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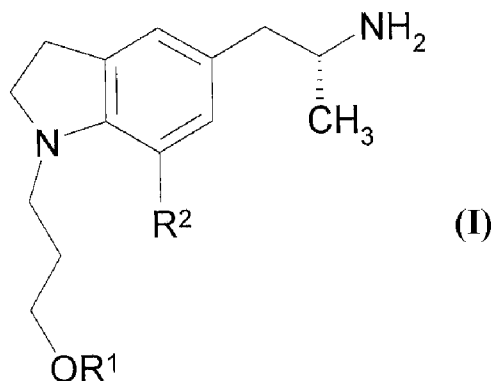
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(54) Title: PROCESS FOR PREPARING AN INTERMEDIATE FOR SILODOSIN

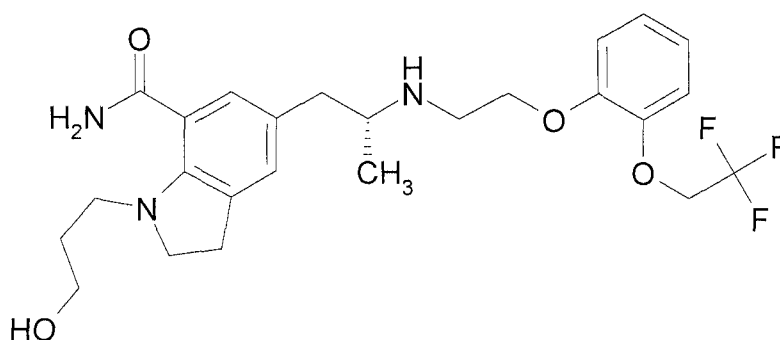


(57) Abstract: The present invention provides a process for preparing a compound of formula (I), wherein R¹ is a hydroxyl-protecting group and R² is a cyano group or a carbamoyl group, wherein the process comprises the direct hydrogenation of the corresponding achiral nitro compound and the resolution of the racemic amino compound. The compound of formula (I) can easily be further transferred to silodosin.

Process for preparing an intermediate for silodosin

The present invention relates to a process for preparing an intermediate which is useful in the synthesis of the known pharmacologically active agent silodosin. The present invention also relates to a process for preparing silodosin using the process for preparing the intermediate.

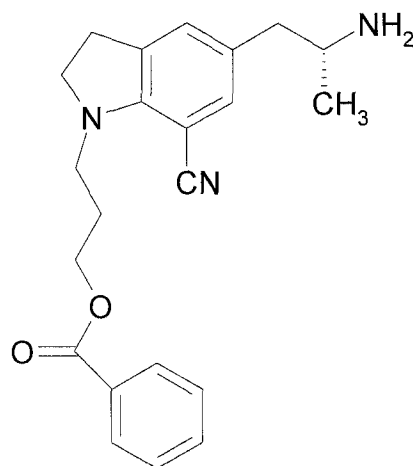
Silodosin is a well-known pharmaceutically active ingredient with the systematic IUPAC name 1-(3-hydroxypropyl)-5-[(2*R*)-({2-[2-[2-(2,2,2-trifluoroethoxy)phenoxy]ethyl}amino)-propyl]indoline-7-carboxamide having the chemical formula



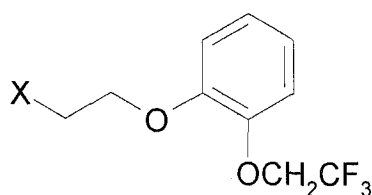
Silodosin is useful for the treatment of dysuria and similar diseases, in particular dysuria associated with benign prostatic hyperplasia. Silodosin is a highly selective inhibitor of the α_{1A} -adrenergic receptor, and it causes practically no orthostatic hypertension. It has been suggested as an agent for male birth control. Presently, silodosin is marketed in the US under the trade name Rapaflo.

Silodosin was first disclosed in EP-A 0 600 675, where a process for producing the compound is also disclosed. However, since silodosin is an optically active compound (a single enantiomer) and has a complex chemical structure, its synthesis is rather complex requiring a number of different synthesis steps and purification steps including an optical resolution. Several patent applications have been filed for improved processes for preparing silodosin.

One synthesis route proceeds over an intermediate of formula

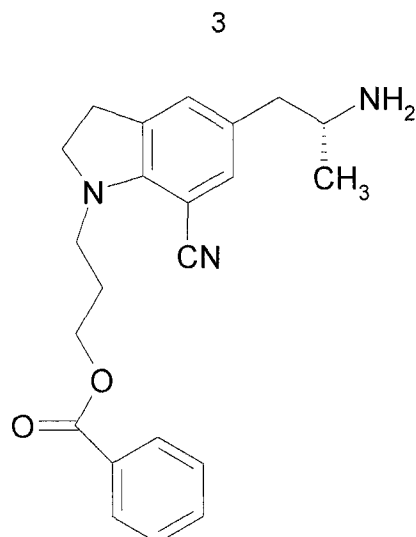


which is then coupled with a compound of formula



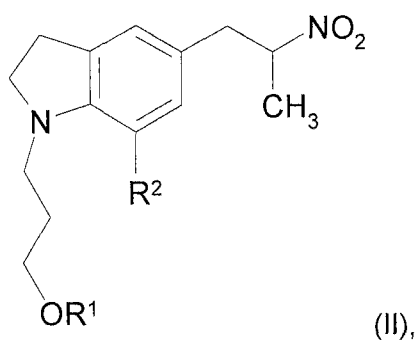
(wherein X is a leaving group). The reaction product is then further reacted to silodosin. This route of synthesis is e.g. disclosed in EP 1 806 340, JP 2002-265444 and JP 2001-199956, and it solves many problems of the prior art, in particular, since the optical resolution to a single enantiomer occurs relatively early in the production process. This is advantageous from an economic point of view.

However, the preparation of the intermediate compound

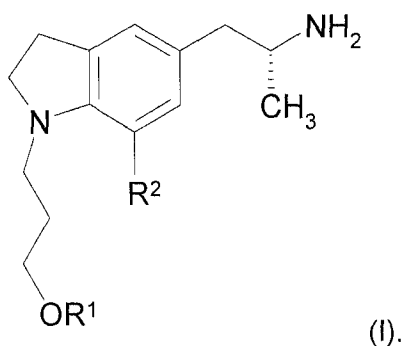


which is a single enantiomer, is not easy. Regarding the process for producing this compound, EP 1 806 340 refers to JP 2001-199956.

In the process of this Japanese document a compound of the formula

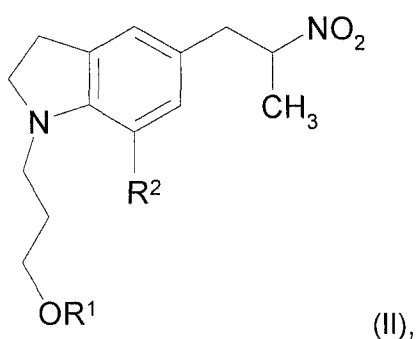


wherein R^2 is a cyano group or a carbamoyl group and R^1 is a hydroxyl-protecting group is produced by methods well-known in the art, and the nitro compound is then transferred to the amino intermediate of general formula (I)

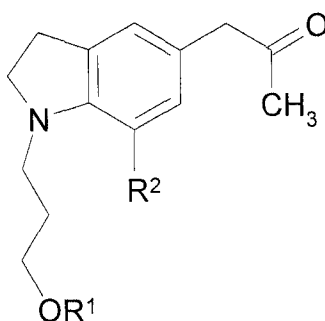


This reaction requires a hydrogenation of the nitro compound, which, however, must be carried out without destroying or negatively affecting the other functional groups of the molecule. Furthermore, some separation of enantiomers has to be carried out during the reaction to obtain the enantiomerically pure compound of formula (I).

