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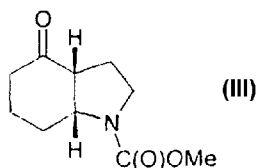
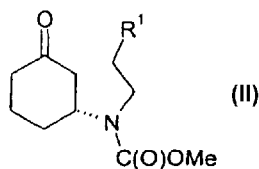
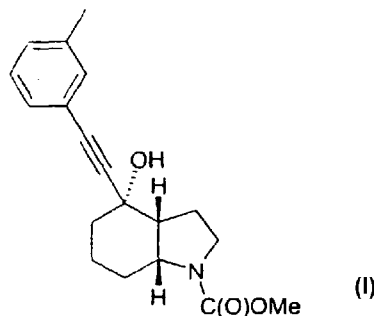
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(54) Title: PROCESSES FOR THE PREPARATION OF 4-OXO-OCTAHYDRO-INDOLE-1-CARBOCYLIC ACID METHYL ESTER AND DERIVATIVES THEREOF



(57) Abstract: The present invention relates to a process for the production of (3aR, 4S, 7aR)-4-hydroxy-4-m-tolyethynyl-octahydro-indole-1-carboxylic acid methyl ester (I), of carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-alkyl ester enantiomers (II), and of 1-carbalkoxy-4-ketoperhydroindole enantiomers (III).



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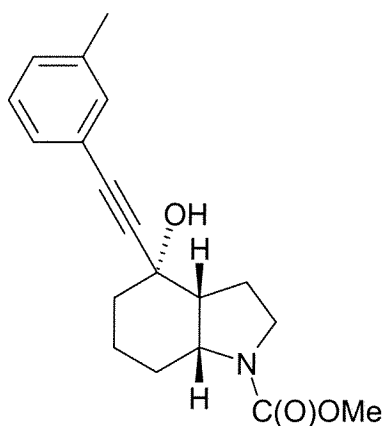
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PROCESSES FOR THE PREPARATION OF 4-OXO-OCTAHYDRO-INDOLE-1-CARBOXYLIC ACID METHYL ESTER AND DERIVATIVES THEREOF.

The present invention relates to a process for the production of carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-alkyl ester enantiomers and of 1-carbalkoxy-4-ketoperhydroindole enantiomers.

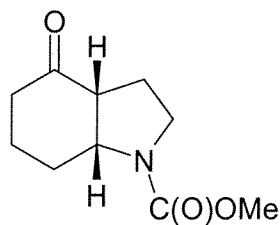
WO 03/47581 discloses a series of acetylene derivatives having activity towards human metabotropic glutamate receptors (mGluRs). In particular, there is disclosed the compound (3aR,4S,7aR)-4-hydroxy-4-m-tolylethynyl-octahydro-indole-1-carboxylic acid methyl ester, which can be obtained in free base or acid addition salt form and has the formula (I):



(I)

WO 03/47581 also discloses a process for the production of the above compound which involves hydrogenation of a 1,5,6,7-tetrahydroindol-4-one derivative. The hydrogenation step is cumbersome, low yielding and has poor selectivity for the (3aR,4S,7aR) stereoisomer. An undesirable by-product is also formed.

According to the present invention, there is provided an alternative process for the production of a compound of the formula (I) or a pharmaceutically acceptable salt thereof, which comprises reacting 3-ethynyltoluene with a compound of the formula (II) or a salt thereof:

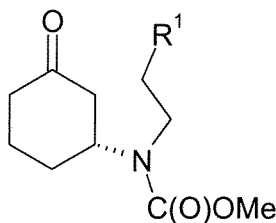


(II)

to form the compound of formula (I) and optionally converting the compound of formula (I) to a pharmaceutically acceptable salt.

The above reaction is preferably performed in the presence of a base which promotes deprotonation of the ethynyl group. In an embodiment, the base is an alkyl lithium reagent such as n-hexyllithium. The reaction may be performed in an aprotic solvent such as tetrahydrofuran.

