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(12) **DEMANDE DE BREVET CANADIEN**  
**CANADIAN PATENT APPLICATION**

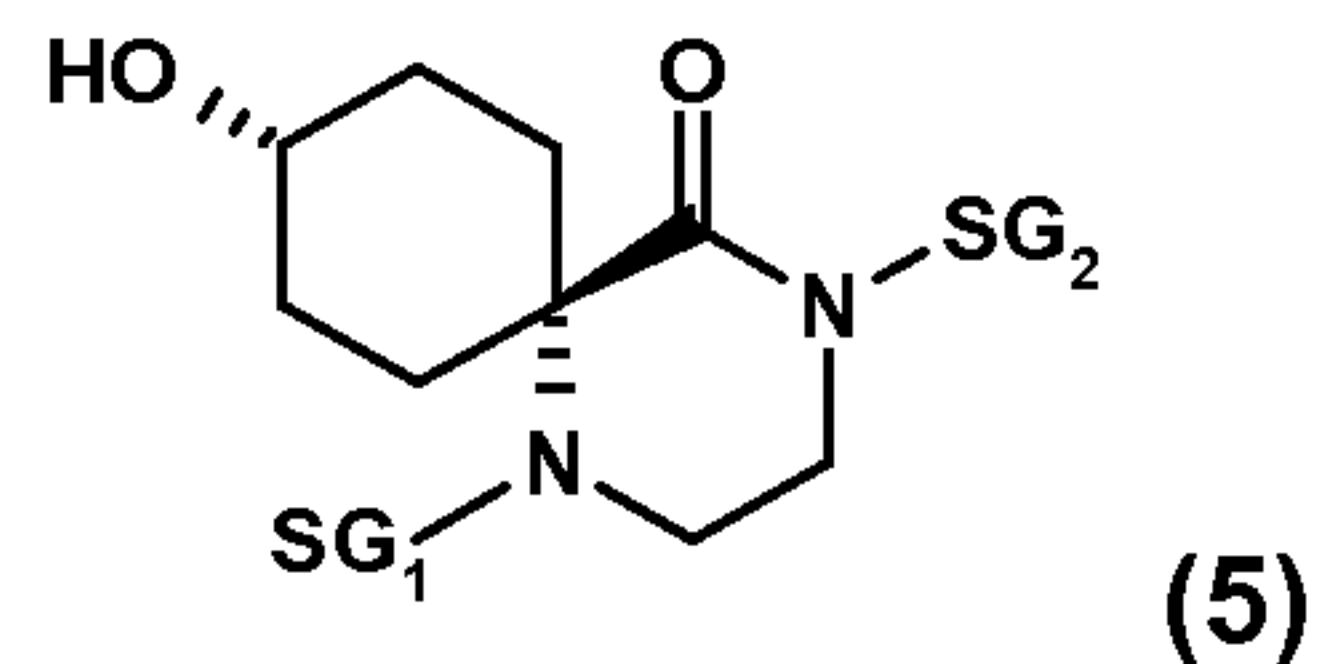
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(71) **Demandeur/Applicant:**  
BOEHRINGER INGELHEIM INTERNATIONAL GMBH,  
DE  
(72) **Inventeurs/Inventors:**  
SCHNAUBELT, JUERGEN, DE;  
TANG, WENJUN, US  
(74) **Agent:** FETHERSTONHAUGH & CO.

(54) **Titre : PROCEDE DE SYNTHESE STEREOSELECTIVE DE 9-HYDROXY-5-OXO-1,4-DIAZA-SPIRO[5.5]UNDECANES QUI SONT 1,4-PROTEGES**  
(54) **Title: METHOD FOR STEREOSELECTIVE SYNTHESIS OF 1,4-PROTECTED 9-HYDROXY-5-OXO-1,4-DIAZA-SPIRO[5.5]UNDECANES**



(5)