According to JP 2001-199956 the hydrogenation thus requires a multi-step process. In a first step the nitro compound of formula (II)

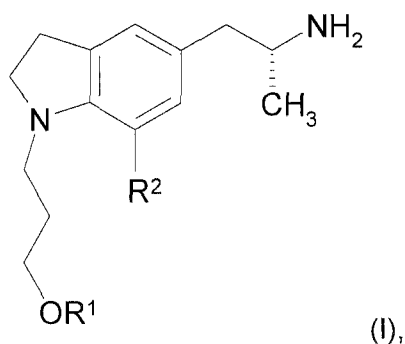


wherein R^1 and R^2 are as disclosed above, is treated with hydrogen peroxide in order to obtain the corresponding keto compound of the formula



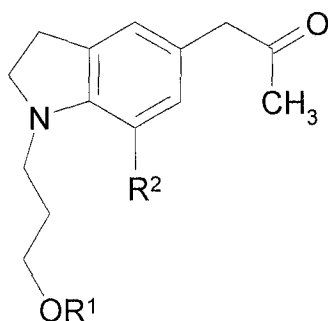
wherein R^1 and R^2 are as defined above. This keto compound is purified by column chromatography followed by crystallization. The pure keto compound is converted into the amino derivative by a series of reactions which involve treating with an optically active compound such as L-2-phenylglycinol with molecular hydrogen in the presence of platinum oxide to obtain a mixture which is not further defined but said to have a diastereomer ratio of 3.8:1. This mixture is then hydrogenated on palladium/carbon and treated with L-tartaric acid in order to obtain the L-tartaric acid salt of the compound of formula (I) which can be

further crystallized to get a higher enantiomeric excess of L-tartaric acid salt of compound (I).



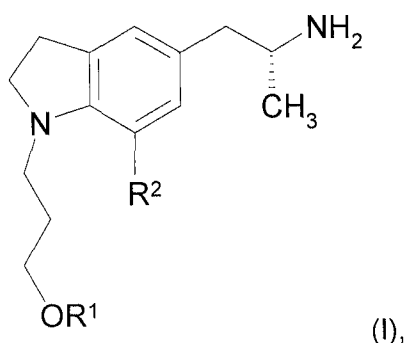
wherein R¹ and R² are as defined above.

This process is complicated and costly, as L-2-phenylglycinol is expensive and not recovered from the reaction. It requires three steps, namely first oxidizing the nitro group with hydrogen peroxide to a keto group and then treating the keto group first with an enantiomerically pure compound and platinum oxide in the presence of hydrogen, and then again with palladium carbon and hydrogen and finally resolving the amino derivative with L-tartaric acid in order to obtain the final amine compound of formula (I). Furthermore, the keto compound



wherein R¹ and R² are as defined above, must be purified by a column chromatography followed by a crystallization, and the inventors, when trying to carry out the purification of JP 2001-199956, found that the crystallization method described in this document cannot be repeated.

Therefore, while the process for preparing silodosin described e.g. in EP 1 806 340 and the earlier Japanese documents is in principle rather advantageous, in practice it requires the cumbersome and expensive production of the amine of formula (I)

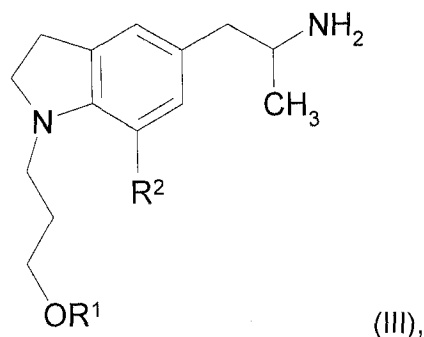


wherein R^1 and R^2 are as defined above, and therefore, in total this method has no significant advantage over other methods for preparing silodosin.

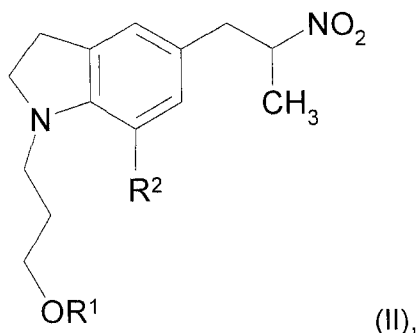
From the above it follows that there is a need in the art to provide an advantageous process for preparing silodosin which is relatively easy and less costly than the prior art processes and which provides silodosin in an excellent yield in a high optical and chemical purity and with low costs.

Reduction of an aliphatic nitro group to an amino group in a multifunctional substrate is a challenging task and that might be the reason that in the earlier Japanese application the reductive amination of an aliphatic keto group has been used. In spite of challenges encountered in the reduction of the aliphatic nitro group, the inventors were successful in reducing an aliphatic nitro group in a multifunctional molecule.

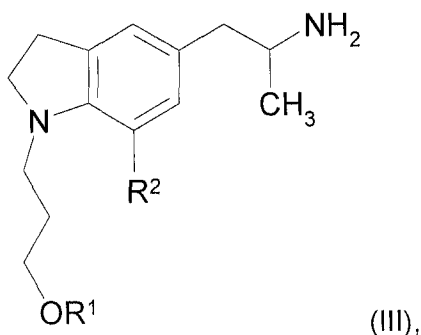
The inventors of the present invention now found that the compound



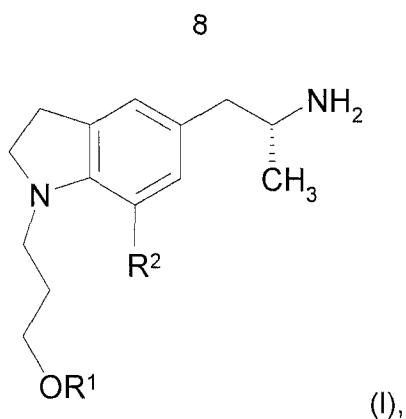
wherein R^1 and R^2 are as defined above, can easily be obtained by direct hydrogenation of the corresponding nitro compound



wherein R^1 and R^2 are as defined above, under non-stereospecific conditions. Unexpectedly, the direct hydrogenation of the aliphatic nitro compound to the aliphatic amine compound in the presence of other functional groups can be carried out without increase in unsuitable by-products. The other functional groups of the molecule are not affected, and the hydrogenation proceeds to the product of formula (II) in an excellent yield and with a high purity. Furthermore, it was unexpectedly not necessary (as in the prior art processes) to carry out a hydrogenation step in the presence of an enantiomerically pure compound such as L-2-phenylglycinol, because the amine of the formula

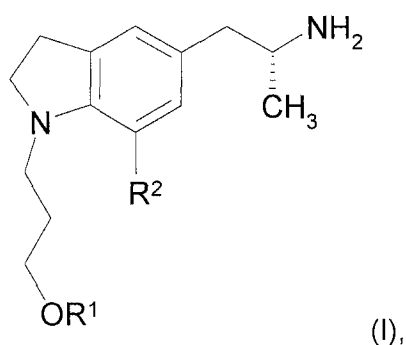


wherein R^1 and R^2 are as defined above, can easily and with excellent yield and purity be separated into its single enantiomers by treating it with an optically pure acid such as L-tartaric acid. With the process of the invention the important intermediate of general formula (I)



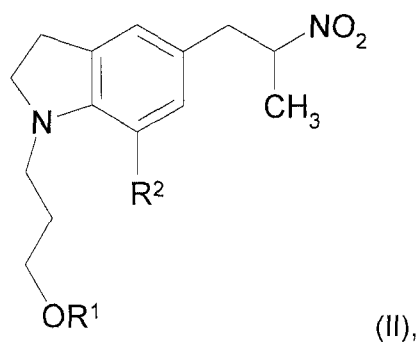
wherein R^1 and R^2 are as defined above, can thus be obtained much more easily in a high yield and with excellent purity and at very low costs, and this makes the overall process for preparing silodosin disclosed e.g. in EP 1 806 340, JP 2002-265444 and JP 2001-199956 much more feasible and economic.

