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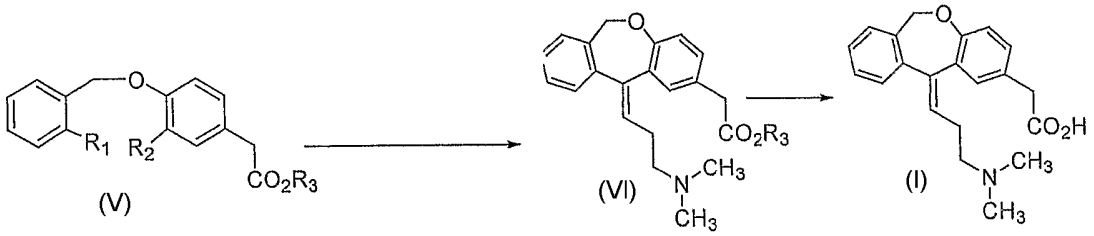
(54) Title: PROCESS FOR THE PREPARATION OF 11-[(Z)-3-(DIMETHYLAMINO)PROPYLIDENE]-6,11-DIHYDRO-DIBENZ[B,E]OXEPIN-2-YL]-ACETIC ACID



(57) Abstract: Process for the preparation of olopatadine (I), which comprises reacting a compound of formula (V) in the presence of a palladium catalyst to provide a compound of formula (VI), wherein the acid protecting group is removed to provide the compound of formula (I) and if desired, transformation into its salts.

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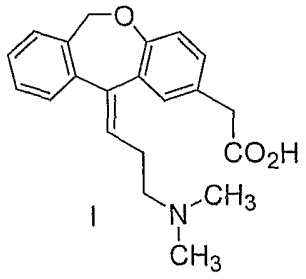
Process for the preparation of 11-[(*Z*)-3-(dimethylamino)propylidene]-6,11-dihydro-dibenz[*b,e*]oxepin-2-yl]-acetic acid

The sector of technology, which the invention refers to

The present invention provides a new process for the preparation of 11-[(*Z*)-3-(dimethylamino)propylidene]-6,11-dihydro-dibenz[*b,e*]oxepin-2-yl]-acetic acid useful as an antihistaminic agent, and its intermediates of the synthesis.

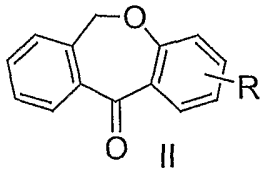
Description of the technical status

The compound of 11-[(*Z*)-3-(dimethylamino)propylidene]-6,11-dihydro-dibenz[*b,e*]oxepin-2-yl]-acetic acid represented by formula I, commonly known as Olopatadine, has been used as an active constituent drug, in form of its hydrochloride salt.



I

The preparation of the compound of formula I has been described previously in patents number US5115883 and US4871865, where it is prepared from the basic structure dibenzo[*b,e*]oxepine-11-one (formula II) suitably substituted,



II

where R is CH_2COOH or a precursor group of CH_2COOH, such as halogen or CH_2CN. This transformation is carried out by means of two different synthetic pathways:

A/ Preparation of compound of formula I by means of a Wittig reaction by reacting a compound of formula II with the triphenylphosphonium salt of formula III.

$$Ph_3P{=}CH(CH_2)_2N(CH_3)_2 \quad (III)$$

B/ Alternatively, the compound of formula I may be prepared by means of a Grignard reaction, reacting compounds of formula II with the reagent of formula IV,

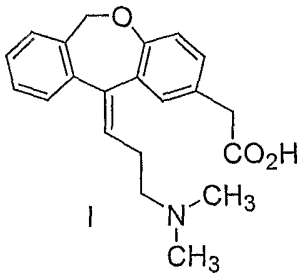
$(CH_3)_2NCH_2CH_2CH_2MgX$ (IV)

where X is halogen, followed by dehydration with a strong acid.

Until now, all processes described for the preparation of olopatadine have some disadvantages for their application at industrial scale. For this reason, it is necessary to find an alternative process for the preparation of olopatadine and/or its pharmaceutically acceptable salts, which is suitable for the preparation at industrial scale. This problem is solved by the new preparation process claimed in this patent.

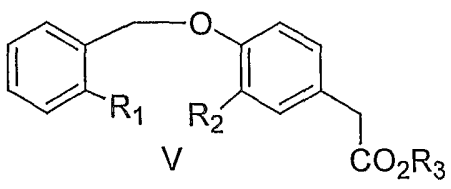
Summary of the invention

One aspect of the present invention relates to the process of the preparation of 11-[(*Z*)-3-(dimethylamino)propylidene]-6,11-dihydro-dibenz[*b,e*]oxepin-2-yl]-acetic acid of formula I and/or its salts,



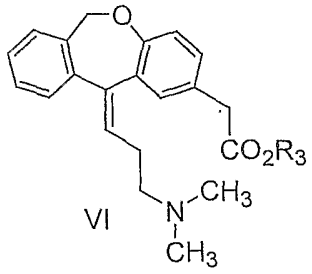
I

comprising reacting the compound of formula V,



V

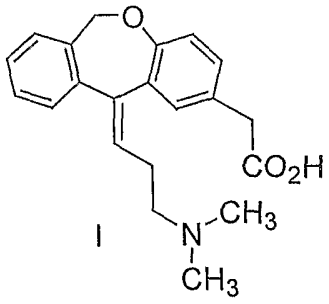
wherein one of R_1 and R_2 is halogen and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is an acid protecting group, in the presence of a palladium catalyst, to provide a compound of formula VI,



VI

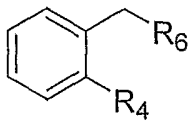
wherein the acid protection group is removed to provide the compound of formula I and if desired, transformation into its salts.