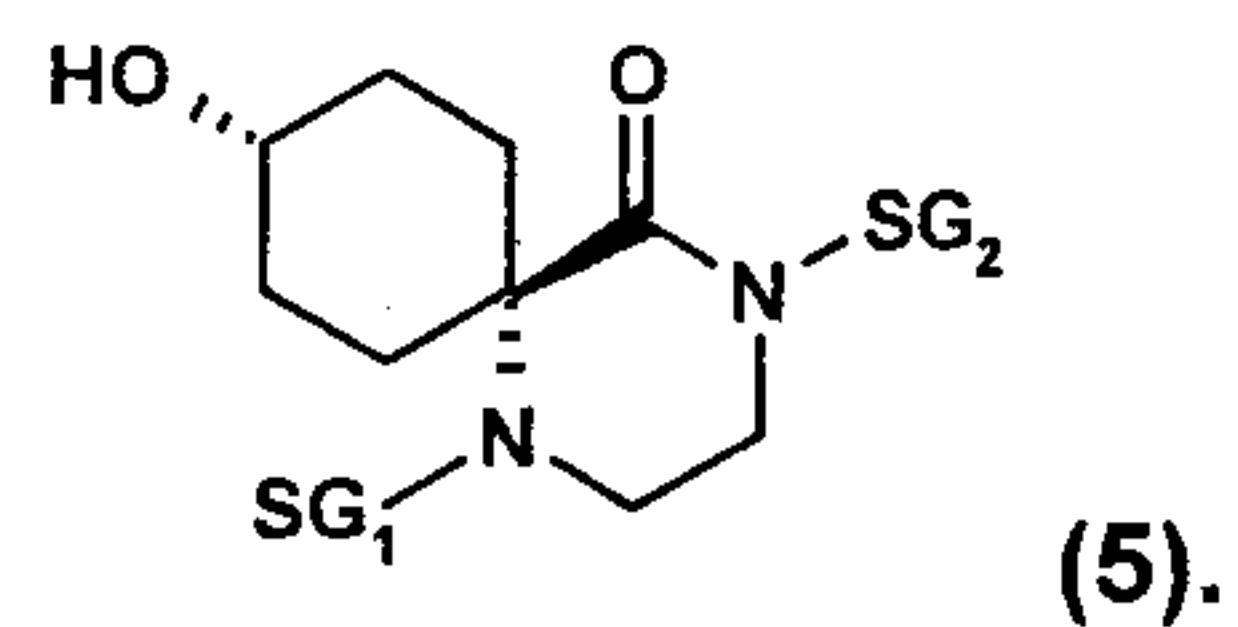
(57) **Abrégé/Abstract:**

The invention relates to a method for stereoselective production of a compound of formula (5), optionally in the form of the tautomers thereof.

**ABSTRACT**

The invention relates to a method for the stereoselective preparation of a compound of formula (5), optionally in the form of the tautomers thereof,

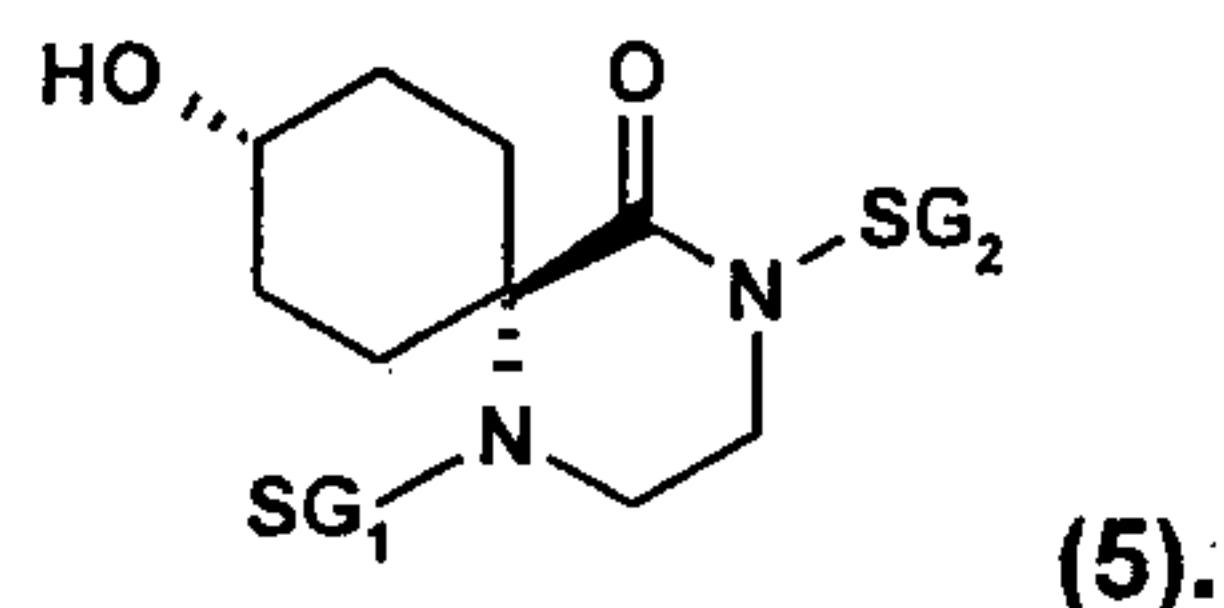
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(5).