The present invention thus provides a process for preparing a compound of formula (I)

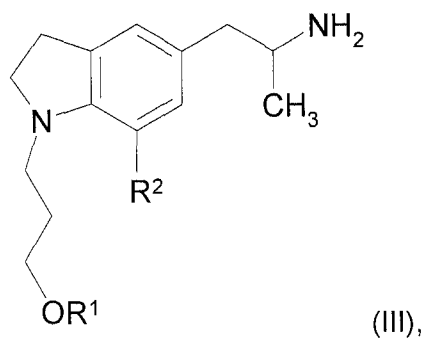


wherein R^1 is a hydroxyl-protecting group and R^2 is a cyano group or a carbamoyl group, the process comprising

- (i) hydrogenating a compound of formula (II)



wherein R^1 and R^2 are as defined above, using Pd/C and/or Pt/C as a catalyst to obtain the compound of formula (III)

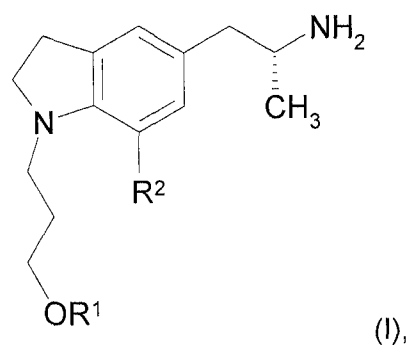


wherein R^1 and R^2 are as defined above, as a racemic mixture and

- (ii) resolving the racemic mixture of formula (III) to obtain the compound of formula (I).

Furthermore, the present invention provides a process for preparing the active ingredient silodosin comprising

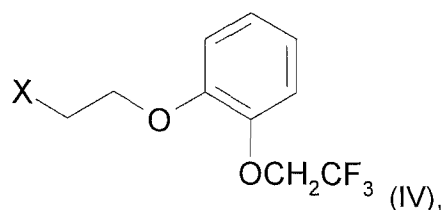
- a) preparing the compound of general formula (I)



wherein R^1 and R^2 are defined as above, by the novel process of the present invention and

- b) treating the compound of formula (I) obtained under a) with a compound of formula (IV)

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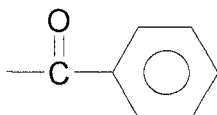


wherein X is a leaving group,

- c) removing the hydroxyl-protecting group R^1 and,
- d) if residue R^2 is a cyano group, hydrolyzing the cyano group to a carbamoyl group.

Residue R^1 is a hydroxyl-protecting group. Suitable hydroxyl-protecting groups are well-known in the art and are disclosed e.g. in the standard textbook "Greens - Protective Groups in Organic Synthesis, 4th edition/Peter G.M. Wuts and Theodora W. Green, Wiley 2007". Preferred hydroxyl-protective groups are an aralkyl group or an aroyl group. Suitable aralkyl groups are e.g. a phenyl group or a naphthyl group, which may optionally be substituted, in particular with a C_1 - C_6 straight or branched chain alkyl group, a halogen atom, such as a fluorine, chlorine or bromine atom or C_1 - C_6 alkoxy group. In general, the aralkyl group has not more than 20 carbon atoms.

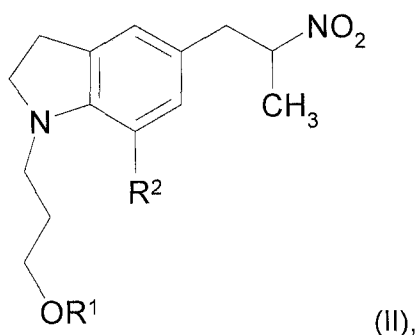
It is particularly preferred that residue R^1 is an aroyl group, in particular a group of the formula



which is preferably unsubstituted but which can also be substituted e.g. with one or two C_1 - C_6 branched-chain or straight-chain alkyl groups, one or two C_1 - C_6 branched-chain or straight-chain alkoxy groups or one or two halogen atoms, such as fluorine, chlorine or bromine atoms.

Residue R^2 is either a cyano group or a carbamoyl group, preferably a cyano group. If residue R^2 is a cyano group, it has to be hydrolyzed to a carbamoyl group during a later stage in the synthesis route for preparing silodosin.

Contrary to the processes of the prior art, the present inventors found that it is possible to directly hydrogenate the nitro group of the compound of formula (II)



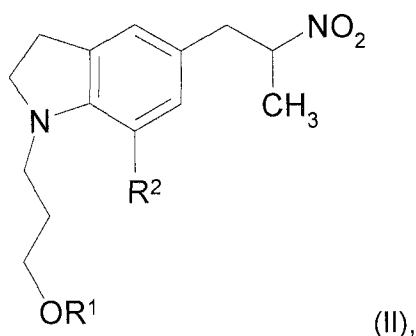
wherein R^1 and R^2 are as defined above, to obtain the compound of formula (III) with the required amino group. Thus, in the process of the present invention the nitro group is not first oxidized to the corresponding keto group but directly hydrogenated to an amino group.

The hydrogenation is carried out using molecular hydrogen and a suitable hydrogenation catalyst. The hydrogenation catalyst is either palladium on carbon or platinum on carbon or a mixture of both. Most preferably palladium on carbon (i.e. Pd/C) is used as the hydrogenation catalyst. Other hydrogenation catalysts and hydrogenation agents such as platinum oxide is not used in the process of the present invention. This significantly reduces the number of process steps, chemical compounds required and production costs.

It is also an advantage of the process of the present invention that the hydrogenation of the nitro group to the amino group can be carried out in standard industrial size hydrogenation reactors. Preferably, the hydrogenation is carried out using a continuous flow hydrogenation reactor, e.g. the hydrogenation reactor H-Cube[®] of the company Thales Nano in Budapest, Hungary. This hydrogenation reactor uses a packed catalyst cartridge CatCart[®] which is based on the preferred Pd/C catalyst system of the present invention. Of course, other commercial hydrogenation reactors can also be used.

The molecular hydrogen can be prepared outside of the reaction (such as with the H-Cube reaction system) and then introduced into the reaction. It is also possible to prepare the molecular hydrogen in situ by a chemical reaction. In a preferred embodiment of the present invention the hydrogen is prepared by adding a suitable compound to the reaction mixture, such as ammonium formate which decomposes to hydrogen, carbondioxide and ammonia. The hydrogen is then absorbed onto the surface of the palladium metal, where it reacts with the nitro groups and reduces the nitro groups to the desired amino groups. If ammonium formate is used as hydrogen source, the ammonium formate is generally added as an aqueous solution.

In a preferred process the hydrogenation can be carried out by dissolving the nitro compound of general formula (II)



wherein R¹ and R² are as defined above, in a suitable solvent. The term solvent as used herein, of course, also encompasses mixtures of different solvents. The solvent is not particularly limited, and each solvent can be used which does not negatively affect the hydrogenation reaction and which is suitable to dissolve the compound of formula (II). A preferred solvent is either a polar protic organic solvent or a mixture of a dipolar aprotic organic solvent and of a polar protic organic solvent.