A compound of formula (II) may be obtained by cyclisation of a compound of the formula (III) or a salt thereof:



(III)

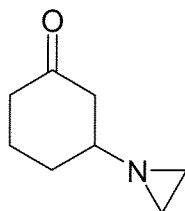
wherein R¹ is a leaving group.

Cyclisation may be performed using a base which deprotonates the 2- position of the cyclohexanone ring. By way of example, the base may comprise a mixture of pyrrolidine and triethylamine. The reaction may be performed in an organic solvent such as toluene.

Suitable leaving groups represented by R¹ will be apparent to those skilled in the art and include, for example, halo, e.g. chloro, bromo or iodo, tosylates, mesylates, alkylsulphonates, e.g. methanesulfonate, and halosulphonates, e.g. fluorosulphonate.

The compound of formula (III) preferably comprises an excess of the (R) enantiomer as depicted in the formula above, more preferably in a substantially pure form of said enantiomer. In an embodiment, the compound of formula (III) comprises greater than 70%, more preferably greater than 90%, more preferably greater than 95% of the (R) enantiomer. The desired enantiomer may be obtained by resolving an enantiomeric mixture, e.g. a racemic mixture, of a compound of formula (III). In an embodiment, resolution is performed using chiral high performance liquid chromatography (HPLC) involving the use of a chiral stationary phase.

A compound of formula (III) may be obtained by reacting a compound of the formula $R^1C(O)OMe$ with a compound of the formula (IV) or a salt thereof:



(IV)

A compound of formula (IV) may be obtained by reacting cyclohexen-2-one with aziridine or a salt thereof. The reaction may be performed in the presence of an organic solvent such as toluene. Suitable procedures are illustrated in the Examples herein.

The invention includes the above processes for making the compound of formula (I) as well as each step thereof and all combinations of sequential steps. As mentioned above, the compound of formula (I) may further be converted to a pharmaceutically acceptable salt form, in particular acid addition salt form. Acid addition salts may be obtained in accordance with known methods, e.g. by addition of acid to the last reaction step or prior to recrystallization.

The invention also relates to the use of the various compounds, e.g. selected from compounds of the formulae (II) and (III), and their salts, for the production of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

The compound of formula (I) or the intermediate compounds may be purified and/or separated by a conventional manner such as recrystallization, column chromatography, distillation, centrifugal separation, washing or drying.

The compound of formula (I) or a pharmaceutically acceptable salt thereof may be formulated with a pharmaceutically acceptable carrier or diluent, to form a pharmaceutical composition.

Pharmaceutical compositions according to the invention may be compositions for enteral, such as nasal, rectal or oral, or parenteral, such as intramuscular or intravenous, administration to warm-blooded animals (human beings and animals) that comprise an effective dose of the pharmacological active ingredient alone or together with a significant amount of a pharmaceutical acceptable carrier. The dose of the active ingredient depends on the species of warm-blooded animal, body weight, age and individual condition, individual pharmacokinetic data, the disease to be treated and the mode of administration.

Pharmaceutical compositions may comprise from approximately 1% to approximately 95%, preferably from approximately 20% to approximately 90%, active ingredient. Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragees, tablets or capsules.

Alternatively compounds may be administered e.g. topically in the form of a cream, gel or the like, or by inhalation, e.g. in dry powder form.

Examples for compositions comprising an agent of the invention include, e.g. a solid dispersion, an aqueous solution, e.g. containing a solubilising agent, a microemulsion and a suspension of an agent of the invention. The composition may be buffered to a pH in the range of e.g. from 3.5 to 9.5, by a suitable buffer.

The pharmaceutical compositions of the present invention may be prepared in a manner known per se, for example by means of conventional dissolving, lyophilizing, mixing, granulating or confectioning processes.

A compound of formula (I) and pharmaceutically acceptable salts thereof are useful in the treatment of disorders associated with irregularities of the glutamatergic signal transmission,

and of nervous system disorders mediated full or in part by mGluR5. Activity towards mGluRs can be determined according to any of the procedures described in WO 03/047581.

Disorders associated with irregularities of the glutamatergic signal transmission are for example epilepsy, cerebral ischemias, especially acute ischemias, ischemic diseases of the eye, muscle spasms such as local or general spasticity and, in particular, convulsions or pain.