Another aspect of the present invention is a process for the preparation of 11-[(*Z*)-3-(dimethylamino)propylidene]-6,11-dihydro-dibenz[*b,e*]oxepin-2-yl acetic acid of formula I and/or its pharmaceutically acceptable salts,



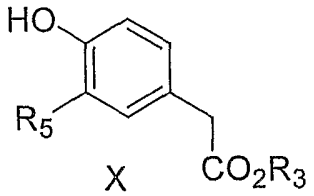
I

comprising reacting compounds of formula IX



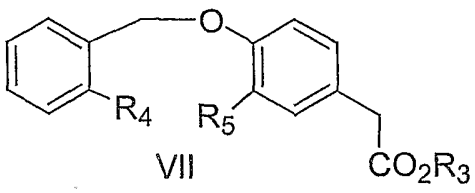
IX

with compounds of formula X,



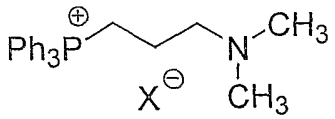
X

wherein R_6 is a leaving group and one of R_4 and R_5 is halogen and the other is CHO and R_3 is as defined above, in the presence of a base to obtain compounds of formula VII,



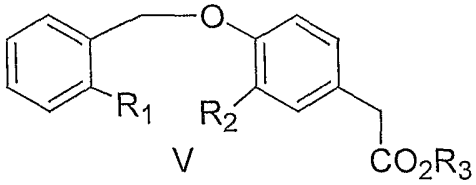
VII

wherein R_4 is as defined for formula IX and R_5 and R_3 are as defined for formula X, reacting compounds of formula VII with compounds of formula VIII or a salt thereof,



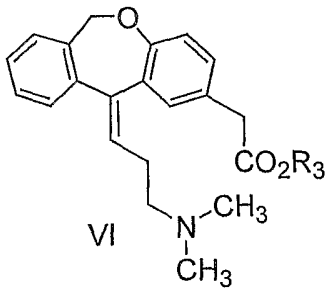
VIII

wherein X is iodine, chlorine or bromine, in the presence of a base to obtain compounds of formula V



V

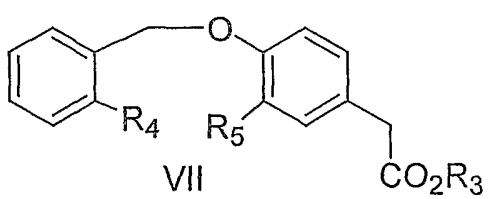
wherein R_1, R_2 and R_3 are as defined above, reacting compounds of formula V in the presence of a palladium catalyst to obtain compounds of formula VI



VI

and removing the acid protecting group R_3 of compounds of formula VI to obtain a compound of formula I; and if desired, converting the compound of formula I into its pharmaceutically acceptable salts.

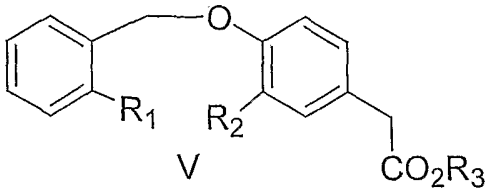
Another aspect of the present invention are the compounds of formula VII,



VII

wherein one of R_4 and R_5 is halogen and the other is CHO and R_3 is an acid protecting group.

Another aspect of the present invention are compounds of formula V,



V

wherein one of R_1 and R_2 is halogen and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is an acid protecting group.

Compounds of formula VII and V are useful as intermediates in the preparation of a compound of formula I.

Description of the invention

Within the definitions that are mentioned, the term leaving group means a group that removes during a removal reaction, such as halogen, for example iodine, chlorine or bromine or an alkylsulphonyloxy or arylsulphonyloxy group, for example methansulphonyl, toluenesulphonyl, trifluoromethansulphonyl or benzenesulphonyl.

Acid protecting group is a term used for any group described in the literature for this purpose, such as C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_1-C_4 alkoxy-C_1-C_4-alkyl, aryl-C_1-C_4-alkyl, C_3-C_6 cycloalkyl or aryl, wherein aryl is phenyl or phenyl substituted by one or more groups such as, C_1-C_4 alkyl, halogen, C_1-C_4 haloalkyl, C_1-C_4 alkoxy or C_1-C_4 haloalkoxy. Preferably the acid protecting group is C_1-C_4 alkyl, and even more preferably it is methyl.

The term halogen, as a group or part of a group, means iodine, chlorine or bromine, preferably iodine.

The term C_1-C_4 alkyl, as a group or part of a group, means a linear or branched chain of 1 to 4 carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, and *tert*-butyl.

The meaning of a group C_1-C_4 haloalkyl is a group resulting from the substitution of one or more hydrogen atoms of a C_1-C_4 alkyl by one or more halogen atoms (that is fluorine, chlorine, bromine or iodine), which may be the same or different. For example trifluoromethyl, trichloromethyl, fluoromethyl, chloromethyl, bromomethyl, iodomethyl, difluoromethyl, dichloromethyl, 2-chloroethyl, 2,2-dichloroethyl, 2,2,2-trichloroethyl, pentachloroethyl, 2-

fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, pentafluoroethyl, 3-chloropropyl, 3,3-dichloropropyl, 3,3,3-trichloropropyl, 2,2,3,3,3-pentachloropropyl, 3-fluoropropyl, 3,3-difluoropropyl, 3,3,3-trifluoropropyl, 2,2,3,3-tetrafluoropropyl, 2,2,3,3,3-pentafluoropropyl, heptafluoropropyl, 4-chlorobutyl, 4-fluorobutyl, 4-iodobutyl and 4-bromobutyl.

