 9H, aromatic H of the 4-methylphenyl and aromatic H of the benzyl).

Stage I

From 0.54 g (1.1 mmol) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-5-methoxy-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate in solution in 100 cm^3 of methanol and in the presence of 54 mg of 10% (w/w) palladium-on-charcoal, 0.5 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride is obtained, after stirring for one hour under hydrogen at atmospheric pressure and at 40°C, filtering off the catalyst and concentrating to dryness under reduced pressure, in the form of a beige solid, the characteristics of which are as follows:

- melting point > 260°C
- IR spectrum (KBr):

3050-2250 cm^{-1} n N^+H + n CH, aromatic and

	aliphatic
2833 cm^{-1}	n CH, OCH_3
1738 cm^{-1}	n C=O, methyl ester
1603, 1584, 1514, 1477 cm^{-1}	breathing of the aromatic nuclei
1258 cm^{-1}	n O-C=O, methyl ester, + n_a C-O, ether
824 cm^{-1}	g CH, para-disubstituted phenyl aromatic
776, 755 cm^{-1}	g CH, trisubstituted phenyl aromatic

Stage J

A solution of 0.058 cm^3 of oxalyl chloride in 5 cm^3 of dichloromethane is added dropwise to a solution of 0.12 g of 2-(2-methoxyphenyl)propenoic acid in 5 cm^3 of dichloromethane containing 3 drops of N,N-dimethylformamide. The reaction mixture is stirred for a further two hours at a temperature in the region of 20°C, then cooled to a temperature in the region of 0°C and run dropwise into a solution of 0.25 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride in 7 cm^3 of dichloromethane and 0.19 cm^3 of triethylamine, the temperature being maintained in the region of 0°C. The reaction mixture is stirred for a further one hour at [lacuna] temperature in the region of 0°C and then at 20°C overnight, and poured into 15 cm^3 of distilled water.

The organic phase is separated by settling, washed with two times 15 cm^3 of distilled water and then 15 cm^3 of a saturated aqueous sodium chloride solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture, 0.17 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate is obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 185°C
- mass spectrum (EI): M/Z = 537 (M^+).

EXAMPLE 99

<u>Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid</u>

0.365 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate are heated at reflux for three hours in 30 cm^3 of ethanol in the presence of 0.82 cm^3 of a normal aqueous sodium hydroxide solution. The reaction mixture is subsequently concentrated under reduced pressure and the residue dissolved in 10 cm^3 of

distilled water. The aqueous phase is washed with two times 10 cm^3 of dichloromethane, acidified with a normal aqueous hydrochloric acid solution to a pH in the region of 2, extracted with 30 cm^3 of dichloromethane, washed with distilled water, dried over magnesium sulphate and then concentrated under reduced pressure. The orange solid obtained is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a dichloromethane/methanol/acetic acid (98/1.5/0.5 by volume) mixture. 0.09 g (26%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid is thus obtained in the form of a white solid, the characteristics of which are as follows:

- melting point > 260°C
- ^1H N.M.R. spectrum (250 MHz, d6-$(CD_3)_2SO$, at a temperature of 383 K, d in ppm): 1.32, 1.60 and from 1.85 to 2.20 (3 mts, respectively 1H, 1H and 2H, CH_2CH_2), 2.38 (s, 3H, $ArCH_3$), 3.34 (mt, 3H, CH_2 at 1 and CH at 9a), 3.62 and 4.04 (2 d, J = 12.5 Hz, each 1H, CH_2 at 3), 3.72 and 3.81 (2 s, each 3H, $ArOCH_3$), 3.93 (mt, 1H, CH at 4), 5.52 and 5.66 (2 broad s, each 1H, $=CH_2$), 6.06 (d, J = 7.5 Hz, 1H, H at 8), 6.82 (d, J = 7.5 Hz, 1H, H at 6), from 6.90 to 7.10 (mt, 3H, H at 7 and 2 aromatic H of the 2-methoxyphenyl), from 7.20 to 7.40 (mt, 6H, 2 aromatic H of the 2-methoxyphenyl and aromatic H of the 4-methoxyphenyl).

EXAMPLE 100

Isolation of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)-2-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

6.5 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid, obtained in Example 99, are resolved, on a chiral silica column carrying N-(3,5-dinitrobenzoyl)-(R)-phenylalanine grafts, in 4 successive injections and by eluting with an n-heptane/dichloromethane/ethanol (50/50/1 by volume) mixture. On collecting the first fractions eluted (retention time 30 min), 2.81 g of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are obtained, after concentrating the solvent under reduced pressure, in the form of a white powder, the characteristics of which are as follows:

- mass spectrum (EI): M/Z = 523 (M^+)
- optical rotation: $[a]_{365}^{20}$ = + 36.5 +/- 1° (c = 0.5, dichloromethane)

EXAMPLE 101

Preparation of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-2-propenoyl]-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

Stage A

A 1.6 N solution of n-butyllithium in hexane is run dropwise into a solution, cooled to the region of -70°C, of 33 g (0.220 mol) of (RS)-2-phenylpropionic acid in 220 cm^3 of tetrahydrofuran and of 44 cm^3 of N,N'-tetramethylethylenediamine. After having stirred the reaction mixture for three hours at -70°C, the reaction mixture is returned to a temperature in the region of 20°C and the solution obtained is run into a solution of 75 cm^3 (0.55 mol) of ethyl oxalate in 110 cm^3 of tetrahydrofuran, the temperature being maintained at -75°C, for 1 hour. The reaction mixture is hydrolysed with 800 cm^3 of a saturated aqueous sodium hydrogencarbonate solution, extracted with three times 100 cm^3 of ethyl acetate, washed with three times 50 cm^3 of a normal aqueous hydrochloric acid solution, dried over sodium sulphate and concentrated under reduced pressure. 44 g (97%) of ethyl (RS)-2-oxo-3-phenyl-butyrate are then obtained in the form of an orange oil, the characteristics of which are as follows:

- ^1H N.M.R. spectrum (250 MHz, $CDCl_3$, d in ppm): 1.20 (t, J = 7 Hz, 3H, CH_3 of the ethyl), 1.47 (d, J = 7 Hz, 3H, CH_3), 4.17 (q, J = 7 Hz, 2H, OCH_2 of the ethyl),

4.49 (q, J = 7 Hz, 1H, ArCH), from 7.15 to 7.45 (mt, 5H, aromatic H).

Stage B

3.5 cm^3 (39 mmol) of methyl vinyl ketone and 72 cm^3 (71.5 mmol) of a normal aqueous sodium hydroxide solution are successively added to a solution, cooled to the region of 7°C, of 6.7 g (32.5 mmol) of ethyl (RS)-2-oxo-3-phenylbutyrate in 68 cm^3 of ethanol and then the reaction mixture is stirred at a temperature in the region of 20°C for two hours. The reaction mixture is cooled to 15°C and 72 cm^3 of a normal aqueous hydrochloric acid solution are added. After concentrating the ethanol, the precipitate formed is filtered off, washed with water and then dried at 50°C. 4.4 g (50%) of (1RS,2RS)-2-methyl-5-oxo-2-phenylcyclohexan-1-ol-1-carboxylic acid are thus obtained in the form of a beige powder, the characteristics of which are as follows:

- ^1H N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): 1.79 (s, 3H, CH_3), from 2.00 to 2.25 and from 2.25 to 2.55 (2 mts, each 2H, CH_2CH_2), 3.59 (s, 3H, $COOCH_3$), 6.72 (s, 1H, =CH), from 7.15 to 7.35 (mt, 5H, aromatic H).