Nervous system disorders mediated full or in part by mGluR5 include, for example acute, traumatic and chronic degenerative processes of the nervous system, such as Parkinson's disease, senile dementia, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis and multiple sclerosis, psychiatric diseases such as schizophrenia and anxiety, depression, pain, itch and drug abuse, e.g. alcohol and nicotine abuse and cocaine use disorders.

For all the above mentioned indications, the appropriate dosage will of course vary depending upon, for example, the compound employed, the host, the mode of administration and the nature and severity of the condition being treated. However, in general, satisfactory results in animals are indicated to be obtained at a daily dosage of from about 0.5 to about 100 mg/kg animal body weight. In larger mammals, for example humans, an indicated daily dosage is in the range from about 5 to 1500 mg, preferably about 10 to about 1000 mg of the compound conveniently administered in divided doses up to 4 times a day or in sustained release form.

A compound of formula (I) can be administered either alone, or in combination with other pharmaceutical agents effective in the treatment of conditions mentioned above.

For the indication pain, compounds of the invention can be used in combination with analgesic agents (opiates) or with non-steroidal anti-inflammatory drugs (NSAIDs) such as Rofecoxib (Vioxx®), Celecoxib (Celebrex®) or Lumiracoxib (Prexige®).

For the indication nicotine use disorders, compounds of the invention can be used in combination with bupropione (Zyban®).

The invention also provides a composition comprising a compound of formula (I) or a pharmaceutically acceptable salt thereof in combination with a relatively minor proportion of one or more intermediate compounds, e.g. selected from compounds of formulae (II), (III) and (IV), and salts thereof.

The following Examples illustrate the invention.

3-(1-aziridinyl) cyclohexanone is synthesized according to literature (J.E. Dolfini et al., Tetrahedron Letters, No 25, pp. 2053-2058, 1965)

Example 1-5: Synthesis of carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-alkyl ester

21.6 mmol 3-(1-aziridinyl) cyclohexanone are dissolved in 15 ml toluene and cooled down to 0°C. To the clear solution 21.6 mmol alkyl chloroformate are added within 20 minutes (exothermic reaction). The temperature is kept between 0 -10°C. The yellowish to brown solution is warmed up to room temperature and stirred for further 1 hour. Solvent and excess reagents are removed under vacuum (60°C/20 mbar) and the remaining oil is treated three times with 5 ml toluene to remove not reacted alkyl chloroformate under vacuum yielding:

4.95 g carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-methyl ester	(example 1)
5.22 g carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-ethyl ester	(example 2)
5.53 g carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-propyl ester	(example 3)
5.92 g carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-butyl ester	(example 4)
6.27 g carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-neopentyl ester	(example 5)

Example 6-15: Synthesis of (R)- and (S)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-alkyl ester

5 g racemic carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-alkyl ester are dissolved in 50 ml heptane/2-propanol = 1/1 (V/V) and injected onto a preparative Chiralpak-AD column (particle size: 20 µm, column dimensions: 30 cm length x 10 cm I.D.). Using heptane/2-propanol/methanol = 90/7.5/2.5 (V/V/V) as the mobile phase at room temperature and a flow rate of 400 ml/min, baseline separation is achieved within 60 min while the R-enantiomer elutes always prior to its S-enantiomer. A second chromatographic run is performed under

identical conditions and the corresponding fractions are combined. The solvents are removed under vacuum yielding:

4.6 g (R)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-methyl ester (example 6)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.47 (m, 1 H) 1.79 (m, 1 H) 1.92 (m, 2 H) 2.13 (d, *J*=1.53 Hz, 1 H) 2.25 (m, 1 H) 2.31 (dt, 1 H) 2.81 (br. m., 1 H) 3.49 (t, *J*=7.17 Hz, 2 H) 3.60 (s, 3 H) 3.61 - 3.68 (m, 2 H) 3.89 - 3.98 (m, 1 H)