Examples for C_3-C_6 cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl.

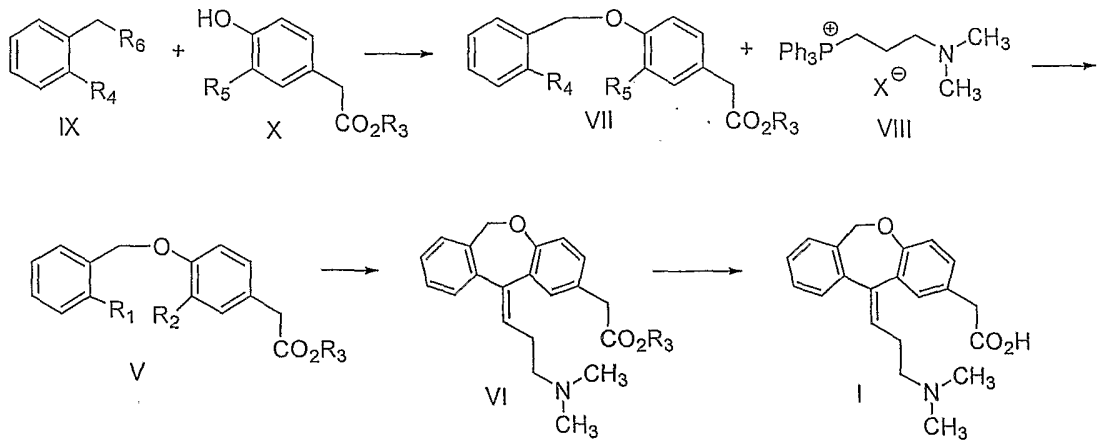
Examples for C_1-C_4 alkoxy are methoxy, ethoxy, propoxy, isopropoxy, butoxy, isobutoxy, *sec*-butoxy and *tert*-butoxy.

The meaning of a group C_1-C_4 haloalkoxy is a group resulting from the substitution of one or more hydrogen atoms of C_1-C_4 alkoxy by one or more halogen atoms, which may be the same or different. For example trifluoromethoxy, fluoromethoxy, 2-chloroethoxy, 2-fluoroethoxy, 2-iodoethoxy, 2,2-difluoroethoxy, 2,2,2-trifluoroethoxy, pentafluoroethoxy, 3-fluoropropoxy, 3-chloropropoxy, 2,2,3,3-tetrafluoropropoxy, 2,2,3,3,3-pentafluoropropoxy, heptafluoropropoxy, 4-fluorobutoxy and 4-chlorobutoxy.

The meaning of a group C_1-C_4 alkoxy- C_1-C_4-alkyl is a group resulting from the substitution by one or more hydrogen atoms of C_1-C_4-alkyl for one or more C_1-C_4-alkoxy, which may be the same or different. For example, metoxymethyl, 1-metoxyethyl, 2-methoxyethyl, 1-methoxypropyl, 2-methoxypropyl, ethoxymethyl, 1-ethoxyethyl, 2-ethoxyethyl, 2-propoxyethyl, isopropoxymethyl, 2-isopropoxyethyl, butoxymethyl, 1-butoxyethyl, 2-butoxyethyl and *sec*-butoxymethyl, 2-*sec*-butoxyethyl, *tert*-butoxymethyl, 2-tert-butoxyethyl and 1-tert-butoxyethyl.

The meaning of a group aryl-C_1-C_4-alkyl is a group resulting from the substitution by one or more hydrogen atoms of C_1-C_4-alkyl for one or more aryl groups, which may be the same or different, such as, phenyl-methyl, phenyl-ethyl, 1,1-diphenylethyl, 1,2-diphenylethyl, 1-phenylpropyl, 4-bromophenylisopropyl, 4-bromophenylmethyl, 4-chlorophenylethyl, 4-methoxyphenylmethyl, 4-bromophenylethyl, 1-(4-bromophenyl)propyl and 2-(4-bromophenyl)propyl,

The process for the preparation of the compound of formula I, one of the objects of this invention can preferably be summarized in the following diagram:



The transformation of compounds of formula V into compounds of formula VI is carried out in the presence of a palladium catalyst, such as any standard catalyst well known in organic synthesis, for example palladium tetrakis(triphenylphosphine) palladium or palladium acetate (the latter being preferred), and optionally in the presence of a phosphine such as triphenylphosphine or tri-O-tolylphosphine and/or a base, such as triethylamine, tetrabutylammonium chloride or a alkaline metal carbonate, for example potassium carbonate or sodium carbonate, with a suitable solvent, such as acetonitrile, dimethylformamide, water or mixtures thereof and at a suitable temperature preferably comprised between room temperature and the reflux temperature of the solvent, more preferably the temperature range is around 60-75°C.

In a preferred embodiment of the transformation process of compounds of formula V into compounds of formula VI, R_3 is C_1-C_4-alkyl.

In a preferred embodiment of the transformation process of compounds of formula V into compounds of formula VI, R_1 is halogen and R_2 is (E)-CH=CH-CH_2-CH_2-$N(CH_3)_2$.

In a preferred embodiment of the transformation process of compounds of formula V into compounds of formula VI, R_1 is (Z)-CH=CH_2-CH_2-$N(CH_3)_2$ and R_2 is halogen.

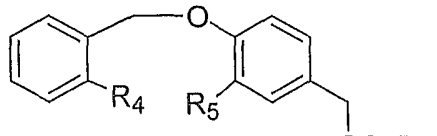
In a preferred embodiment of the process, the transformation of compounds of formula V into compounds of formula VI is preferably carried out using palladium acetate as a palladium catalyst, in the presence of a base,

preferably potassium carbonate and tetrabutylammonium chloride in acetonitrile-water.