**Method for stereoselective synthesis of 1,4-protected 9-hydroxy-5-oxo-1,4-diaza-spiro[5.5]undecanes**

5 The invention relates to a method for the stereoselective preparation of a compound of formula (5), optionally in the form of the tautomers thereof,

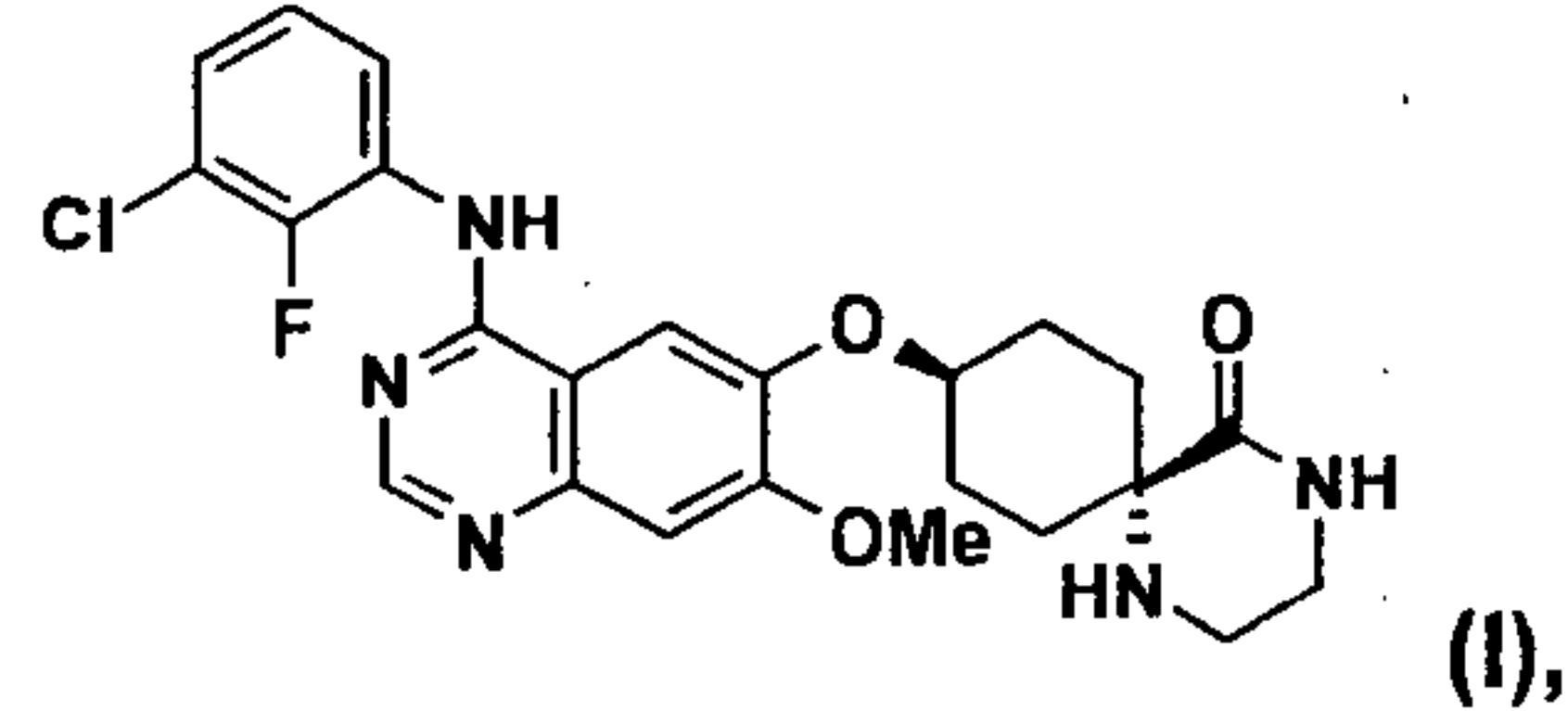


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**BACKGROUND TO THE INVENTION**