Stage C

4.4 g (17.6 mmol) of (1RS,2RS)-2-methyl-5-oxo-2-phenylcyclohexan-1-ol-1-carboxylic acid are heated at reflux for one hour in 100 cm^3 of toluene in the presence of 0.34 g of para-toluenesulphonic acid. The reaction mixture is cooled to 0°C and the

precipitate formed is filtered off, washed with ethyl ether and then dried at 50°C. 2.8 g (69%) of (RS)-2-methyl-5-oxo-2-phenylcyclohexene-1-carboxylic acid are thus obtained in the form of a pink solid, the characteristics of which are as follows:

- melting point = 206°C
- mass spectrum (EI): M/Z = 230 (M^+)

Stage D

0.88 cm^3 (14 mmol) of methyl iodide and 1.8 cm^3 (12 mmol) of 1,8-diazabicyclo[5.4.0]undec-7-ene, dropwise, are successively added to a solution of 2.3 g (10 mmol) of (RS)-2-methyl-5-oxo-2-phenylcyclohexene-1-carboxylic acid in 20 cm^3 of acetone. The reaction mixture is subsequently heated at reflux for two hours. The acetone is subsequently concentrated, the residue is then stirred with 100 cm^3 of water and then extracted with three times 30 cm^3 of ethyl acetate. After drying over magnesium sulphate and concentrating under reduced pressure, 2.3 g (94%) of methyl (RS)-2-methyl-5-oxo-2-phenylcyclohexene-1-carboxylate are obtained in the form of an orange oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 244 (M^+)

Stage E

A solution of 18.3 g (0.075 mol) of methyl (RS)-2-methyl-5-oxo-2-phenylcyclohexene-1-carboxylate and of 0.57 cm^3 of trifluoroacetic acid in 145 cm^3 of dichloromethane is brought to reflux. 31.4 g

(0.112 mol) of N-n-butoxymethyl-N-(trimethylsilylmethyl)benzylamine, which can be obtained according to Chem. Pharm. Bull., 1985, 276, are then added dropwise and the reaction mixture is brought to reflux for four hours. The reaction mixture is then cooled to 20°C. After stirring for one hour with approximately 15 g of potassium carbonate, the organic phase is concentrated and the oil obtained is crystallized from pentane. After filtration, 19 g (67%) of methyl (3aRS,4SR,7aRS)-2-benzyl-4-methyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate are obtained in the form of a yellow solid, the characteristics of which are as follows:

- melting point = 115°C
- mass spectrum (EI): M/Z = 377 (M^+)

Stage F

A solution of 3 g (7.95 mmol) of methyl (3aRS,4SR,7aRS)-2-benzyl-4-methyl-7-oxo-4-phenyloctahydroisoindole-3a-carboxylate and of 1.55 cm^3 (31.8 mmol) of hydrazine hydrate in 30 cm^3 of methanol is brought to reflux for two hours. After concentrating the methanol under reduced pressure, the residue is taken up in dichloromethane, washed with three times 30 cm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. 2.8 g (89%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-hydrazono-4-methyl-4-phenyloctahydroisoindole-3a-carboxylate are thus obtained in the form of a brown oil, the

characteristics of which are as follows:

- ^{1}H N.M.R. spectrum (300 MHz, $CDCl_3$, d in ppm): 1.33 (s, 3H, CH_3), 1.86, 2.24, 2.48 and 2.84 (4 mts, each 1H, CH_2 at 5 and CH_2 at 6), 2.43 and 3.47 (2 d, J = 9 Hz, each 1H, CH_2 at 3), 2.67 and 3.19 (2 t, J = 8.5 Hz, each 1H, CH_2 at 1), 3.10 (s, 3H, $COOCH_3$), 3.53 and 3.71 (2 d, J = 13 Hz, each 1H, NCH_2Ar), 3.78 (t, J = 8.5 Hz, 1H, H at 7a), 4.98 (broad s, 2H, NH_2), from 7.10 to 7.35 (mt, 10H, aromatic H of the phenyl and aromatic H of the benzyl).

Stage G

2.95 cm^3 of triethylamine are added to a solution of 2.8 g (7 mmol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-hydrazono-4-methyl-4-phenyloctahydroisoindole-3a-carboxylate in 80 cm^3 of tetrahydrofuran and a solution of 3.6 g (14.1 mmol) of iodine in 40 cm^3 of tetrahydrofuran is run in dropwise. After addition of ethyl acetate, the organic phases are washed with two times 50 cm^3 of a saturated aqueous sodium hydrogencarbonate solution, washed with two times 50 cm^3 of a saturated aqueous sodium thiosulphate solution, then dried over magnesium sulphate and concentrated under reduced pressure. After purification by chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (85/15 by volume) mixture, 2.4 g (69%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-(2-methoxyphenyl)-1,2,3,4,5,7a-hexahydro-isoindole-3a-carboxylate are

obtained in the form of a yellow oil, the characteristic of which is as follows:

- mass spectrum (EI): M/Z = 487 (M^+)

Stage H

A solution of 20.1 g (0.132 mol) of 4-methoxyphenylboronic acid in 580 cm^3 of methanol and 1170 cm^3 of a 2N aqueous sodium carbonate solution are successively added to a solution of 58.6 g (0.12 mol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-iodo-4-(2-methoxyphenyl)-1,2,3,4,5,7a-hexahydro-isoindole-3a-carboxylate and of 7 g of tetrakis(triphenylphosphine)palladium in 30 cm^3 of toluene and then the mixture is brought to reflux for twenty-four hours. After returning to a temperature in the region of 20°C, the reaction mixture is extracted with ethyl acetate, washed with distilled water, dried over magnesium sulphate and then concentrated under reduced pressure. The residue obtained is purified by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (98/02 by volume) mixture. 29 g (52%) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(4-methoxyphenyl)-4-methyl-4-phenyl-1,2,3,4,5,7a-hexahydro-isoindole-3a-carboxylate are thus obtained in the form of a brown powder, the characteristics of which are as follows:

- melting point = 132°C
- ^1H N.M.R. spectrum (250 MHz, $CDCl_3$, d in ppm): 1.60 (s, 3H, CH_3 at 4), 2.03 (dd, J = 9 and 5 Hz, 1H, 1H of

the CH_2 at 5), from 2.40 to 2.90 (mt, 1H, the other H of the CH_2 at 5), 3.56 (s, 3H, $COOCH_3$), from 3.40 to 3.95 (mt, 2H, NCH_2Ar), 3.79 (mt, 1H, CH at 7a), 3.83 (s, 3H, $ArOCH_3$), 6.08 (mt, 1H, =CH at 6), from 6.75 to 7.45 (mt, 14H, aromatic H of the 4-methoxyphenyl, aromatic H of the benzyl and aromatic H of the phenyl).