The acid protecting group of compounds of formula VI is removed thus obtaining the compound of formula I, by using standard conditions for removing acid protecting groups well known to those skilled in the art, for example following the process described in Protective groups in Organic synthesis by Theodora W. Greene (John Wiley and sons. Inc). Preferably wherein R_3 is a C_1-C_4-alkyl, the removal is carried out in an alkaline medium such as aqueous NaOH and wherein R_3 is an aryl-C_1-C_4-alkyl the removal is carried out by catalytical hydrogenation.

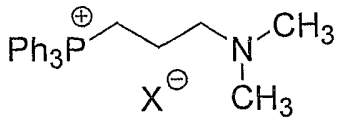
If desired, optionally the compund of formula I can be converted into its pharmaceutically acceptable salts, such as salts prepared with inorganic acids, for example HCl, HI and salts prepared with organic acids such as, methansulfonic acid, trifluoromethansulfonic acid, fumaric acid or oxalic acid, preferably its hydrochloride salt. These salts are prepared by the reaction of compound of formula I with the appropiate acid, in a suitable solvent and at a temperature preferably comprised between room temperature and the reflux temperature of the solvent, more preferably the temperature is room temperature (considered around 15-30°C).

Compounds of formula V can be prepared from compounds of formula VII,



VII

wherein one of R_4 and R_5 is halogen and the other is CHO and R_3 is as defined above, by reaction with compounds of formula VIII or a salt thereof,



VIII

wherein X is iodine, chlorine or bromine, in the presence of a base.

The transformation of compounds VII into compounds of formula V is carried out by reaction of compounds of formula VIII or a salt of acid addition, such as HCl, HBr o HI, preferably HI, in the presence of a base, preferably a lithium base or a sodium base, for example butyl lithium, lithium

diisopropylamide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide or lithium bis(trimethylsilyl)amide, preferably in a suitable solvent, such as toluene or tetrahydrofurane, preferably in an atmosphere of inert gas such as nitrogen or argon and at a suitable temperature, preferably room temperature.

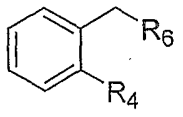
In a preferred embodiment of the process, X is iodine.

In another preferred embodiment of the process, one of R_4 and R_5 is iodine and the other is CHO.

In a more preferred embodiment, in the conversion of compounds of formula VII into compounds of formula V, R_4 is iodine and R_5 is CHO and the reaction is carried out with a lithium base such as butyl lithium, diisopropyl lithium or lithium bis(trimethylsilyl)amide, preferably lithium bis(trimethylsilyl)amide.

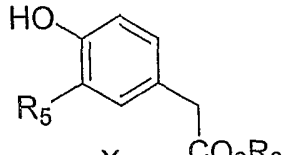
In another more preferred embodiment, in the conversion of compounds of formula VII into V, R_4 is CHO and R_5 is iodine and the reaction is carried out with a sodium base such as sodium hydride, sodium carbonate or sodium bis(trimethylsilyl)amide, preferably sodium bis(trimethylsilyl)amide.

Compounds of formula VII may be prepared from compounds of formula IX



IX

by reaction with compounds of formula X



X

wherein R_6 is a leaving group and R_3, R_4 and R_5 are as defined above, in the presence of a base.

The base used in the preparation of compounds of formula VII may be for example, sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate or potassium fluoride, preferably potassium carbonate, and preferably the reaction is carried out in a suitable solvent, such

as acetone, acetonitrile or N,N-dimethylformamide, preferably acetonitrile, at a temperature preferably between room temperature and reflux temperature, more preferably the temperature is reflux temperature of the solvent.

In a preferred embodiment, R_6 is halogen.

In a more preferred embodiment, R_6 is chlorine, bromine or iodine.

Compounds of formula V and VII are new and are another embodiment of the invention as mentioned above.

A preferred embodiment are compounds of formula VII, wherein one of R_4 and R_5 is halogen and the other is CHO and R_3 is C_1-C_4 alkyl.

A more preferred embodiment are compounds of formula VII wherein one of R_4 and R_5 is iodine and the other is CHO and R_3 is C_1-C_4 alkyl.

A much more preferred embodiment are compounds of formula VII wherein one of R_4 and R_5 is iodine and the other is CHO and R_3 is methyl.

A preferred embodiment are compounds of formula V wherein one of R_1 and R_2 is halogen and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is C_1-C_4 alkyl.

A more preferred embodiment are compounds of formula V wherein one of R_1 and R_2 is iodine and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is C_1-C_4 alkyl.

A more preferred embodiment are compounds of formula V wherein one of R_1 and R_2 is iodine and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is methyl.

A much more preferred embodiment are compounds of formula V wherein R_1 is iodine, R_2 is (*E*)-$CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is methyl.

A much more preferred embodiment are compounds of formula V wherein R_1 is (*Z*)-$CH=CH-CH_2-CH_2-N(CH_3)_2$, R_2 is iodine and R_3 is methyl.

Starting compounds of formula IX, X and VIII are commercially available or can be prepared by methods described in the literature. For example, a compound of formula IX, wherein R_6 is bromine and R_4 is CHO, may be prepared by the process described by Xiao-Xiang and al. in Journal of Organic Chemistry, **2000**, *65*, 5298. The compound of formula X, wherein R_3 is C_1-C_4 alkyl and R_5 is CHO, may be prepared by the process described in Acta Chem. Scand. **1999**, *53(4)*, 258-262 and the compound of formula X, wherein R_3 is C_1-C_4 alkyl and R_5 is iodine, may be prepared by the process described in

WO01/90105. On the other hand, compounds of formula VIII, may be prepared by the process described in J. Am. Chem. Soc **1985**, *107*, 217-226.