Compounds of formula (5), optionally in the form of the tautomers thereof,  
 15 are valuable intermediates in methods for the stereoselective preparation of the compound of formula (I), optionally in the form of the tautomers thereof, and optionally the pharmacologically acceptable acid addition salts thereof,

20



which compound has valuable pharmacological properties, particularly an inhibiting action on signal transduction mediated by tyrosine kinases, and for the treatment of diseases, particularly tumoral diseases, benign prostatic hyperplasia and diseases of the lungs and respiratory tract.  
 25

Quinazoline derivatives are known from the prior art as active substances for example for the treatment of tumoral diseases and also diseases of the lungs and airways. Methods

for preparing quinazoline derivatives are described in WO03082290 and WO07068552. WO2009098061 and WO2011015526 disclose methods of preparing the compound (I).

5 The problem of the present invention is to provide an alternative stereoselective synthesis process for preparing the compound of formula (I) or an advantageous method of preparing important intermediates of this synthesis.

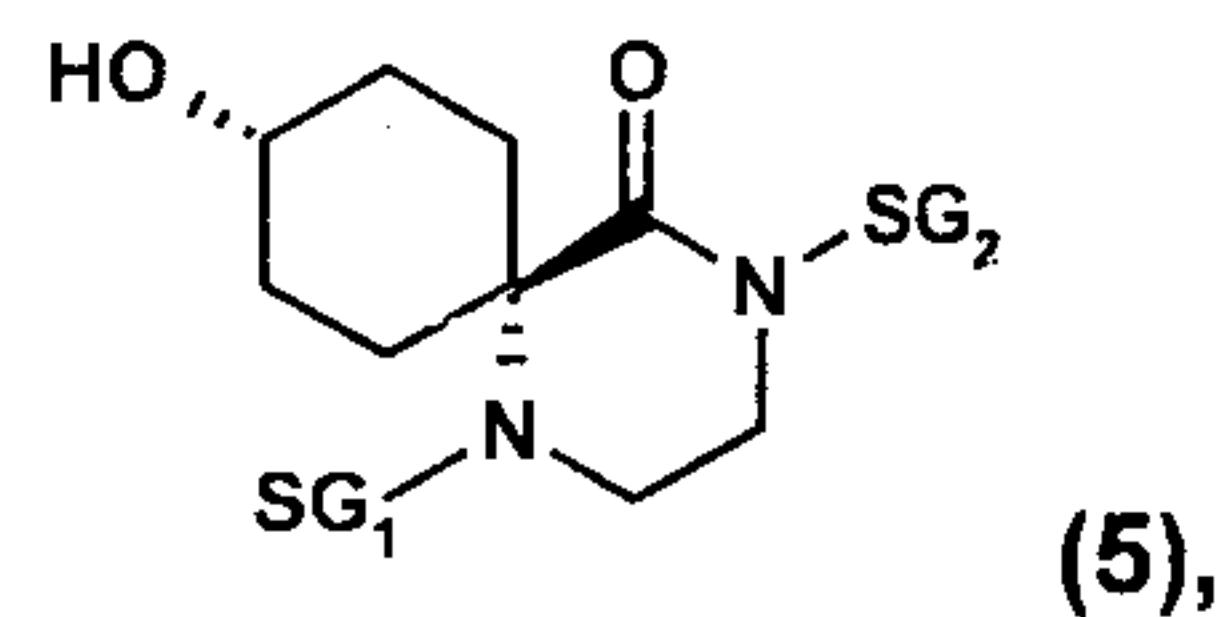
### DETAILED DESCRIPTION OF THE INVENTION

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The present invention solves the problem stated above by means of the method of synthesis described hereinafter.

15

The invention relates to a process for the stereoselective preparation of the compound of formula (5), optionally in the form of the tautomers thereof,