Stage I

105 cm^3 of trifluoromethanesulphonic acid are added dropwise to a solution of 54.7 g (0.117 mol) of methyl (3aRS,4SR,7aRS)-2-benzyl-7-(4-methoxyphenyl)-4-methyl-4-phenyl-1,2,3,4,5,7a-hexahydro-isoindole-3a-carboxylate in 700 cm^3 of dichloromethane maintained at a temperature in the region of 5°C. The reaction mixture is stirred for three hours at a temperature in the region of 20°C and then cooled to a temperature in the region of 0°C. 100 cm^3 of a 10N aqueous sodium hydroxide solution are then added. The organic phase is separated, washed successively with three times 100 cm^3 of distilled water, dried over magnesium sulphate and concentrated under reduced pressure. After washing in petroleum ether, 50 g (92%) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate are thus obtained in the form of a grey solid, the characteristics of which are as follows:

- melting point = 143°C
- ^1H N.M.R. spectrum (400 MHz, $CDCl_3$, d in ppm):

1.21, 1.79, 2.36 and 2.53 (4 mts, each 1H, CH_2CH_2), 1.41 (s, 3H, CH_3), 2.37 and 2.55 (2 mts, each 1H, CH_2 at 1), 2.74 and 3.14 (2 d, J = 10 Hz, each 1H, CH_2 at 3), 3.19 (mt, 1H, CH at 9a), 3.44 (s, 3H, $COOCH_3$), 3.47 and 3.61 (2 d, J = 13 Hz, each 1H, NCH_2Ar), 3.86 (s, 3H, $ArOCH_3$), 6.59 (d, J = 7.5 Hz, 1H, H at 8), 6.96 (broad d, J = 7.5 Hz, 2H, aromatic H at the ortho positions with respect to the OCH_3), from 7.05 to 7.25 (mt, 3H, H at 5, H at 6 and H at 7), from 7.25 to 7.45 (mt, 7H, aromatic H at the meta positions with respect to the OCH_3 and aromatic H of the benzyl).

Stage J

From 13 g (0.028 mol) of methyl (3aRS,4SR,9SR,9aRS)-2-benzyl-4,9-ethano-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate in solution in 260 cm^3 of methanol, and in the presence of 1.7 g of 10% (w/w) palladium-on-charcoal, 10.2 g (97%) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride are obtained, after stirring for four hours under hydrogen at atmospheric pressure and at 40°C, filtering off the catalyst and concentrating to dryness under reduced pressure, in the form of a yellow solid, the characteristics of which are as follows:

- IR spectrum (KBr)

3050-2250 cm^{-1} n N^+H + n CH, aromatic and

	aliphatic
2842 cm^{-1}	n CH, OCH_3
1737 cm^{-1}	n C=O, methyl ester
1611, 1571, 1516, 1460 cm^{-1}	breathing of the aromatic nuclei
1253 cm^{-1}	n O-C=O, methyl ester, + n_a C-O, ether
825 cm^{-1}	g CH, para-disubstituted phenyl aromatic
768 cm^{-1}	g CH, ortho-disubstituted phenyl aromatic

Stage K

A solution of 3.1 cm^3 of oxalyl chloride in 50 cm^3 of dichloromethane is added dropwise to a solution of 4.62 g (0.026 mol) of 2-(2-methoxyphenyl)-propenoic acid in 100 cm^3 of dichloromethane containing 2 drops of N,N-dimethylformamide. The reaction mixture is stirred for a further two hours at a temperature in the region of 20°C, then cooled to a temperature in the region of 0°C and run dropwise into a solution of 8.3 g (0.024 mol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride in 100 cm^3 of dichloromethane and 6.1 cm^3 of triethylamine, the temperature being maintained in the region of 0°C. The reaction mixture is stirred for a further one hour at a temperature in the region of 0°C and then overnight at 20°C. After washing with two times 100 cm^3

of distilled water, the organic phase is separated by settling, washed successively with two times 100 cm^3 of a normal aqueous hydrochloric acid solution and with two times 100 cm^3 of a normal aqueous sodium hydroxide solution, dried over magnesium sulphate and concentrated under reduced pressure. After purification by flash chromatography on silica gel (230-400 mesh), elution being carried out with a cyclohexane/ethyl acetate (70/30 by volume) mixture, 9.1 g of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-4-methyl-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are obtained in the form of an orange-coloured solid, the characteristics of which are as follows:

- melting point = 141°C
- ^1H N.M.R. spectrum (300 MHz, d6-$(CD_3)_2SO$, d in ppm [lacuna]: from 0.95 to 1.25 and from 1.55 to 2.10 (2 mts, 4H in all, CH_2CH_2), 1.38 and 1.46 (2 s, 3H in all, CH_3), from 3.05 to 3.35 (mt, 3H, CH_2 at 1 and CH at 9a), from 3.30 to 3.40 and 3.41 (respectively mt and s, 3H in all, $COOCH_3$), 3.62, 3.72, 3.80 and 3.83 (4 s, 6H in all, $ArOCH_3$), from 3.80 to 4.20 (mt, 2H, CH_2 at 3), 5.43, 5.56, 5.60 and 5.78 (4 s, 2H in all, $=CH_2$), 6.39 and 6.42 (2 d, J = 7.5 Hz, 1H in all, H at 8), from 6.85 to 7.45 (mts, 11H, H at 5, H at 6, H at 7, aromatic H of the 4-methoxyphenyl and aromatic H of the 2-methoxyphenyl).

Stage L

13.4 g (0.025 mol) of methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-4-methyl-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate are heated at reflux for three hours in 250 cm^3 of ethanol in the presence of 52 cm^3 of a normal aqueous sodium hydroxide solution. The reaction mixture is subsequently concentrated under reduced pressure and the residue is dissolved in 250 cm^3 of distilled water. The aqueous phase is washed with two times 100 cm^3 of ethyl ether, acidified with 60 cm^3 of a normal aqueous hydrochloric acid solution, extracted with two times 150 cm^3 of dichloromethane, dried over magnesium sulphate and then concentrated under reduced pressure. The white solid obtained is purified by washing in 100 cm^3 of pentane. 10.8 g (83%) of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are thus obtained in the form of a white solid, the characteristics of which are as follows:

- melting point = 157°C
- mass spectrum (EI): M/Z = 523 (M^+)

<u>Isolation of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid</u>

17.6 g of (3aRS,4SR,9SR,9aRS)-4,9-ethano-

2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid are resolved, in 4 injections, on a Whelk 01 (SS) chiral silica column, elution being carried out with an n-heptane/dichloromethane/propanol (50/48/2 by volume) mixture containing 0.05% of trifluoroacetic acid. On collecting the first fraction eluted (retention time 38 min), 7.01 g of the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methoxyphenyl)-4-methyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid are obtained, after concentrating under reduced pressure, in the form of a white powder, the characteristics of which are as follows:

- melting point = 238°C
- mass spectrum (EI): M/Z = 523 (M^+)
- optical rotation: $[a]_{365}^{20}$ = + 74.4 +/- 1.3°

(c = 0.5, methanol)

EXAMPLE 102

<u>Evaluation of the farnesyl transferase activity of compounds according to the invention</u>

The farnesyl transferase activity is measured by the amount farnesylated of K-ras substrate or of substrate derived from the peptide corresponding to its C-terminal part, the farnesyl group being introduced by farnesyl pyrophosphate (FPP).

Specifically, the biotinylated substrate

used, representative of K-ras: BIOT-$(\beta A)_3$-S-K-D-G-$(K)_6$-S-K-T-K-C-V-I-M, is [^{3}H]-farnesylated on its cysteine C by farnesyl transferase in the presence of [^{3}H]-FPP. It is then brought into contact with PVT*-streptavidin (Amersham)® beads and is quantified by proximity scintillation (SPA assay) between the tritium and the PVT beads, by virtue of the streptavidin/biotin interaction.

Experimentally, farnesyl transferase purified according to the appended protocol is diluted, for this assay, to a concentration such that a consumption of substrates of less than 30% is obtained. The final molar concentrations of each substrate are adjusted to their respective Km: 50 nM for the biotinylated K ras peptide and 120 nM for FPP, introduced at 20 μl into a final volume of 100 μl of the reaction mixture based on 50 mM pH 7.5 Hepes buffer, 5 mM $MgCl_2$, 40 mM KCl, 5 mM dithiothreitol, 0.01% Triton X100.