NaI is preferably used in the course of the preparation of compounds of formula VII, wherein R_6 is halogen, in particular Br, Cl or F.

The invention which is illustrated by the following examples is not to be understood as being limited in any way.

EXAMPLE 1.

[3-Formyl-4-(2-iodo-benzyloxy)-phenyl]-acetic acid methyl ester

A solution of (3-formyl-4-hydroxy-phenyl)-acetic acid methyl ester (17.2g, 85.9mmol) in acetonitrile was slowly added to a solution of 1-chloromethyl-2-iodo-benzene (13.06g, 94.5mmol) and NaI (3.22g, 21.5mmol) in acetonitrile (273ml) at reflux temperature and the mixture was mantained at this temperature for 3 hours. Once the mixture reached room temperature, the residue that had formed was filtered, washed with acetonitrile and concentrated to obtain a residue that was then dissolved in toluene (330ml) and washed with NaOH 0.1N and water. The organic layer was concentrated to dryness, diluted with acetone (330ml) and was stirred into water (500ml) at room temperature. The mixture was filtered and washed with water to obtain 33.95g (96%) of [3-Formyl-4-(2-iodo-benzyloxy)-phenyl]-acetic acid methyl ester, which was purified by crystallization in toluene-cyclohexane (99% HPLC)

^{1}H-RMN (300MHz, $CDCl_3$): 3,61 (s, 2 H, CH_2-CO_2CH_3); 3,69 (s, 3 H, CH_3); 5,15 (s, 2 H, O-CH_2-Ph); 6.99-7.92 (7H, Ar); 10,55 (s, 1 H, CHO).

EXAMPLE 2.

[4-(2-Formyl-benzyloxy)-3-iodo-phenyl]-acetic acid methyl ester

2-Bromomethyl-benzaldehyde (11g, 55.26mmol) in acetonitrile (132ml) was added to a solution of (4-Hydroxy-3-iodo-phenyl)-acetic acid methyl ester (16.06g, 55mmol), K_2CO_3 (8.36g, 60.50mmol) and NaI (2.07g, 13.80mmol) in acetonitrile (88ml). The mixture was heated to reflux temperature and was stirred at this temperature for 3 hours. Once the mixture cooled down to room temperature, it was filtered and was then concentrated to dryness to obtain a residue that was diluted in toluene (212ml) and then it was washed with NaOH 0.05N. Once the layers had separated, the aqueous layer was washed with

toluene (100ml) again and the organic layers were washed with water (2x100ml, 1x50ml), were concentrated to dryness to obtain a residue, which was then diluted with a mixture of acetone-water at 30°C. Then the mixture was cooled until 20-22°C. The solid formed was filtered to obtain 18g (80%) of [4-(2-Formyl-benzyloxy)-3-iodo-phenyl]-acetic acid methyl ester (98%HPLC).

^{1}H-RMN (300MHz, $CDCl_3$): 3.541 (s, 2H, CH_2COOCH_3); 3.69 (s, 3H, -CH_3); 5.54 (s, 2H, O-CH_2-Ph); 6.91 (d, *J*= 8.4 Hz, 1H, Ar); 7.22 (dd, *J*=8.4 y 2.1 Hz, 1H, Ar); 7.54 (t, *J*=7.5Hz, 1H, Ar); 7.69 (dt, *J*= 7.8 Hz y 0.5 Hz, 1H); 7.73 (d, *J*=2.1 Hz, 1H, Ar); 7.86 (dd, *J*=7.8 y 1.5 Hz), 1H, Ar); 8.08 (d, J=7.8 Hz, 1H, Ar) 10.15 (s, 1H, CHO).

EXAMPLE 3.

(*E*)-[3-(4-Dimethylamino-but-1-enyl)-4-(2-iodo-benzyloxy)-phenyl]-acetic acid methyl ester

Lithium bis(trimethylsilyl)amide (LiHMDS) (1M THF, 51.5ml, 51.5mmol) was added drop by drop to a dispersion of (3-Dimethylamino-propyl)-triphenyl-phosphonium iodide (24.33g, 51.2mmol) in anhydrous toluene (300ml) at room temperature and in an inert atmosphere. The mixture was stirred at this temperature for 1hour. Following this a solution of and [3-Formyl-4-(2-iodo-benzyloxy)-phenyl]-acetic acid methyl ester (5g, 12.2mmol) in anhydrous toluene was added to the mixture and they were stirred at room temperature for 2h 30min. Hydrochloric acid 2N was added to the mixture and organic layers were washed by HCl 2N. Aqueous layers were washed with toluene and then they were alkalized with K_2CO_3. Aqueous layers were extracted with ethyl acetate, filtered, dried and concentrated to dryness to obtain 4.74g (83%) of [3-(4-Dimethylamino-but-1-enyl)-4-(2-iodo-benzyloxy)-phenyl]-acetic acid methyl ester, which was used, without having been purified in the following step.

An analytical sample of the isomerically pure compound of the title was obtained by silica gel column chromatography from an aliquot of the reaction mixture.

(*E*): ^{1}H-RMN (300MHz, $CDCl_3$): 2.26 (s, 6H, $N(CH_3)_2$); 2.43 (s, 4H, CH_2-CH_2); 3.52 (s, 2H, $CH_2COOCH3$); 3.69 (s, 3H, OCH_3); 5.14 (s, 2H, CH_2OPh); 6.14 (dm, 1H, =CH-CH_2); 6.72 (d, *J*=15.6Hz, Ph-CH=CH-); 6.83 (d, *J*=8.4Hz, 1H, Ar); 7.24 (m, 3H, Ar); 7.49 (m, 2H, Ar); 7.71 (d, *J*=2.1Hz, Ar).