4.5 g (S)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-methyl ester (example 7)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.47 (m, 1 H) 1.79 (m, 1 H) 1.92 (m, 2 H) 2.13 (d, *J*=1.53 Hz, 1 H) 2.25 (m, 1 H) 2.31 (dt, 1 H) 2.81 (br. m., 1 H) 3.49 (t, *J*=7.17 Hz, 2 H) 3.60 (s, 3 H) 3.61 - 3.68 (m, 2 H) 3.89 - 3.98 (m, 1 H)

4.2 g (R)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-ethyl ester (example 8)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.17 (t, *J*=7.02 Hz, 3 H) 1.47 (m, 1 H) 1.78 (m, 1 H) 1.92 (m, 2 H) 2.12 (dd, *J*=14.27, 1.91 Hz, 1 H) 2.25 (d, 1 H) 2.31 (dt, *J*=14.04, 7.02 Hz, 1 H) 2.80 (br. m., 1 H) 3.49 (t, *J*=7.25 Hz, 2 H) 3.63 (m, 2 H) 3.93 (m, 1 H) 4.05 (q, *J*=7.02 Hz, 2 H)

4.4 g (S)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-ethyl ester (example 9)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.17 (t, *J*=7.02 Hz, 3 H) 1.47 (m, 1 H) 1.78 (m, 1 H) 1.92 (m, 2 H) 2.12 (dd, *J*=14.27, 1.91 Hz, 1 H) 2.25 (d, 1 H) 2.31 (dt, *J*=14.04, 7.02 Hz, 1 H) 2.80 (br. m., 1 H) 3.49 (t, *J*=7.25 Hz, 2 H) 3.63 (m, 2 H) 3.93 (m, 1 H) 4.05 (q, *J*=7.02 Hz, 2 H)

3.8 g (R)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-propyl ester (example 10)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.40 Hz, 3 H) 1.47 (qt, *J*=13.49, 3.87 Hz, 1 H) 1.58 (m, *J*=7.25, 7.00, 7.00, 7.00, 7.00 Hz, 2 H) 1.79 (br. m, 1 H) 1.92 (m, 2 H) 2.12 (m, 1 H) 2.25 (br. m, 1 H) 2.29 (dt, *J*=14.04, 7.02 Hz, 1 H) 2.79 (br. m., 1 H) 3.50 (m, 2 H) 3.63 (m, 2 H) 3.85 - 4.09 (m, 3 H)

3.8 g (S)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-propyl ester (example 11)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.40 Hz, 3 H) 1.47 (qt, *J*=13.49, 3.87 Hz, 1 H) 1.58 (m, *J*=7.25, 7.00, 7.00, 7.00, 7.00 Hz, 2 H) 1.79 (br. m, 1 H) 1.92 (m, 2 H) 2.12 (m, 1 H) 2.25 (br. m, 1 H) 2.29 (dt, *J*=14.04, 7.02 Hz, 1 H) 2.79 (br. m., 1 H) 3.50 (m, 2 H) 3.63 (m, 2 H) 3.85 - 4.09 (m, 3 H)

3.2 g (R)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-butyl ester (example 12)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.40 Hz, 3 H) 1.32 (sxt, *J*=7.42 Hz, 2 H) 1.47 (m, *J*=13.54, 3.76 Hz, 1 H) 1.55 (m, 2 H) 1.78 (br. s., 1 H) 1.92 (m, 2 H) 2.12 (dd, *J*=14.19, 1.68 Hz, 1 H) 2.25 (br. m, 1 H) 2.31 (dt, *J*=14.11, 6.33 Hz, 1 H) 2.81 (br. m., 1 H) 3.49 (t, *J*=7.17 Hz, 2 H) 3.63 (m, 2 H) 3.93 (m, 1 H) 4.00 (t, *J*=6.41 Hz, 2 H)