The inhibitors to be tested, initially dissolved at 1 mM in an appropriate solvent (DMF or DMSO), are diluted in the assay buffer and are added in the form of 10 μl, in triplicate, to the reaction mixture at a concentration 10 times greater than their final concentration.

The reaction, carried out in Optiplates 96® microtitration plates, is initiated by the enzyme and lasts sixty minutes at 37°C. It is stopped by addition of 150 μl of mixture of a blocking buffer at pH 4

composed of 0.2M H_3PO_4, 1.5 mM $MgCl_2$, 0.5% (w/v) BSA, 0.05% (w/v) sodium azide containing 200 μg of PVT-streptavidin beads.

After slow agitation for thirty minutes (in order to remove the chemiluminescence), the plates are read as [^{3}H]CPM in a Top Count® (Packard) scintillation counter for microplates, where they are converted into [^{3}H]DPM from a range of coloured agent attenuating the scintillation (quenching).

The percentages of inhibition are calculated with respect to an inhibitor-free control after subtraction from all the values of that of a blank which only contains the substrates and the buffer.

The IC_{50} values are calculated or measured, from the inhibitions obtained at nine different concentrations, with Enzfitter® or Grafit® software. The IC_{50} values which appear in the results are the mean of measurements and calculations of two IC_{50} values. The results obtained are collated in Table I.

TABLE I

Product	[lacuna] vitro inhibitory activity (KiRas) IC_{50} (μM)
Example 1	0.305
Example 2	0.045
Example 3	0.028
Example 4	1.80
Example 5	0.050
Example 6	0.0575
Example 7	0.050
Example 8	0.100
Example 9	0.055
Example 10	0.160
Example 11	0.345
Example 12	0.045
Example 13	0.140
Example 14	0.210
Example 15	0.170
Example 16	0.360
Example 17	0.235
Example 18	0.050

Example 19	0.181
Example 20	0.140
Example 21	0.111
Example 22	0.131
Example 23	0.277
Example 24	0.084
Example 25	0.193
Example 26	0.145
Example 27	0.009
Example 28	0.054
Example 29	0.140
Example 30	0.074
Example 31	0.101
Example 32	0.106
Example 33	0.242
Example 34	< 0.02
Example 35	0.084
Example 36	0.120
Example 37	0.088
Example 38	0.099
Example 39	0.273

Example 40	0.083
Example 41	0.009
Example 42	0.083
Example 43	0.590
Example 44	0.369
Example 45	0.181
Example 46	0.132
Example 47	0.207
Example 48	0.095
Example 49	0.229
Example 50	0.059
Example 51	0.068
Example 52	0.181
Example 53	0.020
Example 54	0.078
Example 55	0.558
Example 56	0.589
Example 57	0.280
Example 58	0.138
Example 59	0.408
Example 60	0.124

Example 61	0.178
Example 62	0.036
Example 63	< 0.020
Example 64	0.325
Example 65	0.040
Example 66	0.379
Example 67	0.101
Example 68	0.431
Example 69	0.053
Example 70	0.067
Example 71	0.335
Example 72	0.098
Example 73	0.460
Example 74	0.048
Example 75	0.008
Example 76	0.244
Example 77	0.204
Example 78	0.048
Example 79	0.045
Example 80	0.067
Example 81	0.018

Example 82	0.097
Example 83	0.319
Example 84	0.008
Example 85	0.508
Example 86	0.005
Example 87	0.064
Example 88	0.404
Example 89	0.005
Example 90	0.068
Example 91	0.183
Example 92	0.028
Example 93	0.786
Example 94	0.557
Example 95	0.177
Example 96	0.955
Example 97	0.040
Example 98	0.663
Example 99	0.018
Example 100	< 0.019
Example 101	< 0.019

EXAMPLE 103

The activity of the compounds according to the invention can also be evaluated by the ability of the said compounds to inhibit the growth in agar of clones resulting from human tumour lines. For example, cells from the HCT116 human colic carcinoma line, supplied by the ATCC, are grown as a monolayer in a culture medium, Dulbecco's modified Eagle, containing 2 mM of L-glutamine, 200 U/ml of penicillin, 200 μg/ml of streptomycin complemented by 10% by volume of heat inactivated foetal calf serum. The cells in exponential growth are trypsinized, washed with PBS and diluted to a final concentration of 5000 cells/ml in the complete culture medium. The inhibitors to be tested, or the control solvent, are then added, at a volume of 50 μl, to 2.5 ml of cell suspension, prepared above. 0.4 ml of an agar solution, Noble Difco, maintained at 45°C, is subsequently added and mixing is then carried out. The medium thus obtained is immediately placed in Petri dishes, maintained for five minutes at 4°C and then incubated at 37°C under an atmosphere containing 5% of CO_2. The number of cell clones (> 50 cells) is counted after incubating for twelve days at 37°C under an atmosphere containing 5% of CO_2. Each inhibitor is tested in duplicate at the final concentrations in agar of 10, 1, 0.1, 0.01 and 0.001 μg/ml. The results are expressed as percentage of inhibition of clonogenicity with respect to the untreated controls. The inhibitory

doses IC_{50} are determined graphically from the semi-logarithmic means of the values obtained for each concentration.

The products according to the invention inhibit farnesylation of the Ras protein by 50% at concentrations of between 0.1 nM and 100 μM.

EXAMPLE 104

The antitumour activity of the compounds according to the invention can also be demonstrated by an *in vivo* test in mice, according to the tests and methodologies conventionally used (Corbett et al., Cancer Research 42, 1707-1715 (1982), Corbett et al., Cancer Treatment Report, 66, 1187-1200 (1982), Corbett et al., 40, 2660-2680 (1977)).

The influence of the compounds according to the invention, administered to mice, on the growth of carcinomas of human origin grafted subcutaneously into these mice is studied.

On day 0 of the experiment, the mice receive a tumour fragment (30-60 mg) bilaterally under the skin using a trocar. The bilateral implantation of the tumours ensures a more uniform tumour weight per mouse and thus makes it possible to reduce the number of animals per group. The mice are then divided into the different treated and untreated groups.

The product is suspended in an aqueous solution at concentrations ranging from 0.01 to 1200 mg/ml, corresponding to doses of 0.1 to

10,000 mg/kg.

The treatments or their possible excipient are administered every day orally, at a maximum volume of 0.2 ml, the duration of administration depending on the doubling time of the tumour.

The tumours are measured 2 to 3 times per week, using a calliper rule, according to two measurements in mm, which are subsequently converted into tumour weight according to the following formula:

$$\text{tumour weight (mg)} = \frac{\text{Length (mm)} \times \text{width}^2 \text{ (mm}^2\text{)}}{2}$$

An active product is a product which makes it possible to limit the growth of the tumour after it has been administered.

The following example may be mentioned by way of illustration and without implied limitation of the present invention:

Tumour stabilization was obtained at a dose of 400 mg/kg/adm. of the product of Example 3, administered orally to mice grafted subcutaneously with the HCT116 human colic carcinoma line supplied by the ATCC (Brattain et al., Cancer Research, 41, 1751-1756 (1981)).