EXAMPLE 4.

(*Z*)-{4-[2-(4-Dimethylamino-but-1-enyl)-benzyloxy]-3-iodo-phenyl}-acetic acid methyl ester

Potassium bis(trimethylsilyl)amide (KHMDS) (0.5M in toluene, 102.5ml, 51mmol) was slowly added to a dispersion of (3-Dimethylamino-propyl)-triphenyl-phosphonium iodide (24.3g, 51mmol) in anhydrous toluene (60ml) at room temperature and in an inert atmosphere. The mixture was stirred at this temperature for 1hour and then [4-(2-Formyl-benzyloxy)-3-iodo-phenyl]-acetic acid methyl ester (5g, 12 mmol) in anhydrous toluene was added and was stirred at this temperature for 2h 30min. Hydrochloric acid 2N was added to the mixture and organic layers were washed with HCl 2N. Watery layers were washed with toluene and were alkalized with K_2CO_3. The aqueous layers were extracted with ethyl acetate, were filtered, dried and concentrated to dryness to obtain 10.2g (73%) {4-[2-(4-Dimethylamino-but-1-enyl)-benzyloxy]-3-iodo-phenyl}-acetic acid methyl ester (72:28 *Z/E*), that was used, without having been purified in the following step.

An analytical sample of the isomerically pure compound of the title was obtained by silica gel column chromatography from an aliquot of the reaction mixture.

(Z): ^{1}H-RMN (300MHz, $CDCl_3$): 2.16 (s, 6H, $N(CH_3)_2$); 2.33 (s, 4H, CH_2-CH_2); 3.51 (s, 2H, CH_2COOCH_3); 3.68 (s, 3H, OCH_3); 5.04 (s, 2H, CH_2O); 5.80 (m, 1H, =CH-CH2); 6.59 (d, *J*=11.4Hz, 1H, Ph-CH=CH); 6.77 (d, *J*=8.1Hz, 1H, Ar); 7.24 (m, 4H, Ar); 7.64 (m, 1H, Ar); 7.70 (d, *J*=2.4Hz, 1H, Ar).

EXAMPLE 5.

(*Z*)-[11-(3-Dimethylamino-propylidene)-6,11-dihydro-dibenzo[b,e]oxepin-2-yl]-acetic acid methyl ester

Method A:

A mixture of the compound of example 3 (10g, 18mmol), K_2CO_3 (7.2g, 52mmol) and tetrabutylammonium chloride (5.8g, 20mmol) in acetonitrile-water 10:1 (v/v) (400ml) was stirred for 15min at room temperature. Palladium acetate (II) (0.945g, 4mmol) was added to the previous mixture and stirred at 60°C for 24 hours. Once the mixture cooled down to room temperature, it was concentrated

to dryness, diluted in toluene (100ml) and washed with aqueous acetic acid 10% (v/v). Aqueous layers were washed with toluene (100ml) alkalized with K_2CO_3 and then extracted with ethyl acetate, The organic layers were washed with water, were dried, filtered and concentrated to dryness thus obtaining 3.1g of (Z)-[11-(3-Dimethylamino-propylidene)-6,11-dihydro-dibenzo[b,e]oxepin-2-yl]-acetic acid methyl ester (97.27% of purity by HPLC).

An analytical sample of the isomerically pure compound of the title was obtained by silica gel column chromatography from an aliquot of the reaction mixture.

(Z): ^{1}H-RMN (300MHz, $CDCl_3$): 2.15 (s, 6H, $N(CH_3)_2$); 2.37 (m, 4H, CH_2-CH_2); 3.52 (s, 2H, CH_2-$COOCH_3$); 3.67 (s, 3H, CH_3); 4.80 (broad, 1H, $\underline{CH_2}$-O); 5.48 (broad, 1H, CH_2-O); 6.02 (t, 1H, =$\underline{CH}$-CH_2); 6.70 (d, *J*= 8.4Hz, 1H, Ar); 7.02 (dd, *J*=8.4 y 2.4Hz, 1H, Ar); 7.25 (mc, 5H, Ar).

Method B:

A mixture of the compound from example 4 (10g, 21mmol), K_2CO_3 (7.3g, 53mmol) and tetrabutylammonium chloride (5.9g, 21mmol) in acetonitrile-water 10:1 (v/v) (80ml) was stirred at room temperature for 15 min. Palladium acetate (II) (0.96g, 4.2mmol) was added to this mixture and it was stirred at 60ºC for 24 hours. Once the mixture cooled down to room temperature, it was concentrated to dryness, diluted in ethyl acetate (160ml), and then washed with a saturated solution of sodium bicarbonate and aqueous solution of NaCl. The organic layer was dried, filtered and concentrated to dryness to obtain 7.8g of (Z)-[11-(3-Dimethylamino-propylidene)-6,11-dihydro-dibenzo[b,e]oxepin-2-yl]-acetic acid methyl ester (85.87% of purity by HPLC).

EXAMPLE 7.