3.4 g (S)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-butyl ester (example 13)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.40 Hz, 3 H) 1.32 (sxt, *J*=7.42 Hz, 2 H) 1.47 (m, *J*=13.54, 3.76 Hz, 1 H) 1.55 (m, 2 H) 1.78 (br. s., 1 H) 1.92 (m, 2 H) 2.12 (dd, *J*=14.19, 1.68 Hz, 1 H) 2.25 (br. m, 1 H) 2.31 (dt, *J*=14.11, 6.33 Hz, 1 H) 2.81 (br. m., 1 H) 3.49 (t, *J*=7.17 Hz, 2 H) 3.63 (m, 2 H) 3.93 (m, 1 H) 4.00 (t, *J*=6.41 Hz, 2 H)

4.8 g (R)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-neopentyl ester (example 14)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.90 (s, 9 H) 1.47 (m, 1 H) 1.79 (br. m., 1 H) 1.94 (br. m., 2 H) 2.13 (m, 1 H) 2.24 (br. m, 1 H) 2.31 (dt, *J*=14.04, 6.10 Hz, 1 H) 2.82 (br. m, 1 H) 3.52 (t, *J*=7.17 Hz, 2 H) 3.64 (m, 2 H) 3.73 (br. m., 2 H) 3.94 (m, 1 H)

5.2 g (S)- carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-neopentyl ester (example 15)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.90 (s, 9 H) 1.47 (m, 1 H) 1.79 (br. m., 1 H) 1.94 (br. m., 2 H) 2.13 (m, 1 H) 2.24 (br. m, 1 H) 2.31 (dt, *J*=14.04, 6.10 Hz, 1 H) 2.82 (br. m, 1 H) 3.52 (t, *J*=7.17 Hz, 2 H) 3.64 (m, 2 H) 3.73 (br. m., 2 H) 3.94 (m, 1 H)

Example 16-20: Synthesis of 1-carbalkoxy-4-ketoperhydroindole

15 mmol carbamic acid (2-chloroethyl)(3-oxocyclohexyl)-alkyl ester are dissolved in 15 ml methylene chloride. To the orange coloured solution 1.07 g pyrrolidine and 1.52 g triethylamine are added. The reaction mixture is stirred 16 h at room temperature and finally diluted with 45 ml isopropyl acetate and 30 ml of water. Under stirring the pH of the emulsion is adjusted to pH = 2 and stirring is continued for further 30 min. After phase separation the aqueous phase is extracted two times with 20 ml isopropyl acetate and the combined organic phase is washed three times with 20 ml water each. The solvent is removed under vacuum (50°C/20 mbar) yielding:

2.55 g 1-carbmethoxy-4-ketoperhydroindole (example 16)

2.70 g 1-carbethoxy-4-ketoperhydroindole (example 17)

2.98 g 1-carbpropoxy-4-ketoperhydroindole (example 18)

3.15 g 1-carbbutoxy-4-ketoperhydroindole (example 19)

3.34 g 1-carbneopentoxo-4-ketoperhydroindole (example 20)

Example 21-30: Synthesis of (S,S)- and (R,R)- 1-carbalkoxy-4-ketoperhydroindole

5 g racemic 1-carbalkoxy-4-ketoperhydroindole are dissolved in 50 ml heptane/2-propanol = 1/1 (V/V) and injected onto a preparative Chiralpak-AD column (particle size: 20 μ m, column dimensions: 30 cm length x 10 cm I.D.). Using heptane/2-propanol/methanol = 90/7.5/2.5 (V/V/V) as the mobile phase at room temperature and a flow rate of 400 ml/min, baseline separation is achieved within 60 min while the S,S-enantiomer elutes always prior to its R,R-enantiomer. The solvents are removed under vacuum yielding:

2.5 g (S,S)- 1-carbmethoxy-4-ketoperhydroindole (example 21)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.58 (br. m., 2 H) 1.73 (br. m., 1 H) 1.88 (m, 1 H) 2.01 (m, 1 H) 2.14 (m, 1 H) 2.19 (m, 1H) 2.37 (td, *J*=10.76, 5.65 Hz, 1 H) 2.82 (m, 1 H) 3.29 (m, 2 H) 3.57 (s, 3 H) 4.04 (m, 1 H)