Examples of a dipolar aprotic organic solvent are DMF, DMSO, acetone, methylethylketone, etc. The most preferred dipolar aprotic solvent is DMF. Suitable polar protic solvents are C₁-C₈ alcohols, such as methanol, ethanol and isopropanol. Preferred is ethanol.

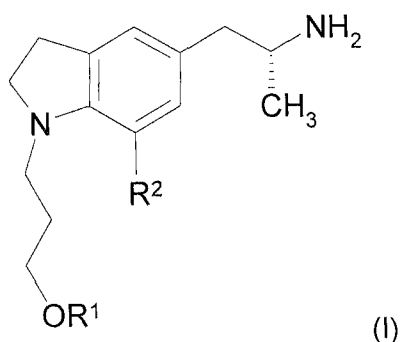
In a preferred process the catalyst, most preferred Pd/C, is added to the solution of the nitro compound of formula (II) in a suitable solvent as defined above. Then, hydrogen is added to the reaction solution by a manner known per se (either prepared in situ or added to the

reaction mixture as such). The hydrogenation is carried out under a suitable reaction temperature for a suitable reaction time. The reaction temperature is preferably from room temperature (20°C) to below 100°C, and the reaction time is generally from 10 hours to several days, e.g. one week. Preferred reaction conditions are disclosed in detail in the examples.

After the hydrogenation is completed (monitored e.g. by TLC), the reaction solution is treated and worked-up in a usual way, e.g. by filtering off the solid components, evaporating the filtrate and/or crystallizing the amino compound. It is for example possible to extract the amino compound with a suitable extraction solvent, such as DCM (dichloromethane), and purifying the compound by a suitable method, such as silica chromatography.

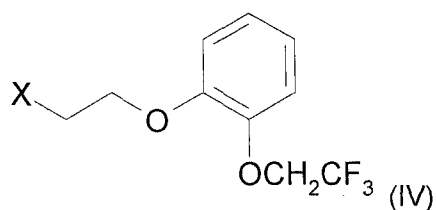
The amino compound of formula (III) is obtained by this process in the form of a racemic mixture (racemate), both enantiomers are present in essentially the same amounts. The racemate can be resolved by known methods, preferably by reaction with a chiral acid and subsequent crystallization. Known chiral acids can be used, preferably L-(+)-tartaric acid is used. The salt of the compound of formula (I), in particular the L-tartaric acid salt, is precipitated and can be purified, e.g. by recrystallization.

The compound of formula (I)

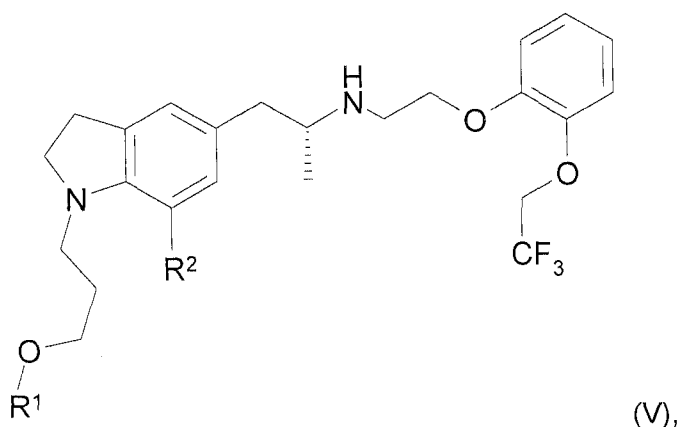


can then be obtained from the L-tartrate salt in a usual way e.g. by dissolving the L-tartrate salt in a suitable solvent, such as water, and adding a base, such as a solution of an alkaline or alkaline earth carbonate or a solution of an alkaline or alkaline earth hydrogen carbonate. The compound of formula (I) can be isolated in a usual manner by usual extraction processes. The so-obtained compound of formula (I) can be purified as is known in the art, e.g. by column chromatography.

The compound of formula (I) can then be coupled with a compound of formula (IV)

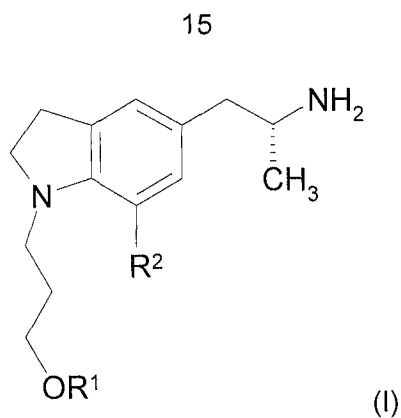


to obtain a compound of general formula (V)

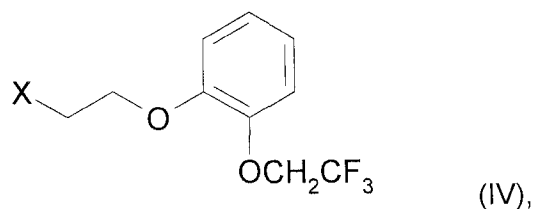


wherein R^1 and R^2 are as defined above. In the above formula (IV) residue X is a known leaving group, e.g. a halogen atom, such as a chlorine atom, a bromine atom or an iodine atom, a C_1 - C_6 -alkylsulfonyloxy group, such as a methanesulfonyloxy group, a C_6 - C_{12} -arylsulfonyloxy group, such as a benzenesulfonyloxy group or a toluenesulfonyloxy group. Preferably residue X is a C_1 - C_4 -alkylsulfonyloxy group and in particular a methanesulfonyloxy group.

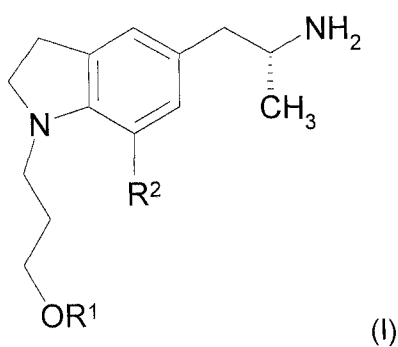
The compound of formula (V) can easily be further reacted to silodosin by removing the hydroxyl-protecting group R^1 in a well-known manner as disclosed e.g. in the above-mentioned standard textbook "Greens, Protective groups in organic synthesis", and if residue R^2 is a cyano group, this cyano group can be hydrolyzed to a carbamoyl group. The reaction of the compound of formula (I)



with the compound of formula (IV)



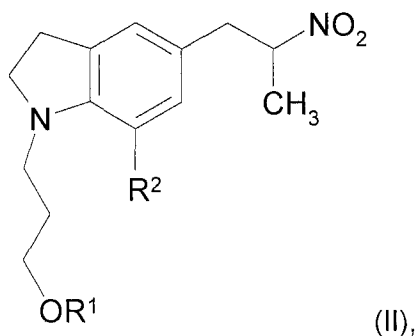
wherein residues R¹, R² and X are as defined above, and the further reaction to silodosin is well known in the art and described e.g. in EP-A 1 806 340, JP 2002-265444 and JP 2001-199956. It can be explicitly referred to the corresponding disclosure in EP-A 1 806 340, and the disclosure of this document is included herein by reference insofar as the reaction of the compound of formula (I)



to silodosin is disclosed.

The starting compound of the process of the present invention, namely the nitro compound of formula (II)

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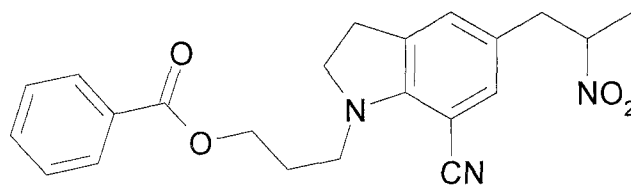
is also well-known in the art and can be prepared by methods known in the art. No further explanation of these known methods is considered necessary, and it can again be referred to the documents already mentioned above and in particular to JP 2001-199956 which is included herein by reference in this respect. However, an explicit example how this starting compound can be prepared is described in the examples.