(Z)-[11-(3-Dimethylamino-propylidene)-6,11-dihydro-dibenzo[b,e]oxepin-2-yl]-acetic acid hydrochloride

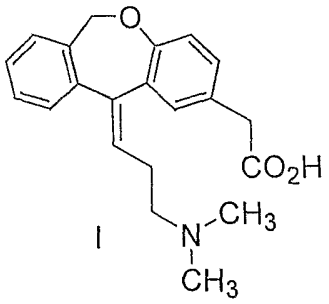
A mixture of the compound obtained in example 5 (method A) (1.31g, 3.57mmol) in methanol (25ml) and water (5ml) was stirred for 5 hours at room temperature in the presence of NaOH 5N (1.5ml, 7.50mmol). The mixture was neutralized with HCl 2N and concentrated to dryness. The product obtained was diluted with water and washed through an ionic exchange resin with a mixture of methanol-water as a mobile phase. Organic layers were concentrated to

dryness to obtain 1.16g (92%) (Z)-[11-(3-Dimethylamino-propylidene)-6,11-dihydro-dibenzo[b,e]oxepin-2-yl]-acetic acid (95% purity by HPLC).

HCl 2N (2ml, 4.10mmol) was added to a solution of the acid in water. The mixture was stirred and concentrated to dryness. The solution of resultant oil in acetone (25ml) was refluxed for 30min and the suspension obtained was cooled, filtered, washed and dried to obtain 0.88g (70% global) of (Z)-[11-(3-Dimethylamino-propylidene)-6,11-dihydro-dibenzo[b,e]oxepin-2-yl]-acetic acid hydrochloride (99.17% of purity by HPLC).

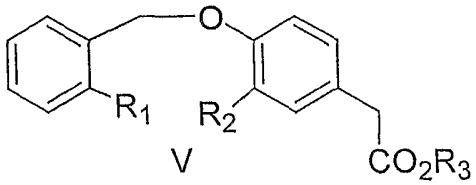
CLAIMS

1. A process for the preparation of 11-[(Z)-3-(dimethylamino)propylidene]-6,11-dihydro-dibenz[*b,e*]oxepin-2-yl acetic acid of formula I and/or its pharmaceutically acceptable salts,



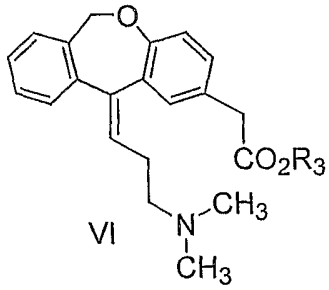
I

comprising reacting compounds of formula V,



V

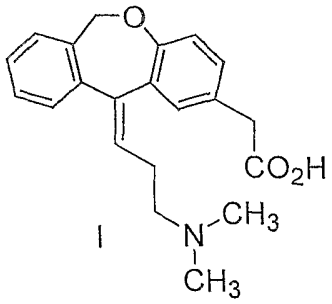
wherein one of R_1 and R_2 is halogen and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is an acid protecting group, in the presence of a palladium catalyst, to obtain compounds of formula VI,



VI

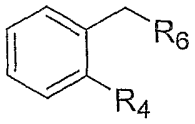
and removing the acid protecting group R_3 of compounds of formula VI to obtain a compound of formula I; and if desired, converting the compound of formula I into its pharmaceutically acceptable salts.

2. A process for the preparation of 11-[(Z)-3-(dimethylamino)propylidene]-6,11-dihydro-dibenz[*b,e*]oxepin-2-yl acetic acid of formula I and/or its pharmaceutically acceptable salts,



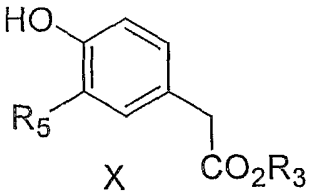
I

comprising reacting compounds of formula IX



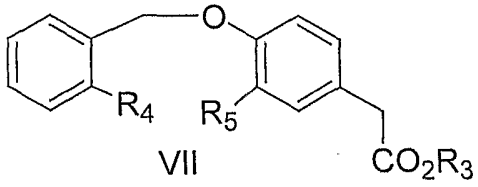
IX

with compounds of formula X,



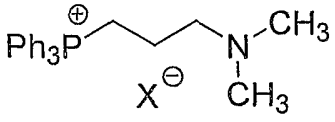
X

wherein R_6 is a leaving group, one of R_4 and R_5 is halogen and the other is CHO and R_3 is as defined in claim 1, in the presence of a base to obtain compounds of formula VII,



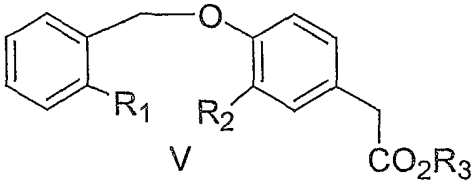
VII

wherein R_4 is as defined for formula IX and R_5 and R_3 are as defined for formula X, reacting compounds of formula VII with compounds of formula VIII or a salt thereof,



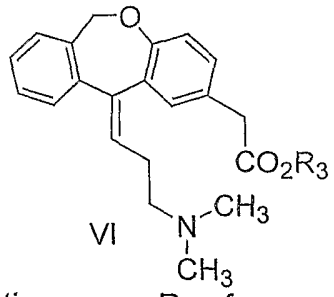
VIII

wherein X is iodine, chlorine or bromine, in the presence of a base to obtain compounds of formula V



V

wherein R_1, R_2 and R_3 are as defined in claim 1, reacting compounds of formula V in the presence of a palladium catalyst to obtain compounds of formula VI



VI

and removing the acid protecting group R_3 of compounds of formula VI to obtain a compound of formula I; and if desired, converting the compound of formula I into its pharmaceutically acceptable salts.

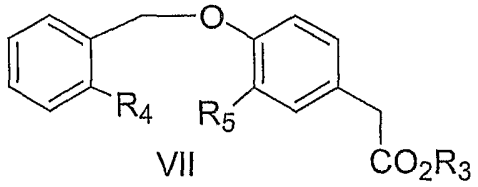
3. A process according to claim 1 or 2, wherein R_3 is C_1-C_4 alkyl.