2.4 g (R,R)- 1-carbmethoxy-4-ketoperhydroindole (example 22)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.58 (br. m., 2 H) 1.73 (br. m., 1 H) 1.88 (m, 1 H) 2.01 (m, 1 H) 2.14 (m, 1 H) 2.19 (m, 1H) 2.37 (td, *J*=10.76, 5.65 Hz, 1 H) 2.82 (m, 1 H) 3.29 (m, 2 H) 3.57 (s, 3 H) 4.04 (m, 1 H)

1.5 g (S,S)- 1-carbethoxy-4-ketoperhydroindole (example 23)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.16 (t, *J*=7.10 Hz, 3 H) 1.57 (m, 2 H) 1.75 (br. m., 1 H) 1.88 (m, 1 H) 2.02 (d, *J*=4.58 Hz, 1 H) 2.13 (m, 1 H) 2.19 (m, 1H) 2.38 (td, *J*=10.64, 5.57 Hz, 1 H) 2.83 (m, 1 H) 3.28 (m, 2 H) 4.03 (m, 3 H)

2.4 g (R,R)- 1-carbethoxy-4-ketoperhydroindole (example 24)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 1.16 (t, *J*=7.10 Hz, 3 H) 1.57 (m, 2 H) 1.75 (br. m., 1 H) 1.88 (m, 1 H) 2.02 (d, *J*=4.58 Hz, 1 H) 2.13 (m, 1 H) 2.19 (m, 1H) 2.38 (td, *J*=10.64, 5.57 Hz, 1 H) 2.83 (m, 1 H) 3.28 (m, 2 H) 4.03 (m, 3 H)

2.3 g (S,S)- 1-carbpropoxy-4-ketoperhydroindole (example 25)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.40 Hz, 3 H) 1.56 (m, 4 H) 1.76 (br. m., 1 H) 1.88 (m, 1 H) 2.02 (m, 1 H) 2.14 (br. m, 1H) 2.05 (m, 1 H) 2.36 (dt, *J*=10.68, 5.34 Hz, 1 H) 2.83 (m, 1 H) 3.29 (m, 2 H) 3.93 (m, 2 H) 4.04 (m, 1 H)

2.1 g (R,R)- 1-carbpropoxy-4-ketoperhydroindole (example 26)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.40 Hz, 3 H) 1.56 (m, 4 H) 1.76 (br. m., 1 H) 1.88 (m, 1 H) 2.02 (m, 1 H) 2.14 (br. m, 1H) 2.05 (m, 1 H) 2.36 (dt, *J*=10.68, 5.34 Hz, 1 H) 2.83 (m, 1 H) 3.29 (m, 2 H) 3.93 (m, 2 H) 4.04 (m, 1 H)

2.3 g (S,S)- 1-carbbutoxy-4-ketoperhydroindole (example 27)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.40 Hz, 3 H) 1.32 (dq, *J*=14.97, 7.42 Hz, 2 H) 1.54 (m, 4 H) 1.75 (br. m., 1 H) 1.88 (m, 1 H) 2.02 (m, 1 H) 2.13 (br. m, 1 H) 2.19 (m, 1H) 2.73 (dt, *J*=10.83, 5.42 Hz, 1 H) 2.83 (m, 1 H) 3.29 (m, 2 H) 3.99 (m, 3 H)

2.0 g (R,R)- 1-carbbutoxy-4-ketoperhydroindole (example 28)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.88 (t, *J*=7.40 Hz, 3 H) 1.32 (dq, *J*=14.97, 7.42 Hz, 2 H) 1.54 (m, 4 H) 1.75 (br. m., 1 H) 1.88 (m, 1 H) 2.02 (m, 1 H) 2.13 (br. m, 1 H) 2.19 (m, 1H) 2.73 (dt, *J*=10.83, 5.42 Hz, 1 H) 2.83 (m, 1 H) 3.29 (m, 2 H) 3.99 (m, 3 H)

1.7 g (S,S)- 1-carbneopentoxo-4-ketoperhydroindole (example 29)