The following examples further illustrate the present invention, but the examples should not be considered as limiting.

Examples

Example 1

Preparation of the nitro compound



The title compound was prepared as disclosed in the examples of JP 2001-199956 as shown in the following reference examples.

Reference example 11-(3-Benzoyloxypropyl) indoline hydrochloric acid salt

Benzoic acid (26.8 g) was dissolved in 90 ml of dry N,N-dimethylformamide, 30.6 ml of triethylamine and 22.0 ml of 1-bromo-3-chloropropane were added and the mixture was stirred overnight at room temperature and for 3 hours at 50°C. Indoline (23.6 ml) and 30.6 ml of triethylamine were added to the reaction mixture and the mixture was stirred for 6 hours at 100°C. Water was added to the reaction mixture, the mixture was extracted with ethyl acetate and the organic layer was washed successively with sodium bicarbonate aqueous solution and salt water. The organic layer was dried with anhydrous magnesium sulphate and then the solvent was distilled off under reduced pressure. The residue was dissolved in 350 ml of acetone, 20 ml of concentrated hydrochloric acid were added dropwise, with stirring, and then the mixture was stirred as it was overnight. The crystals which precipitated out were filtered off and washed with acetone and then dried, and 40.2 g of light brown colored crystals of 1-(3-benzoyloxypropyl) indoline hydrochloric acid salt were obtained.

¹H-NMR (CDCl₃) δ ppm: 2.35-2.5 (2H, m), 3.3-3.4 (2H, m), 3.5-3.6 (2H, m), 3.8-4.0 (2H, m), 4.4-4.5 (2H, m), 7.3-7.5 (6H, m), 7.55-7.65 (1H, m), 7.95-8.05 (2H, m).

Reference example 21-(3-Benzoyloxypropyl)-5-formylindoline

Phosphorus oxychloride (18.8 ml) was added dropwise over a period of about 10 minutes, with ice cooling and stirring, to 62.5 ml of dry N,N-dimethylformamide and the mixture was stirred for 30 minutes. Then 31.8 g of 1-(3-benzoyloxypropyl) indoline hydrochloric acid salt were added to the mixture little by little and the mixture was stirred for 3 hours at room temperature. The reaction mixture was poured into ice water and stirred for 30 minutes and, after being neutralized with sodium carbonate, the mixture was stirred a further period of 30 minutes. The reaction mixture was extracted with ethyl acetate, the organic layer was washed successively with sodium bicarbonate aqueous solution and salt water. The organic layer was dried with anhydrous magnesium sulphate and then the solvent was distilled off

under reduced pressure and 32.7 g of brown colored crystals of 1-(3-benzoyloxypropyl)-5-formylindoline were obtained.

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.0-2.2 (2H, m), 3.05 (2H, t, $J = 8.5$ Hz), 3.35-3.45 (2H, m), 3.55-3.65 (2H, m), 4.43 (2H, t, $J = 6.2$ Hz), 6.40 (1H, d, $J = 8.0$ Hz), 7.4-7.6 (5H, m), 8.0-8.1 (2H, m), 9.66 (1H, s).

Reference example 3

1-(3-Benzoyloxypropyl)-5-(2-nitropropenyl) indoline

1-(3-Benzoyloxypropyl)-5-formylindoline (32.7 g) was dissolved in 26.5 ml of nitroethane, 10.7 g of ammonium acetate were added and the mixture was heated under reflux for 1 hour. After being left to cool, sodium bicarbonate aqueous solution was added to the reaction mixture and the mixture was extracted with ethyl acetate. The organic layer was washed sequentially with sodium bicarbonate aqueous solution and salt water and dried with anhydrous magnesium sulphate and then the solvent was distilled off under reduced pressure. The residue was suspended in 250 ml of isopropanol, seeded and the mixture was stirred overnight. The crystals which had precipitated out were recovered by filtration, washed with cold isopropanol and dried and 25.6 g of red coloured crystals of 1-(3-benzoyloxypropyl)-5-(2-nitropropenyl) indoline were obtained.

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 2.05-2.15 (2H, m), 2.48 (3H, s), 3.0-3.1 (2H, m), 3.3-3.4 (2H, m), 3.5-3.6 (2H, m), 4.4-4.5 (2H, m), 6.44 (1H, d, $J = 8.5$ Hz), 7.2-7.3 (2H, m), 7.4-7.5 (2H, m), 7.55-7.65 (1H, m), 8.0-8.1 (3H, m).

Reference example 4

1-(3-Benzoyloxypropyl)-5-(2-nitropropyl) indoline

Sodium borohydride (14.4 g) was suspended with ice cooling in 150 ml of dry tetrahydrofuran and 50 ml of dry ethanol, a 150 ml dry tetrahydrofuran solution of 50 g of 1-(3-benzoyloxypropyl)-5-(2-nitropropenyl) indoline was added dropwise and the mixture was stirred for 1.5 hours at room temperature. The reaction mixture was poured into 350 ml of ice water, 50% (V/V) acetic acid solution was added to adjust to pH 4 and, after stirring for 1

hour, the mixture was neutralized with sodium bicarbonate. The reaction mixture was extracted with ethyl acetate and then the organic layer was washed with saturated salt water and dried with anhydrous magnesium sulphate, after which the solvent was distilled off under reduced pressure and 50.1 g of a reddish brown oily material comprising 1-(3-benzoyloxypropyl)-5-(2-nitropropyl) indoline were obtained.

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.51 (3H, d, $J = 6.6$ Hz), 2.0-2.1 (2H, m), 2.8-3.0 (3H, m), 3.15-3.25 (3H, m), 3.3-3.4 (2H, m), 4.4-4.5 (2H, m), 4.65-4.75 (1H, m), 6.39 (1H, d, $J = 8.0$ Hz), 6.82 (1H, d, $J = 8.0$ Hz), 6.85 (1H, s), 7.4-7.5 (2H, m), 7.55-7.65 (1H, m), 8.0-8.1 (2H, m).

Reference example 5

1-(3-Benzoyloxypropyl)-7-formyl-5-(2-nitropropyl) indoline

Phosphorus oxychloride (36.2 ml) was added dropwise over a period of about 20 minutes, with ice cooling, to 86 ml of dry dimethylformamide and the mixture was stirred for about 30 minutes with ice cooling. Then a 57 ml dry N,N-dimethylformamide solution of 67.8 g of 1-(3-benzoyloxypropyl)-5-(2-nitropropyl) indoline was added dropwise to the mixture over a period of about 35 minutes and the mixture was stirred for 2 hours at 50°C. After being left to cool, the reaction mixture was added dropwise with stirring to 870 ml of water, seeded and the mixture was stirred overnight. The crystals which had precipitated out were filtered off and then washed sequentially with water and methanol and dried and 58.8 g of yellow colored crystals of 1-(3-benzoyloxypropyl)-7-formyl-5-(2-nitropropyl) indoline were obtained.

$^1\text{H-NMR}$ (CDCl_3) δ ppm: 1.54 (3H, d, $J = 6.6$ Hz), 2.1-2.2 (2H, m), 2.92 (1H, dd, $J = 6.4, 14.2$ Hz), 3.0-3.1 (2H, m), 3.19 (1H, dd, $J = 7.7, 14.2$ Hz), 3.6-3.7 (4H, m), 4.4-4.5 (2H, m), 4.65-4.75 (1H, m), 6.93 (1H, brs), 7.22 (1H, s), 7.4-7.5 (2H, m), 7.5-7.6 (1H, m), 8.0-8.1 (2H, m), 9.94 (1H, s).