wherein

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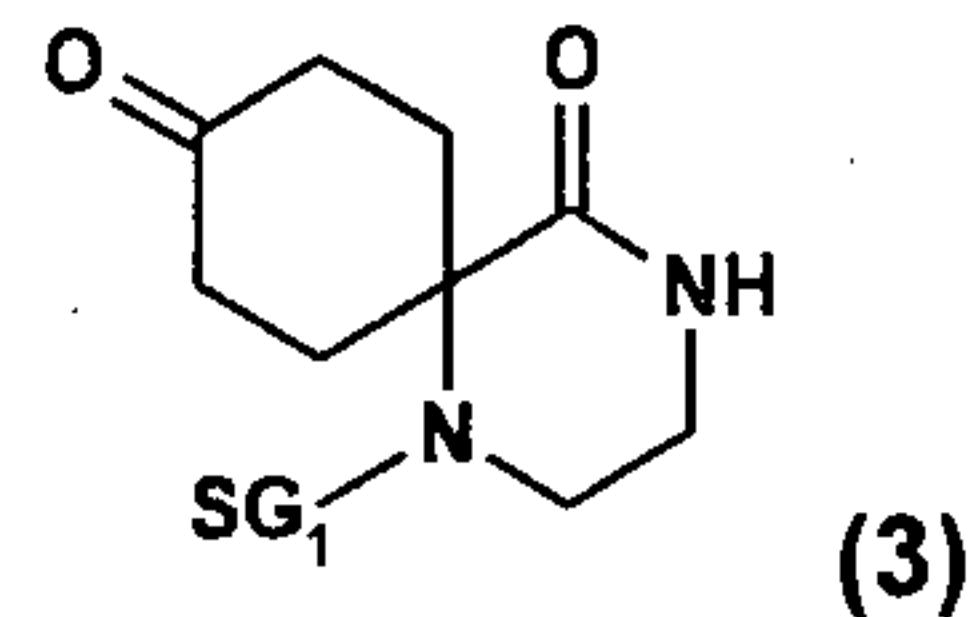
**SG<sub>1</sub>** denotes a protective group selected from among trifluoroacetyl, acetyl, benzoyl and pivaloyl,

**SG<sub>2</sub>** denotes a protective group selected from among tert.-butoxycarbonyl, ethoxycarbonyl and methoxycarbonyl,

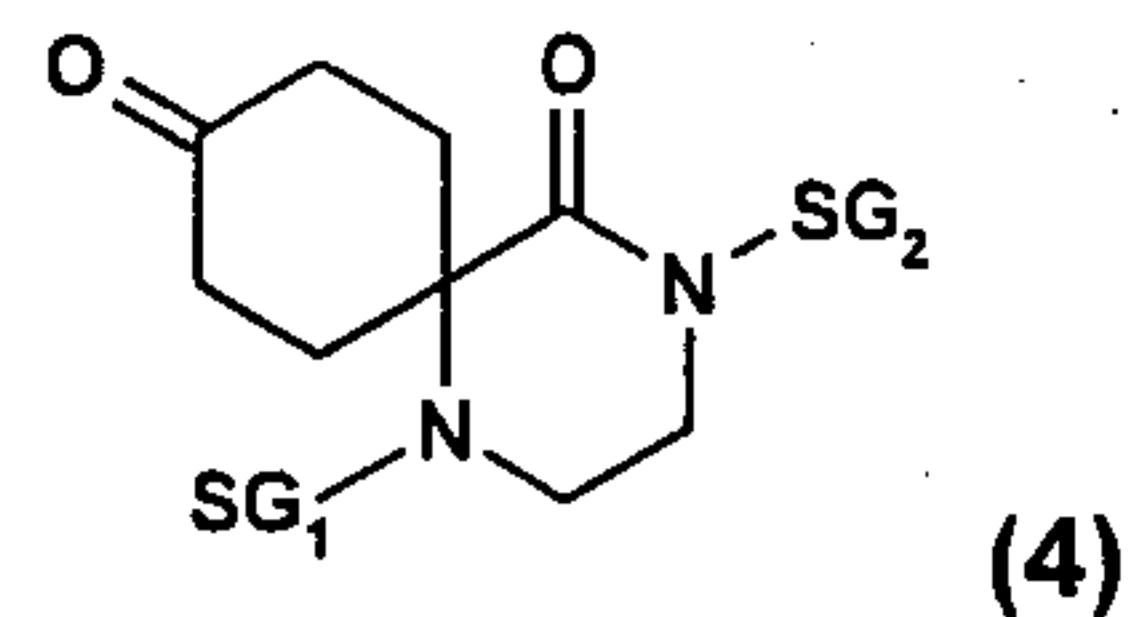
characterised in that the process comprises reaction steps (C) and (D), where

25

(C) is the reaction of the compound of formula (3)



to form a compound of formula (4)