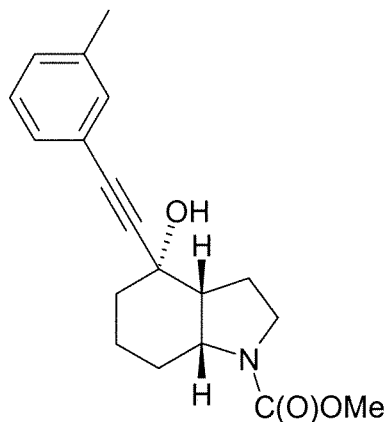
¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.90 (s, 9 H) 1.59 (m, 2 H) 1.75 (br. sm, 1 H) 1.90 (m, 1 H) 2.03 (m, 1 H) 2.14 (br. M, 1H) 2.20 (m, 1 H) 2.36 (dt, *J*=10.83, 5.34 Hz, 1 H) 2.84 (m, 1 H) 3.33 (m, 2 H) 3.68 (br. m, 2 H) 4.07 (br. m., 1 H)

1.5 g (R,R)- 1-carbneopentoxo-4-ketoperhydroindole (example 30)

¹H NMR (500 MHz, DMSO-*d*₆) δ ppm 0.90 (s, 9 H) 1.59 (m, 2 H) 1.75 (br. sm, 1 H) 1.90 (m, 1 H) 2.03 (m, 1 H) 2.14 (br. M, 1H) 2.20 (m, 1 H) 2.36 (dt, *J*=10.83, 5.34 Hz, 1 H) 2.84 (m, 1 H) 3.33 (m, 2 H) 3.68 (br. m, 2 H) 4.07 (br. m., 1 H)

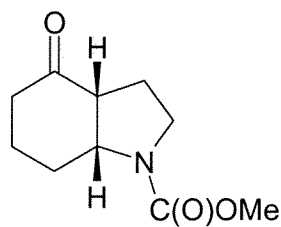
Claims

1. A process for the production of a compound of the formula (I) or a pharmaceutically acceptable salt thereof:



(I)

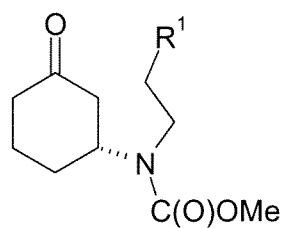
which comprises reacting 3-ethynyltoluene with a compound of the formula (II) or a salt thereof:



(II)

to form the compound of formula (I) and optionally converting the compound of formula (I) to a pharmaceutically acceptable salt.

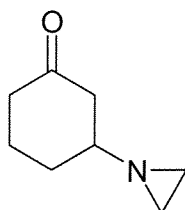
2. A process according to claim 1, wherein the compound of formula (II) is obtained by cyclisation of a compound of the formula (III) or a salt thereof:



(III)

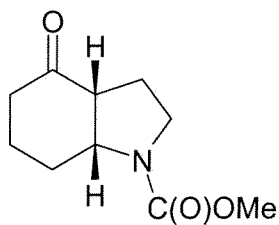
wherein R¹ is a leaving group.

3. A process according to claim 2, wherein the compound of formula (III) is obtained by reacting a compound of the formula R¹C(O)OMe with a compound of the formula (IV) or a salt thereof:



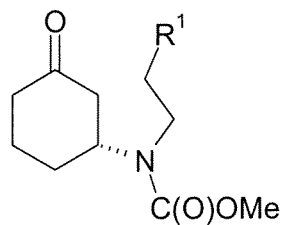
(IV)

4. A process according to claim 3, wherein the compound of formula (IV) is obtained by reacting cyclohexen-2-one with aziridine or a salt thereof.
5. A process according to any preceding claim, which further comprises formulating the compound of formula (I) into a pharmaceutical composition.
6. A process for the production of a compound of the formula (II) or a salt thereof:



(II)

which comprises cyclisation of a compound of the formula (III) or a salt thereof:

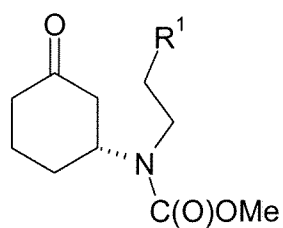


(III)

wherein R¹ is a leaving group.