EXAMPLE 105

EXAMPLE A

Hard gelatin capsules containing 50 mg of active product are prepared, according to the usual technique, which have the following composition:

- Active product . . . . . 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 50 mg of active product are prepared, according to the usual technique, which have the following composition:

- Active product . . . . . 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, glycerol and titanium oxide (72/3.5/24.5) q.s. for 1 coated tablet completed to . . . . . 245 mg

EXAMPLE C

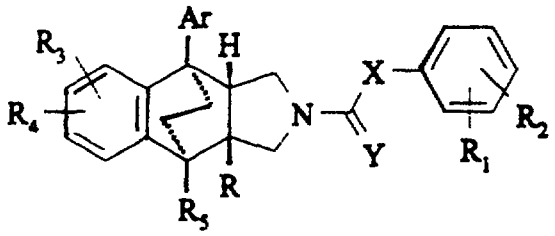
An injectable solution containing 50 mg of active product is prepared which has the following composition:

- Active product . . . . . 50 mg
- Benzoic acid . . . . . 80 mg

- Benzyl alcohol . . . . . 0.06 ml
- Sodium benzoate . . . . . 80 mg
- 95% Ethanol . . . . . 0.4 ml
- Sodium hydroxide . . . . . 24 mg
- Propylene glycol . . . . . 1.6 ml
- Water . . . . . q.s. for 4 ml

CLAIMS

1. Compounds of general formula I



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in which:

- Ar represents

  - a phenyl radical substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and the following radicals: alkyl containing 1 to 4 carbon atoms, such as methyl, alkenyl containing 2 to 4 carbon atoms, hydroxyl, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, formyl, alkylcarbonyl, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, cyano or trifluoromethyl, or alkoxy containing 1 to 4 carbon atoms, such as methoxy, the alkyl portion of which is optionally perhalogenated, such as trifluoromethoxy, or
  - a phenyl radical condensed with a 4- to 7-membered heterocycle containing one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms,

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- an aromatic or non-aromatic polycyclic radical,
- a 5- to 12-membered aromatic or non-aromatic heterocyclic radical incorporating one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, bonded to the condensed ring via a carbon-carbon bond, the said radical being substituted, if appropriate, by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and the following radicals: alkyl, alkenyl containing 2 to 4 carbon atoms, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, formyl, alkylcarbonyl, carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, cyano or trifluoromethyl,

with, for all of these radicals, alkyl containing 1 to 4 carbon atoms,

- R represents

a radical of general formula

$$-(CH_2)_m-X_1-(CH_2)_n-Z$$

in which

- X_1 represents a single bond or an oxygen or sulphur atom,
- m represents an integer equal to 0 or 1,

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- n represents an integer equal to 0, 1 or 2,
- one or more methylene radicals can be substituted by a carboxyl, alkoxycarbonyl, carbamoyl, alkylcarbamoyl, dialkylcarbamoyl, amino, alkylamino or dialkylamino radical with, for all of these radicals, alkyl containing 1 to 4 carbon atoms,
- Z represents

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- a carboxyl radical,
- a $COOR_6$ radical, in which R_6 represents a straight or branched alkyl radical containing 1 to 3 carbon atoms, such as the methyl, or
- a radical of formula $CON(R_7)(R_8)$ in which
  - R_7 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms and
  - R_8 represents
    - a hydrogen atom,
    - a hydroxyl radical,
    - an arylsulphonyl radical, such as phenylsulphonyl, optionally substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,
    - a 5- to 7-membered heterocycle incorporating one or more heteroatoms chosen from nitrogen, oxygen or sulphur atoms, it

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being possible for the said heterocycle to be bonded via a heteroatom,

- an amino radical optionally substituted by one or two radicals, which are identical or different, chosen from the following radicals:
  - alkyl containing 1 to 4 carbon atoms,
  - aryl, such as phenyl, optionally substituted by one or more radicals, which are identical or different, chosen from alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,
  - 5- to 7-membered heterocyclyl containing one or more heteroatoms chosen from nitrogen, oxygen and sulphur atoms,
  - arylcarbonyl, such as benzoyl, optionally substituted by one or more radicals, which are identical or different, chosen from alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,
- an alkyloxy radical containing 1 to 6 straight- or branched-chain carbon atoms optionally substituted by a phenyl radical,
- a straight or branched alkyl radical containing 1 to 6 carbon atoms, such as methyl, optionally substituted by an amino,

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alkylamino, dialkylamino, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkyloxycarbonyl, carboxyl or cyano radical, an optionally substituted mono- or polycyclic aromatic radical having from 5 to 12 ring members which may or may not incorporate one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, or also being able to be a phenyl radical optionally substituted by one or more halogen atoms or by one or more hydroxyl, amino or trifluoromethyl groups or by one or more alkyl or alkenyl, alkoxy, alkylthio, alkylamino, alkylcarbonyl or C_2 to C_4 alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, the alkyl part of which contains 1 to 8 carbon atoms, or formyl radicals, or alternatively a 1- or 2-naphthyl radical, or

- Z represents

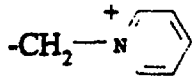
- a $PO(OR_9)_2$ radical in which R_9 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms, or

- an -NH-CO-T radical in which T represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms optionally substituted by an amino, carboxyl, alkyloxycarbonyl, hydroxyl, alkyloxy, mercapto or alkylthio radical, or



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alternatively

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having an anion, such as trifluoromethanesulphonate, as counterion,

with, for all of the radicals possessing an alkyl group provided in the definition of Z, alkyl containing 1 to 4 carbon atoms,

- R_1 and R_2, which are identical or different, represent a hydrogen atom, a halogen atom or an alkyl radical, an alkyloxy radical, such as methoxy, each optionally substituted by a dialkylamino radical, each alkyl part of which contains 1 to 4 carbon atoms or forms, with the nitrogen atom, a saturated heterocycle containing 5 or 6 ring members, an alkylthio radical or an alkyloxycarbonyl radical, or alternatively situated at the ortho position with respect to one another, R_1 and R_2 form a saturated or unsaturated heterocycle containing 1 or 2 heteroatoms chosen from nitrogen and oxygen, optionally substituted by a halogen atom or by an alkyl or alkyloxy radical, with, for all of the radicals possessing an alkyl group provided in the definition of R_1 and R_2, alkyl containing 1 to 4 carbon atoms,

- R_3 and R_4, which are identical or different, represent a hydrogen or halogen atom or an alkyl, hydroxyl, alkyloxy, alkylcarbonyloxy, mercapto,

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alkylthio, alkylsulphonyl or alkylsulphinyl, amino, alkylamino or dialkylamino, alkyloxycarbonylamino, carboxyl, alkyloxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, formyl, alkylcarbonyl, cyano or trifluoromethyl radical,

with, for all of the radicals possessing an alkyl group provided in the definition of R_3 and R_4, alkyl containing 1 to 4 carbon atoms,

- R_5 represents a hydrogen atom or an alkyl radical or an alkylthio radical, with, for the definition of R_5, alkyl containing 1 to 4 carbon atoms;
- X represents an oxygen or sulphur atom or one of the following groups: -NH-, -CO-, methylene, alken-1,1-diyl, such as vinyldiyl, or cycloalkan-1,1-diyl containing 3 to 6 carbon atoms,

and

- Y represents an oxygen or sulphur atom,

in the racemic form or their optical isomers, as well as the salts of the product of general formula (I).

2. Compounds according to claim 1, characterized in that Ar represents a 2,3-dihydro-1,4-benzodioxin-6-yl, 2,3-dihydrobenzofuran-5-yl, 2,3-dihydrobenzopyran-6-yl, 1- or 2-naphthyl, 5-indanyl or 1,2,3,4-tetrahydronaphth-6-yl radical or a phenyl radical substituted at the 4 position by a methyl, trifluoromethyl or methoxy radical.

3. Compounds according to any one of the preceding claims, characterized in that R represents a

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carboxyl radical or a -COOMe radical or alternatively a -CON(R_7)(R_8) radical in which, when R_7 represents a hydrogen atom, R_8 represents a methyl radical substituted by a 2-, 3- or 4-pyridyl radical or the N-oxide of pyridine.