Reference example 6

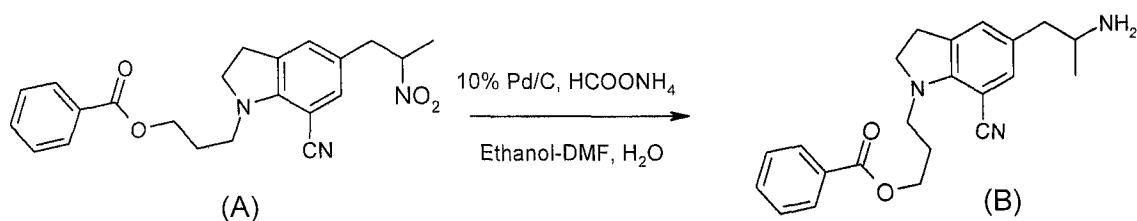
1-(3-Benzoyloxypropyl)-7-cyano-5-(2-nitropropyl) indoline

1-(3-Benzoyloxypropyl)-7-formyl-5-(2-nitropropyl) indoline (110 g) was dissolved in 150 ml of dry tetrahydrofuran, 23.2 g of hydroxylamine hydrochloride and 84.2 ml of pyridine were

added and the mixture was stirred for 1 hour at 50°C. Acetic anhydride (52.5 ml) was added slowly and, after stirring for 0.5 hour as it was at 50°C, the mixture was heated under reflux for 3 hours. Water (500 ml) was added and the mixture was extracted with ethyl acetate, the organic layer was washed sequentially with 1 mol/l hydrochloric acid, saturated sodium bicarbonate solution and saturated salt water and dried with anhydrous sodium sulphate and then concentrated under reduced pressure. The residue was dissolved in 100 ml of acetone, 500 ml of isopropanol were added and the mixture was seeded and stirred overnight. The crystals which had precipitated out were recovered by filtration and then washed with acetone/isopropanol (2/9) and dried and 68.3 g of light yellow colored crystals of 1-(3-benzoyloxypropyl)-7-cyano-5-(2-nitropropyl) indoline were obtained.

¹H-NMR (CDCl₃) δ ppm: 1.53 (3H, d, J = 6.7 Hz), 2.1-2.2 (2H, m), 2.85 (1H, dd, J = 6.2, 14.3 Hz), 2.9-3.0 (2H, m), 3.12 (1H, dd, J = 7.8, 14.3 Hz), 3.55-3.65 (2H, m), 3.7-3.8 (2H, m), 4.4-4.5 (2H, m), 4.6-4.7 (1H, m), 6.89 (1H, brs), 6.93 (1H, s), 7.4-7.5 (2H, m), 7.5-7.6 (1H, m), 8.0-8.1 (2H, m).

Example 2



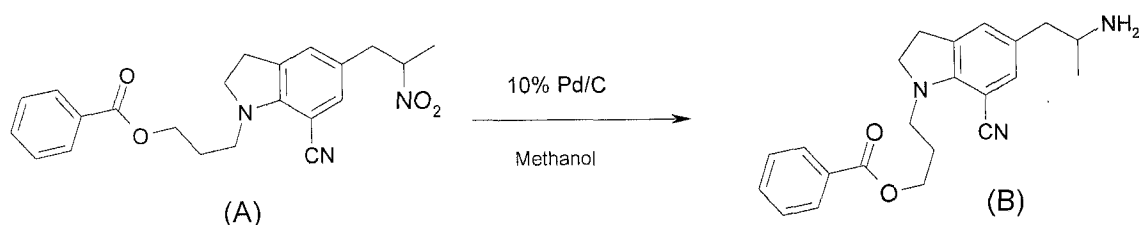
Two reductions each with 10 g of the starting compound were started and were combined during work up.

30 ml EtOH and 30 ml DMF was added to 10 g A (25.416 mmol) resulting in a clear solution. 10% Pd/C (0.700 g) was added under nitrogen atmosphere followed by aqueous ammonium formate (8.0 g, 127.08 mmol, 5 eq) solution in water (12 ml, minimum amount possible) and heated to 85-90 °C for 20 h and 31 h at room temperature. Reaction was monitored by TLC (Two solvent systems were used i) 40% EtOAc pet ether ii) 10% MeOH in DCM).

Both reaction mixtures were filtered through celite and washed with ethanol (50-60 ml). The filtrate was evaporated to half of its volume and 400 ml water added. pH was adjusted to basic with 1 N NaOH followed by extraction with DCM (3x80 ml) to give 25 g of the crude which was purified on 200 g of 70-230 mesh Silica column using 3% MeOH-DCM as eluent. Fraction 1 = 4.4 g (LCMS shows 79% peak at 10.23 min & 11% impurity)
 Fraction 2 = 5.3 g (LCMS showed 95% peak at 10.18 min)

Total yield = 9.7 g (53%, 26.68 mmol)

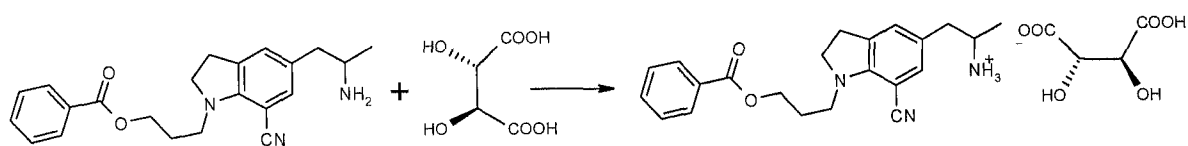
Example 3



60 mg of compound A was dissolved in 50 ml MeOH and was reduced using 10% Pd/C catalyst in a commercial H-Cube[®] reactor. Solution was passed through catalyst cartridge at 40°C at a rate of 1 ml/min. Pressure = 1 bar.

Reaction was complete in 60 minutes. Solution was concentrated to give 37 mg (67% yield) of product. HNMR was satisfactory.

Example 4a

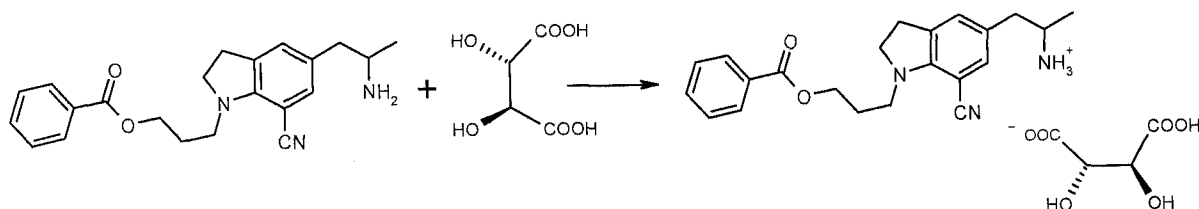


To the solution of the amine obtained in example 2 above (4.3 g, 11.831 mmol, 1 eq) in acetone (27 ml, 6.25 volumes) an aqueous solution (6.25 volumes) of L-(+)-tartaric acid (0.977 g, 6.507 mmol, 0.55 eq) was added drop wise at room temperature over 10 min. The reaction mixture was stirred overnight (approx. 18-20 h). The precipitated salt was filtered

and washed with 10 ml solvent mixture of acetone:water (1:1) to give 1.7 g (28%, 3.310 mmol) of off white solid as L-tartrate salt.