7. A process according to claim 6, wherein the compound of formula (III) is obtained according to claim 3 or claim 4.

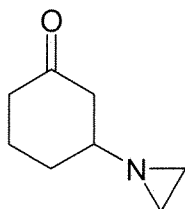
8. A process for the production of a compound of the formula (III) or a salt thereof:



(III)

wherein R¹ is a leaving group;

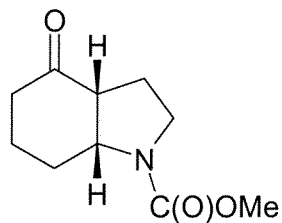
which comprises reacting a compound of the formula R¹C(O)OMe with a compound of the formula (IV) or a salt thereof:



(IV)

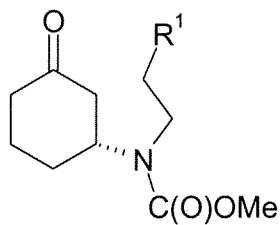
9. A process according to claim 8, wherein the compound of formula (IV) is obtained according to claim 4.

10. A compound of the formula (II) or a salt thereof:



(II)

11. A compound of the formula (III) or a salt thereof:

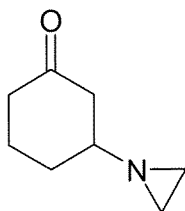


(III)

wherein R¹ is a leaving group, e.g. halo.

12. Use of a compound of claim 10 or claim 11, for the manufacture of a compound of the formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

13. Use of a compound of the formula (IV) or a salt thereof:



(IV)

for the manufacture of a compound of the formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

14. Use of cyclohexen-2-one, aziridine or a salt thereof for the manufacture of a compound of the formula (I) as defined in claim 1 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/060351

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/08 C07C271/24 C07D203/14

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 C07C

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, 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.
Y	WO 03/047581 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; GASPARINI FABRIZIO [CH];) 12 June 2003 (2003-06-12) cited in the application page 8 - page 10; example 1 -----	1-14
Y	DOLFINI J E ET AL: "AziridinyI compounds as intermediates in pyrrolidine synthesis" TETRAHEDRON LETTERS, ELSEVIER, AMSTERDAM, vol. 6, no. 25, 1 January 1965 (1965-01-01), pages 2053-2058, XP025402190 ISSN: 0040-4039 [retrieved on 1965-01-01] cited in the application the whole document; in particular, pages 2056-2057 ----- -/--	1-14



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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E earlier document but published on or after the international filing date

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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

18 November 2009

Date of mailing of the international search report

07/12/2009

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2009/060351

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SEPULVEDA-ARQUES J ET AL: "Stereoselective Ring Transformation of N-Alkyl Aziridines into Oxazolidin-2-ones" TETRAHEDRON, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL, vol. 52, no. 6, 5 February 1996 (1996-02-05), pages 2097-2102, XP004104440 ISSN: 0040-4020 the whole document; in particular, page 2099, the first two lines and the following table and page 2101, the first two lines -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2009/060351

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 03047581	A	12-06-2003	AT 327755 T	15-06-2006
			AU 2002358585 A1	17-06-2003
			BR 0214666 A	03-11-2004
			CA 2466560 A1	12-06-2003
			CN 1592623 A	09-03-2005
			CN 101366714 A	18-02-2009
			DE 60211944 T2	16-05-2007
			DK 1453512 T3	28-08-2006
			EC SP045139 A	23-07-2004
			EP 1453512 A1	08-09-2004
			ES 2263842 T3	16-12-2006
			HK 1071510 A1	29-12-2006
			HU 0402191 A2	28-02-2005
			JP 4176020 B2	05-11-2008
			JP 2005514381 T	19-05-2005
			JP 2008303226 A	18-12-2008
			KR 20050044657 A	12-05-2005
			MX PA04005456 A	11-10-2004
			NO 327005 B1	06-04-2009
			NZ 533266 A	25-02-2005
			PT 1453512 E	31-10-2006
			RU 2341515 C2	20-12-2008
			US 2008146647 A1	19-06-2008
			US 2005065191 A1	24-03-2005
			ZA 200403713 A	10-08-2005