4. Compounds according to any one of the preceding claims, characterized in that Ar represents a 2,3-dihydro-1,4-benzodioxin-6-yl or 2,3-dihydrobenzofuran-5-yl radical or a phenyl radical substituted at the 4 position by a methyl, trifluoromethyl or methoxy radical.

5. Compounds according to any one of the preceding claims, characterized in that R represents a carboxyl radical or a -COOMe radical or alternatively a -CON(R_7)(R_8) radical in which, when R_7 represents a hydrogen atom, R_8 represents a methyl radical substituted by the 3-pyridyl radical.

6. Compounds according to any one of the preceding claims, characterized in that one of the R_1 or R_2 symbols represents a hydrogen atom and the other of the symbols represents a methoxy radical.

7. Compounds according to any one of the preceding claims, characterized in that either R_3 and R_4 each represent a hydrogen atom or one of the R_3 or R_4 symbols represents a hydrogen atom and the other of the R_3 or R_4 symbols represents a methoxy radical.

8. Compounds according to any one of the preceding claims, characterized in that R_5 represents a



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hydrogen atom or a methyl radical.

9. Compounds according to any one of the preceding claims, characterized in that X represents a methylene or vinyldiyl group.

10. Compounds according to any one of the preceding claims, characterized in that Y represents an oxygen atom.

11. Compound, characterized in that it is a compound chosen individually from

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-(2-methoxyphenyl)-propenoyl-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-acetyl]-9-(4-methylsulphanylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-

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acetyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-methoxyphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-3a-N-benzylcarbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

(3aRS,4SR,9SR,9aRS)-3a-carbamoyl-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

benzyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)-carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxy-



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phenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(4-pyridylmethyl)-carboxamide

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N',N'-dimethylcarbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N',N'-pentamethylenecarbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(methoxyphenyl)propenoyl]-9-(4-methylphenyl)-3a-phenylsulphonylaminocarbonyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(N-oxo-3-pyridyl)methylcarboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxy-



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phenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(4-methoxyphenyl)-carbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-methyl-N'-phenylcarbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(2-methylphenyl)carbohydrazide

methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(2-thienylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[(2-methoxyphenyl)-

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acetyl]-9-(3,4,5-trimethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(2-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(4-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-benzoyl-carbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenyl-carbohydrazide

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-



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propenoyl]-9-(2-naphthyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(5-methyl-2-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

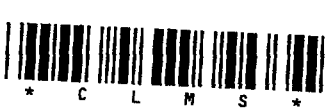
(3aRS,4SR,9SR,9aRS)-9-(4-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-9-(3,4-dichlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-chlorophenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(4-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methoxy-3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid



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methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-indolyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[(2-methoxyphenyl)acetyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-isopropylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-thienyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-ethylphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

methyl(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate acid

(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-



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ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)-carboxamide

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(4-chloro-3-fluorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(3-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(1,3-benzodioxol-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

methyl (3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-



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ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3,4-dimethylphenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-phenylcarbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-hydroxamic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N'-(3-pyridyl)carbohydrazide

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-thienylmethyl)carboxamide

(RS)- and (SR)-2-{(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-

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2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carbonylamino}phenylacetic acids

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-trifluoromethoxyphenyl)-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3-bromophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-fluorophenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

methyl (3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-9-(3-chlorophenyl)-4,9-ethano-2-[2-

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(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

methyl (3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethyl-aminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(3-N,N-dimethylaminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3-aminophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate hydrochloride

methyl (3aRS,4SR,9SR,9aRS)-9-(4-N,N-dimethylamino-phenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-9-(4-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-9-(3-cyanophenyl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(3-hydroxy-4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-



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carboxylic acid

methyl (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylate

(3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

(3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-2-propenoyl]-4-methyl-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

in the racemic form or their optical isomers, as well as their salts.

12. Compound, characterized in that it is (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

in the racemic form or its optical isomers, as well as its salts.

13. Compound, characterized in that it is (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide in the racemic form or its optical isomers, as well as its salts.

14. Compound, characterized in that it is



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(3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

in the racemic form or its optical isomers, as well as its salts.

15. Compound, characterized in that it is (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-propenoyl]-9-(4-trifluoromethylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

in the racemic form or its optical isomers, as well as its salts.

16. Compound, characterized in that it is (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydrobenzofuran-5-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridylmethyl)carboxamide

in the racemic form or its optical isomers, as well as its salts.

17. Compound, characterized in that it is (3aRS,4SR,9SR,9aRS)-4,9-ethano-9-(4-methoxyphenyl)-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

in the racemic form or its optical isomers, as well as its salts.

18. Compound, characterized in that it is (3aRS,4SR,9SR,9aRS)-4,9-ethano-5-methoxy-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-

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2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

in the racemic form or its optical isomers, as well as its salts.

19. Compound, characterized in that it is (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)-2-propenoyl]-4-methyl-9-(4-methoxyphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-carboxylic acid

in the racemic form or its optical isomers, as well as its salts.

20. Compounds according to any one of the preceding claims, characterized in that they are provided in the dextrorotatory form.

21. Compound, characterized in that it is the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-9-(4-methylphenyl)-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]-isoindole-3a-carboxylic acid.

22. Compound, characterized in that it is the dextrorotatory enantiomer of (3aRS,4SR,9SR,9aRS)-9-(2,3-dihydro-1,4-benzodioxin-6-yl)-4,9-ethano-2-[2-(2-methoxyphenyl)propenoyl]-2,3,3a,4,9,9a-hexahydro-1H-benzo[f]isoindole-3a-N-(3-pyridyl-methyl)carboxamide.

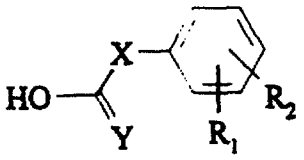
23. Process for the preparation of a compound of general formula (I) according to any one of claims 1 to 22, in which Y represents an oxygen or



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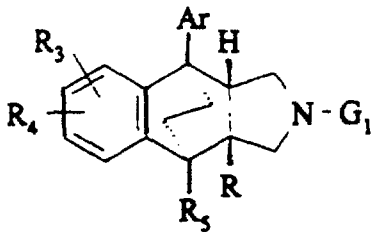
sulphur atom and X represents one of the following groups: -CO-, methylene, alken-1,1-diyl, such as vinyldiyl, or cycloalkan-1,1-diyl containing 3 to 6 carbon atoms, characterized in that an acid of general formula:

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(II)

in which R_1 and R_2 are defined according to claim 1, X such as defined above and Y represents an oxygen or sulphur atom, of its methyl ester or of a derivative of this acid, such as a halide or the anhydride, is reacted with a product of general formula:



(III)

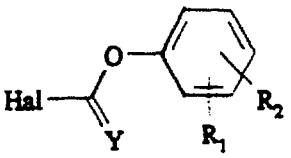
in which Ar, R, R_3, R_4 and R_5 are defined according to claim 1 and G_1 represents a hydrogen atom.

24. Process for the preparation of a compound of general formula (I) according to any one of claims 1 to 22, in which Y represents an oxygen or sulphur atom and X represents an oxygen atom, characterized in that a haloformate or of a halothioformate of general formula (IV):

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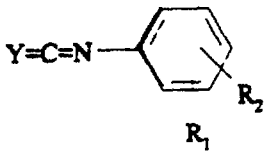
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(IV)

in which Y represents an oxygen or sulphur atom, R_1 and R_2 are defined according to claim 1 and Hal represents a halogen atom, is reacted with a product of general formula (III) as defined in claim 23.