4. A process according to claim 1, 2 or 3, wherein the palladium catalyst is palladium acetate.

5. A process according to anyone of claims 1 to 4, wherein R_1 is halogen and R_2 is (*E*)-CH=CH-CH_2-CH_2-N(CH_3)$_2$.

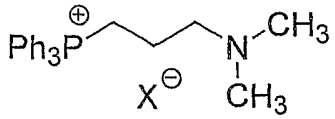
6. A process according to anyone of claims 1 to 4, wherein R_1 is (*Z*)-CH=CH-CH_2-CH_2-N(CH_3)$_2$ and R_2 is halogen.

7. A process according to anyone of claims 1 to 6, comprising the preparation of compounds of formula V from compounds of formula VII,



VII

wherein one of R_4 and R_5 is halogen and the other is CHO and R_3 is as defined in claims 1 to 3, by reaction with compounds of formula VIII or a salt thereof,



VIII

wherein X is iodine, chlorine or bromine, in the presence of a base.

8. A process according to claim 7, wherein X is iodine.

9. A process according to claim 7 or 8, wherein one of R_4 and R_5 is iodine and the other is CHO.

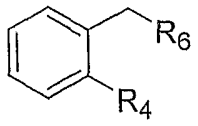
10. A process according to claim 9, wherein R_4 is iodine and R_5 is CHO and the reaction is carried out in the presence of a lithium base.

11. A process according to claim 10, wherein lithium base is lithium bis(trimethylmethylsilyl)amide.

12. A process according to claim 9, wherein R_4 is CHO and R_5 is iodine and the reaction is carried out in the presence of a sodium base.

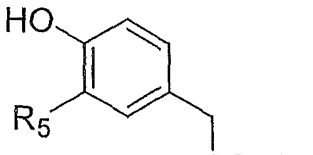
13. A process according to claim 12, wherein the sodium base is sodium bis(trimethylsilyl)amide.

14. A process according to anyone of claims 7 to 13, comprising the preparation of compounds of formula VII from compounds of formula IX



IX

by reaction with compounds of formula X



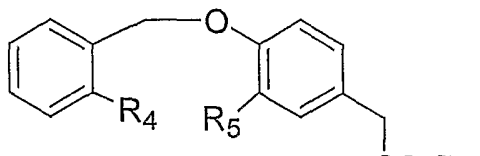
X

wherein R_6 is a leaving group and R_3, R_4 and R_5 are as defined in any of the preceding claims , in the presence of a base.

15. A process according to claim 14, wherein the base for the preparation of compounds of formula VII from compounds of formula IX is potassium carbonate.

16. A process according to claim 14, wherein R_6 is halogen.

17. Compounds of formula VII,



VII

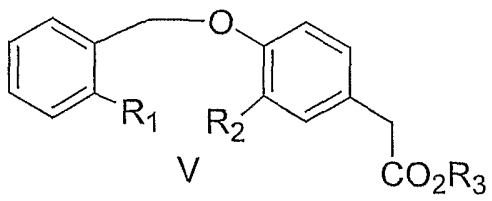
wherein one of R_4 and R_5 is halogen and the other is CHO and R_3 is an acid protecting group.

18. A compound according to claim 17, wherein one of R_4 and R_5 is halogen and the other is CHO and R_3 is C_1-C_4 alkyl.

19. A compound according to claim 18, wherein one of R_4 and R_5 is iodine and the other is CHO and R_3 is C_1-C_4 alkyl.

20. A compound according to claim 19, wherein one of R_4 and R_5 is iodine and the other is CHO and R_3 is methyl.

21. Compounds of formula V,



V

wherein one of R_1 and R_2 is halogen and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is an acid protecting group.

22. A compound according to claim 21, wherein one of R_1 and R_2 is halogen and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is C_1-C_4 alkyl.

23. A compound according to claim 22, wherein one of R_1 and R_2 is iodine and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is C_1-C_4 alkyl.

24. A compound according to claim 23, wherein one of R_1 and R_2 is iodine and the other is $CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is methyl.

25. A compound according to claim24, wherein R_1 is iodine, R_2 is (*E*)-$CH=CH-CH_2-CH_2-N(CH_3)_2$ and R_3 is methyl.

26. A compound according to claim 24, wherein R1 is (*Z*)-$CH=CH-CH_2-CH_2-N(CH_3)_2$, R_2 is iodine and R_3 is methyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/007501

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D313/12

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 116 863 A (OSHIMA ET AL) 26 May 1992 (1992-05-26) examples	1-26
A	US 4 871 865 A (LEVER, JR. ET AL) 3 October 1989 (1989-10-03) cited in the application column 3 - column 4	1-26

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 November 2005	15/11/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fazzi, R

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/007501

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	FINCH ET AL.: "The Synthesis of a Conformationally Restrained, Combined Thromboxane Antagonist / Synthase Inhibitor using an Intramolecular "Stille"-or "grigg"-Palladium-Catalyst Cyclisation Strategy" TETRAHEDRON LETTERS, vol. 34, no. 51, 1993, pages 8353-8356, XP002352271 page 8354 - page 8355	1-26
A	CHAUDHURI G ET AL: "A highly regio- and steroselective synthesis of (Z)-3-arylidene-2,3-dihydro-5H-1,4-benzodioxepin-5-ones and (Z)-3-arylidene-1,2,3,5-tetrahydro-4,1-benzoxazepin-5-ones through palladium-copper catalysis" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCHWORTH, GB, 2000, pages 775-779, XP002253289 ISSN: 0300-922X page 775	1-26

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2005/007501

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