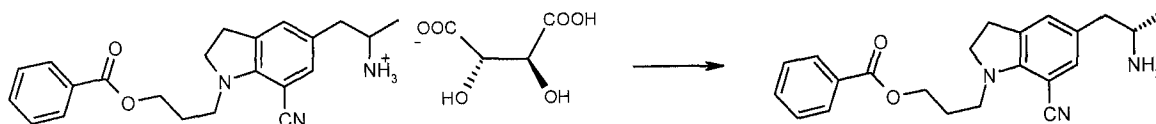
Above salt (1.6 g) was taken in 10 ml solvent mixture of acetone:water (1:1) and heated to reflux. Slowly more of solvent mixture was added to get a clear solution (total volume = 33 ml). Heating switched off after 15 min. The reaction mixture was allowed to cool to room temperature without removing it from the oil bath and stirred for 2 days. The resulting solid was filtered and washed with 1:1-acetone:water (10 ml) to give 1.0 g (62.5%, 1.947 mmol) after drying on buchi at 45°C.

Example 4b

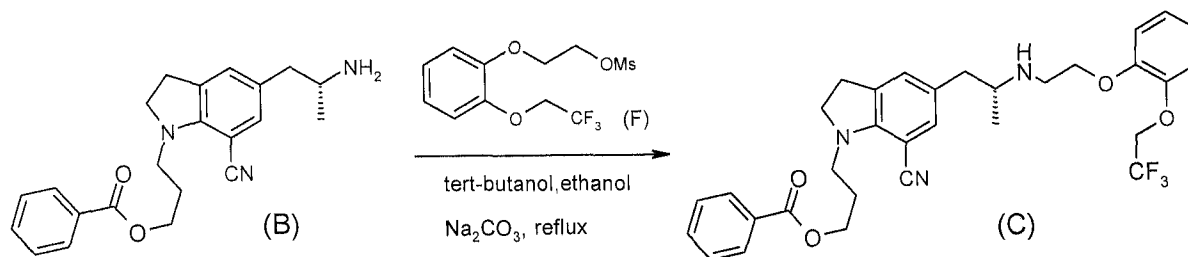


To the solution of the amine obtained in example 2 (1.0 g, 2.751 mmol, 1 eq) in acetone (3 ml), an aqueous solution of L-(+)-tartaric acid (0.227 g, 1.513 mmol, 0.55 eq) in water (1 ml) was added drop wise at reflux temperature. Heating was stopped after 15 min and the reaction was allowed to cool to ambient temperature. Crystallisation of the salt started slowly and stirring became less effective. After 3 h of stirring, the salt was filtered and washed with 4 ml solvent mixture of acetone:water (1:1) to give 0.468 g (33%, 0.911 mmol).

Above salt (0.450 g) was taken in 5 ml solvent mixture of acetone:water (1:1) and heated to reflux. Slowly more of the solvent mixture was added to get a clear solution (total volume = 14 ml). Heating switched off after 15 min. The reaction mixture was allowed to cool to room temperature without removing it from the oil bath and stirred for 16 h. The resulting solid was filtered and washed with 1:1-acetone:water (3-4 ml) to give 0.296 g (66%, 0.576 mmol) after drying on buchi at 40 °C.

Example 5

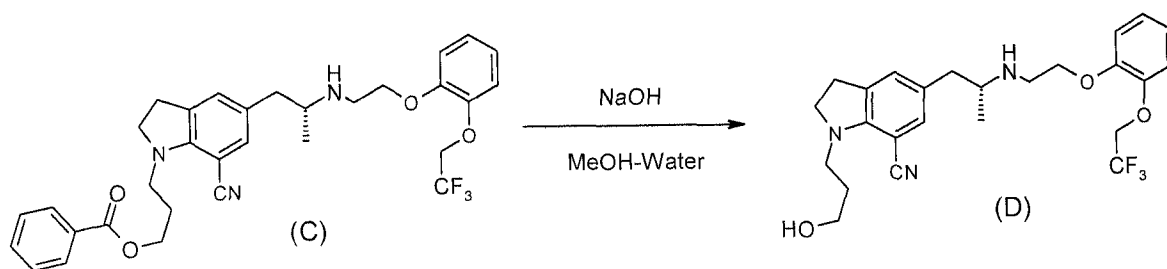
2.34 g of the L-tartrate salt of the amine obtained as in example 4 was dissolved in 20 ml water and pH was adjusted to 8-9 by adding saturated Na_2CO_3 solution. The basified mixture was extracted with 3 x 20 ml DCM, the combined organic extracts were washed with 10 ml water, dried over Na_2SO_4 , concentrated and dried under high vacuum to yield 1.65 g (almost 100% yield) of a brown viscous mass.

Example 6

Sodium carbonate (0.541 g, 5.106 mmol, 1.16 eq) was added to a solution of compound B (1.6 g, 4.402 mmol, 1.0 eq) obtained in example 5 above and compound (F) (1.6 g, 5.150 mmol, 1.17 eq) in tert-butanol (14 ml) + ethanol (2 ml). The reaction mixture was stirred at 85-90°C for 10 h and 32 h at 50°C. The reaction was monitored by TLC (4% MeOH in DCM on Silica plates). TLC showed the product and a minor amount of the dialkylated product.

The reaction mixture was cooled to ambient temperature and was concentrated to half of its volume and 50 ml water was added. This was extracted with ethyl acetate (3 x 20 ml), dried over sodium sulphate and evaporated in vacuo to give 2.9 g of a viscous brown oil.

The above was repeated to give a second amount of 1.5 g crude reaction product as a viscous brown oil. The reaction product from the two reaction runs were mixed and purified by using combiflash companion on a 40 g column using 2% MeOH-DCM as eluent to give 2.1 g (54%, 3.610mmol) end product. LCMS showed 89.4% peak area with $M+1 = 582.3$. HNMR is OK.

Example 7

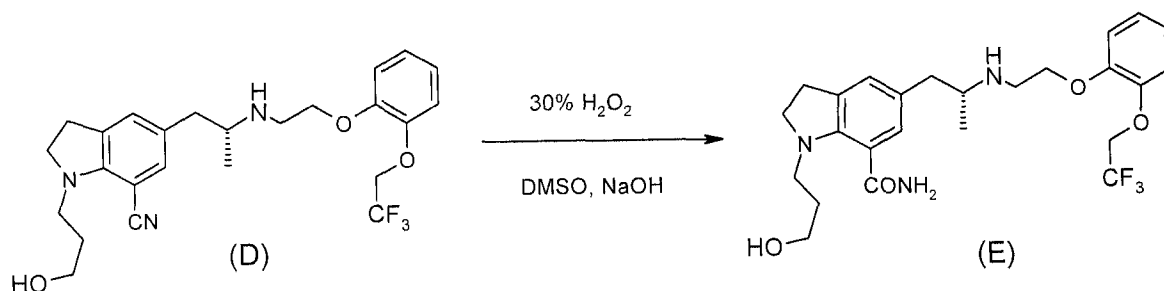
A solution of compound (C) (2.0 g, 3.438 mmol, 1 eq) obtained in example 6 above in 20 ml methanol was cooled with an ice-water bath and 4.8 ml 1 N NaOH (1.4 equivalent) was added drop wise over a period of 15 min. During addition of NaOH, the reaction mixture becomes turbid. The ice-water bath removed and stirred at room temperature for 1 h. TLC showed completion of the reaction. The reaction mixture was concentrated and 50 ml water was added. This was extracted with ethyl acetate (3 x 20 ml), dried over sodium sulphate and evaporated in vacuo to give 1.8 g of the crude end product as brown oil. The crude compound was purified by combiflash on a 40 g silica column.