25. Process for the preparation of a compound of general formula (I) according to any one of claims 1 to 22, in which Y represents an oxygen or sulphur atom and X represents an NH group, characterized in that an isocyanate or of an isothiocyanate of general formula (V):



(V)

in which Y represents an oxygen or sulphur atom and R_1 and R_2 are defined according to claim 1, is reacted with a product of general formula (III) as defined in claim 23.

26. Process for the preparation of a compound of general formula (I) according to any one of claims 1 to 22, in which

R represents a radical of general formula

$$-(CH_2)_m-X_1-(CH_2)_n-Z$$

in which:

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X_1, m and n are defined as above and Z represents a $-CON(R_7)(R_8)$ radical in which:

- R_7 represents a hydrogen atom or a straight or branched alkyl radical containing 1 to 6 carbon atoms and
- R_8 represents
- a hydrogen atom,
- a hydroxyl radical,
- an arylsulphonyl radical, such as phenylsulphonyl, optionally substituted by one or more atoms or radicals, which are identical or different, chosen from halogen atoms and alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,
- a 5- to 7-membered heterocycle incorporating one or more heteroatoms chosen from nitrogen, oxygen or sulphur atoms, it being possible for the said heterocycle to be bonded via a heteroatom,
- an amino radical optionally substituted by one or two radicals, which are identical or different, chosen from the following radicals:
  - alkyl containing 1 to 4 carbon atoms,
  - aryl, such as phenyl, optionally substituted by one or more radicals, which are identical or different, chosen from alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,
  - 5- to 7-membered heterocyclyl containing one or

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more heteroatoms chosen from nitrogen, oxygen and sulphur atoms,

- arylcarbonyl, such as benzoyl, optionally substituted by one or more radicals, which are identical or different, chosen from alkyl or alkyloxy radicals with, for these radicals, alkyl containing 1 to 4 carbon atoms,

- an alkyloxy radical containing 1 to 6 straight- or branched-chain carbon atoms optionally substituted by a phenyl radical,

- a straight or branched alkyl radical containing 1 to 6 carbon atoms, such as methyl, optionally substituted by an amino, alkylamino, dialkylamino, hydroxyl, alkoxy containing 1 to 4 carbon atoms, mercapto, alkylthio, alkyloxycarbonyl, carboxyl or cyano radical, an optionally substituted mono- or polycyclic aromatic radical having from 5 to 12 ring members which may or may not incorporate one or more heteroatoms chosen from oxygen, nitrogen and sulphur atoms, or also being able to be a phenyl radical optionally substituted by one or more halogen atoms or by one or more hydroxyl, amino or trifluoromethyl groups or by one or more alkyl or alkenyl, alkoxy, alkylthio, alkylamino, alkylcarbonyl or C_2 to C_4 alkoxycarbonyl, carbamoyl, alkylcarbamoyl or dialkylcarbamoyl, the alkyl part of which contains 1 to 8 carbon atoms, or formyl radicals, or alternatively a 1- or 2-naphthyl radical,

characterized in that a product of general formula:

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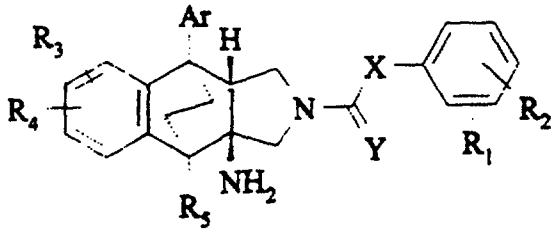
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$HN(R_7)(R_8)$

in which R_7 and R_8 are defined as above is reacted with a product of general formula (I) in which Z represents a carboxyl radical.

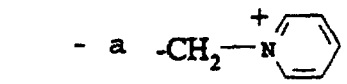
27. Process for the preparation of a compound of general formula (I) according to any one of claims 1 to 22, in which R represents a radical of general formula -NHCO-T in which T represents a hydrogen atom or an alkyl radical (1 to 6 carbon atoms) optionally substituted by an amino, carboxyl, alkyloxycarbonyl, hydroxyl, alkyloxy, mercapto or alkylthio radical, characterized in that an acid of general formula T-CO-OH, in which T is defined as above, is reacted with a product of general formula (VI):



(VI)

in which Ar, R_1, R_2, R_3, R_4, R_5, X and Y are defined according to claim 1.

28. Process for the preparation of a compound of general formula (I) according to any one of claims 1 to 22, in which which R represents

- a  radical,

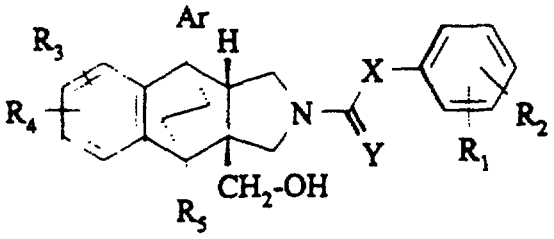
characterized in that an excess of pyridine and of a

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strong acid or of a derivative of this acid are reacted with a product of general formula:

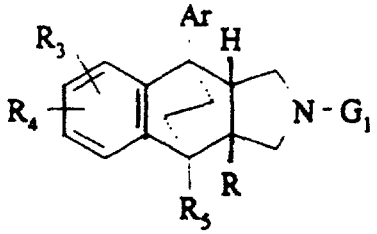
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(VII)

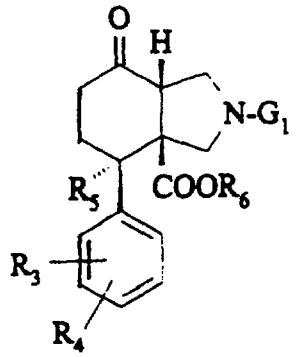
in which Ar, R_1, R_2, R_3, R_4, R_5, X and Y are defined according to claim 1.

29. Process for the preparation of a compound of general formula (III)



(III)

in which R_3, R_4, R_5, Ar and R are as defined in claim 1 and G1 represents a benzyl radical, from compounds of general formula (IX):



(IX)

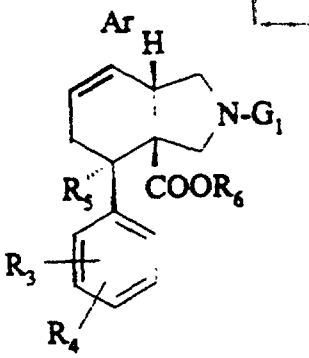
in which R_3, R_4, R_5, R_6 and G_1 are as defined above, characterized in that an intermediate of general

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formula (XV)

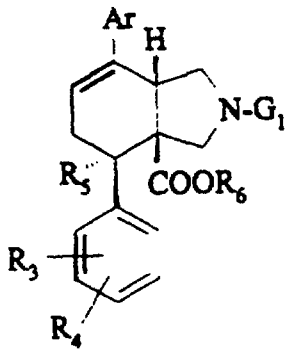
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(XV)

in which R_3, R_4, R_5, R_6, Ar and G_1 are as defined above, is formed and the conversion of which by intramolecular cyclization of Friedel-Crafts type results in the product (III) as defined in claim 23.

30. Compound, characterized in that it is represented by the general formula XV



(XV)

in which R_3, R_4, R_5 and Ar are as defined in claim 1, G_1 represents a benzyl radical and R_6 represents an alkyl radical containing 1 to 3 carbon atoms, in the racemic form, as well as its optical isomers.

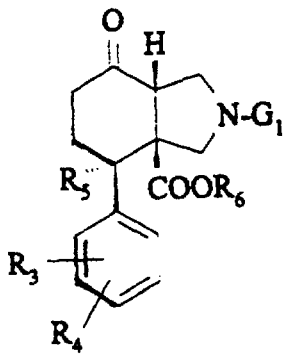
31. Process for the preparation of a compound of general formula (XV) according to claim 29,

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characterized in that a compound of general formula (IX)

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(IX)

in which R_3, R_4, R_5 and Ar are as defined in claim 1, G_1 represents a benzyl radical and R_6 represents an alkyl radical containing 1 to 3 carbon atoms, is converted at the 7 position, either into an iodoethylene derivative, by a Barton reaction, or into an enol triflate, and is then subjected to a palladium coupling reaction, the so-called Suzuki reaction with an arylboronic acid or the so-called Stille reaction with an arylstannane.

32. Process for the preparation of a compound of general formula (III) according to claim 23, in which Ar preferably represents

- a phenyl nucleus substituted at the para, meta-para or meta-para-meta' position by electron-donating groups,
- an electron-rich heterocyclic radical or
- a heterocyclic radical suitably substituted by electron-donating groups,

characterized in that an aromatic or heterocyclic hydrocarbon Ar-H is reacted, according to

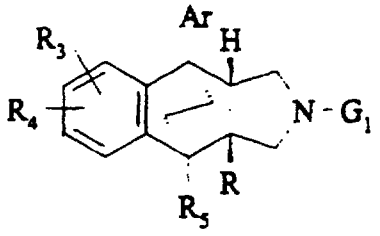
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intermolecular and then intramolecular cyclization reactions of Friedel-Crafts type, with a compound of general formula (IX), in which R_3, R_4, R_5 and Ar are as defined in claim 1, G_1 represents a benzyl radical and R_6 represents an alkyl radical containing 1 to 3 carbon atoms, in an organic solvent in the presence of an excess of strong acid or of a Lewis acid.

33. Process for the preparation of a product of general formula (III)

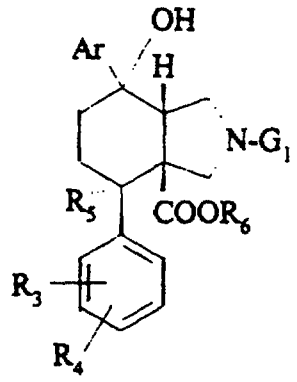


(III)

in which R_3, R_4, R_5 and Ar are as defined in claim 1, G1 represents a benzyl radical and R represents a carboxyl radical or a radical of general formula $COOR_6$ and R_6 represents an alkyl radical containing 1 to 3 carbon atoms, characterized in that intramolecular cyclization of Friedel-Crafts type is carried out by the action of trifluoromethanesulphonic acid on a product of general formula (VIII):



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(VIII)

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in which:

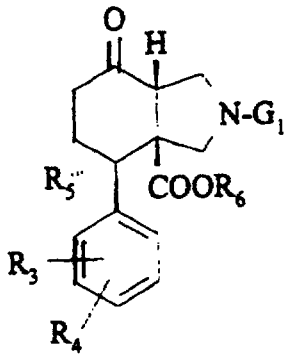
Ar, R_3, R_4 and R_5 are as defined in claim 1, G_1 represents a benzyl radical and R_6 represents an alkyl radical containing 1 to 3 carbon atoms,

followed by replacement of the G_1 group by a hydrogen atom, either by hydrogenolysis and then optionally by replacement of the hydrogen atom by a tert-butoxycarbonyl radical, by reaction with *tert*-butoxycarbonyl anhydride in an organic solvent, or by a benzyloxycarbonyl radical, by reaction with benzyloxycarbonyl chloride; or by reaction with an alkyl chloroformate, followed by acid hydrolysis of the carbamate formed as an intermediate, optionally followed by saponification of the product obtained.

34. Process for the preparation of a compound of general formula (VIII), in which Ar, R_3, R_4, R_5, R_6 and G_1 are as defined in claim 33, characterized in that it is carried out from a compound of general formula (IX)

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in which R_3, R_4, R_5, R_6 and G_1 are as defined in claim 32,

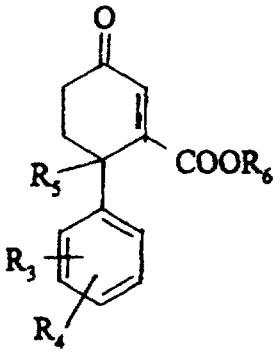
either by reaction with an organomagnesium derivative of general formula Ar-Mg-X, in which Ar is as defined above and X represents a halogen atom, in the presence of anhydrous cerium(III) chloride in an organic solvent at a temperature of between 0°C and the reflux temperature of the reaction mixture,

or by reaction with an organolithium derivative of general formula Ar-Li, in which Ar is as defined in claim 1, the reaction being carried out in an organic solvent at a temperature of between -78° and -20°C.

35. Process for the preparation of a compound of general formula (IX) as defined in claim 31 or 34, in which in which R_3, R_4, R_5 and Ar are as defined in claim 1, G_1 represents a benzyl radical and R_6 represents an alkyl radical containing 1 to 3 carbon atoms, characterized in that an N-trialkylsilylmethyl-N-(alkoxymethyl)amine, carrying a protective group for the amine functional group, is reacted with a derivative of a cyclohexenone of general formula:

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(X)

in which R_3, R_4 and R_5 are as defined in claim 1 and R_6 represents an alkyl radical containing 1 to 3 carbon atoms.

36. Pharmaceutical composition, characterized in that it contains at least one product according to one of the preceding claims 1 to 22 in combination with one or more pharmaceutically acceptable diluents or adjuvants, whether inert or biologically active.

37. Use of the compounds according to one of the preceding claims 1 to 22 in the preparation of pharmaceutical compositions useful in inhibiting farnesyl transferase.

38. Use of the compounds according to one of claims 1 to 22 in the preparation of pharmaceutical compositions for the treatment of diseases related to cell proliferations, malignant or benign, of cells of various tissues and/or organs, comprising muscle, bone or connective tissues, the skin, the brain, the lungs, the sexual organs, the lymphatic or renal systems, mammary or blood cells, the liver, the digestive

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system, the colon, the pancreas and the thyroid or adrenal glands, and including the following pathologies: psoriasis, restenosis, solid tumours, Kaposi's sarcoma, carcinomas, cholangiocarcinoma, choriocarcinoma, neuroblastoma, Wilms' tumour, Hodgkin's disease, melanomas, teratocarcinomas, gliomas, multiple myelomas, chronic lymphocytic leukaemias, acute or chronic granulocytic lymphomas, and cancers, such as cancers of the pancreas, colon, lung, ovary, breast, brain, prostate, liver, stomach, bladder or testicles.

39. Use of the compounds of general formula (I) according to one of claims 1 to 22 in the preparation of pharmaceutical compositions useful in the treatment of diseases related to cell proliferations by inhibition of farnesyl transferase.

40. Use of the compounds of general formula (I) according to one of claims 1 to 22 in the preparation of pharmaceutical compositions for the treatment of cancers.

41. Use of the compound of claim 21 in the preparation of pharmaceutical compositions for the treatment of cancers.

42. Use of the compounds of general formula (I) according to one of claims 1 to 22 in the preparation of pharmaceutical compositions for the treatment of cancer of the colon.

43. Use of the compounds of general formula

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(I) according to one of claims 1 to 22 in the preparation of pharmaceutical compositions for the treatment of cancer of the pancreas.

44. Use of the compound of claim 21 in the preparation of pharmaceutical compositions for the treatment of cancer of the colon.

45. Use of the compound of claim 21 in the preparation of pharmaceutical compositions for the treatment of cancer of the pancreas.

46. Combinations of a product according to one of the preceding claims 1 to 22 with one or more compatible and pharmacologically active compounds and/or with a radiotherapy treatment, in order to obtain a synergic therapeutic effect.

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