Elution was started with 1.8% MeOH in DCM and completed with 2.5% MeOH in DCM.

Yield 1.1 g (67%, 2.303 mmol) of a pure light brown viscous oil.

LCMS showed 93.5% peak area with $M+1 = 478.2$.

¹H NMR is OK.

Example 8

Compound (D) (1.0 g, 2.094 mmol) obtained in example 7 above was dissolved in DMSO (10 ml) and to the solution was added 5 M sodium hydroxide (0.7 ml). The reaction mixture was cooled in an ice water bath and 30% hydrogen peroxide (0.42 ml) was added little by

little so that the reaction temperature did not rise above 25°C. The ice bath was removed after 15 min and the reaction mixture was stirred at room temperature for 2 h. An aqueous sodium sulfite (0.350 g) solution dissolved in water (25 ml) was added carefully. The addition is exothermic, the reaction mixture becomes turbid. The reaction mixture was extracted with ethyl acetate (3 x 15 ml). The combined ethyl acetate layers were extracted with 2 N HCl (3 x 15 ml). The aqueous hydrochloric acid solution extracted was neutralized with sodium bicarbonate and extracted with ethyl acetate (3 x 10 ml). The combined organic layers were dried over sodium sulphate and evaporated in vacuo to give 0.957 g of off a white sticky semi-solid which on triturating and stirring with diethyl ether (10 ml) gave 0.950 g (91.5%, 1.917 mmol) of silodosin as a white solid.

LCMS showed 96.8% peak area with $M+1 = 496.1$

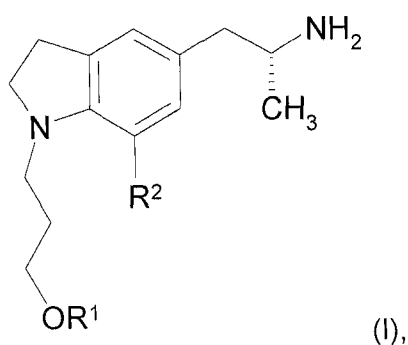
¹H NMR is OK.

DSC showed a sharp endotherm at 105.29°C (-98.39 J/g) indicating crystalline nature of compound.

IR: 3383, 3202, 2941, 2841.4, 1635.5, 1507.7 cm^{-1} .

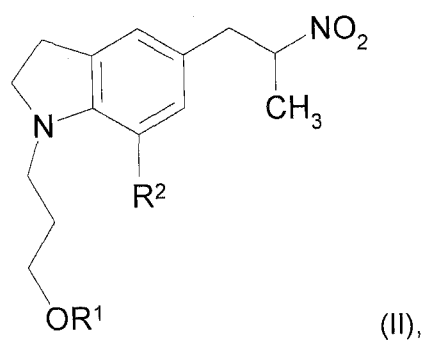
Claims:

1. Process for preparing a compound of formula (I)



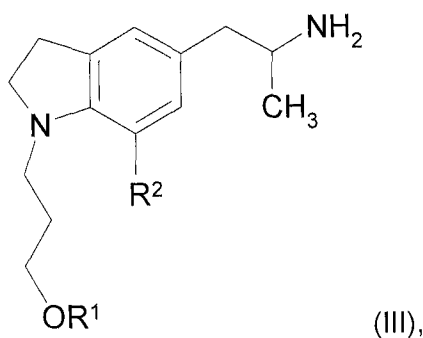
wherein R¹ is a hydroxyl-protecting group and R² is a cyano group or a carbamoyl group, the process comprising

- (i) hydrogenating compound of formula (II)



wherein R¹ and R² are as defined above, using Pd/C and/or Pt/C as a catalyst to obtain the compound of formula (III)

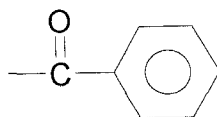
27



wherein R¹ and R² are as defined above, as a racemic mixture and

(ii) resolving the racemic mixture of formula (III) to obtain the compound of formula (I).

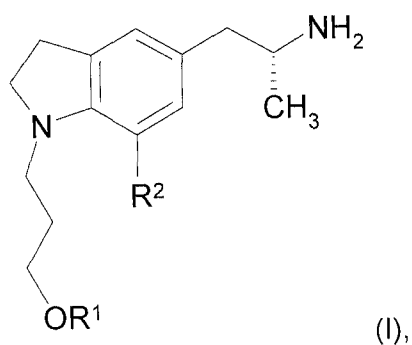
2. Process according to claim 1, wherein residue R² is a cyano group.
3. Process according to claim 1 or 2, wherein residue R¹ is a residue



4. Process according to any of claims 1 to 3, wherein the catalyst in step (i) is Pd/C.
5. Process according to any of claims 1 to 4, wherein in step (ii) the racemic mixture of formula (III) is resolved by treating the racemic mixture of formula (III) with an optically active acid to obtain a mixture of diastereomeric salts and isolating the salt of the compound of formula (I) by crystallization and filtration and treating the isolated salt of the compound of formula (I) with a base to obtain the compound of formula (I).
6. Process according to claim 5, wherein the optically active acid is L-tartaric acid.
7. Process according to claim 5 or 6, wherein the base is a compound of formula M_nH_lCO₃, wherein M is an alkali metal ion or an alkaline earth metal ion, n is 1 or 2 and l is 0 or 1 with the limitation that n + l is 2.

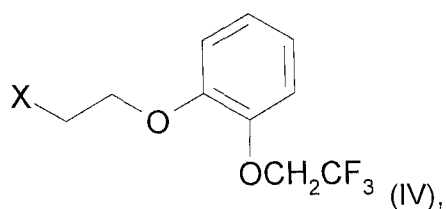
8. Process for preparing silodosin comprising

- a) preparing the compound of formula (I)



wherein R¹ and R² are defined as in any of claims 1 to 3, by a process as defined in any of claims 1 to 7,

- b) treating the compound of formula (I) obtained under a) with a compound of formula (IV)



wherein X is a leaving group,

- c) removing the hydroxyl-protecting group R¹ and,
- d) if residue R² is a cyano group, hydrolyzing the cyano group to a carbamoyl group.

9. Process according to claim 8, wherein residue X is a C₁₋₄ alkylsulfonyloxy group.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/055551

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D209/08 ADD.		
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) 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, CHEM ABS Data, WPI Data		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	CN 101 993 406 A (ZHEJIANG HUAHAI PHARMACEUTICAL CO.) 30 March 2011 (2011-03-30) The whole document; in particular, page 7, paragraf [0028]. -----	1-9
A,P	CN 101 993 407 A (ZHEJIANG HUAHAI PHARMACEUTICAL CO.) 30 March 2011 (2011-03-30) The whole document; in particular page 11, paragraph [0034]. -----	1-9
A	JP 2001 199956 A (KISSEI PHARMACEUTICAL) 24 July 2001 (2001-07-24) cited in the application The whole document. ----- -/--	1-9
☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "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 22 June 2011		Date of mailing of the international search report 13/07/2011
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2011/055551

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 2002 265444 A (KISSEI PHARMACEUTICAL) 18 September 2002 (2002-09-18) Page 8, reaction scheme. -----	1-9
A	March: "Advanced Organic Chemistry, 2nd ed.", 1977, McGraw-Hill, Auckland, XP002644343, ISBN: 0070855404 pages 1116-1127, Page 1116, table 2; page 1122, chapter 9-41; page 1125, chapter 9-49. -----	1-9
A	US 4 252 803 A (WEBB COLIN F) 24 February 1981 (1981-02-24) Column 32, lines 7-21: example 19, step (iii). -----	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2011/055551

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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CN 101993407	A	30-03-2011	NONE
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