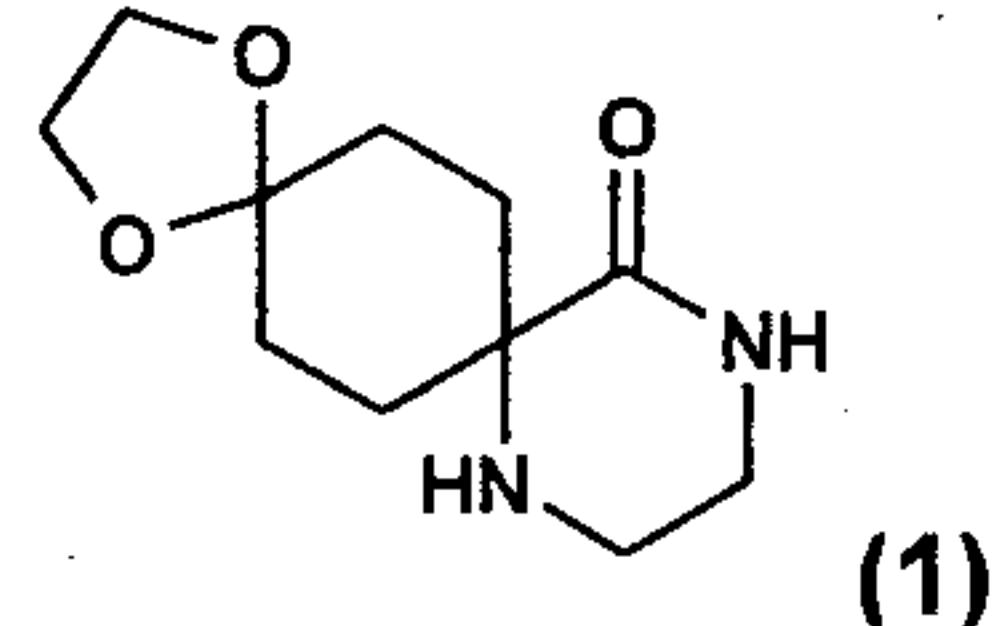
and

5 (D) is the reduction of the compound of formula (4) to form a compound of formula (5),

wherein process steps (C) and (D) are carried out successively in the order stated.

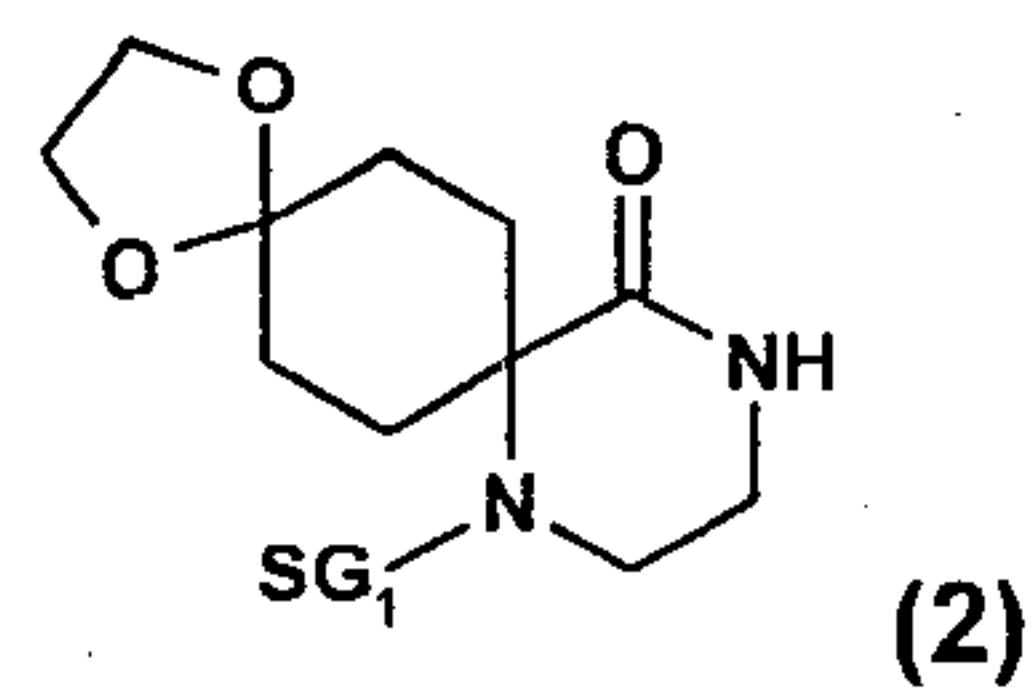
10 In a preferred process the reaction steps (C) and (D) are preceded by further reaction steps (A) and (B),  
where

(A) denotes the reaction of the compound of formula (1)



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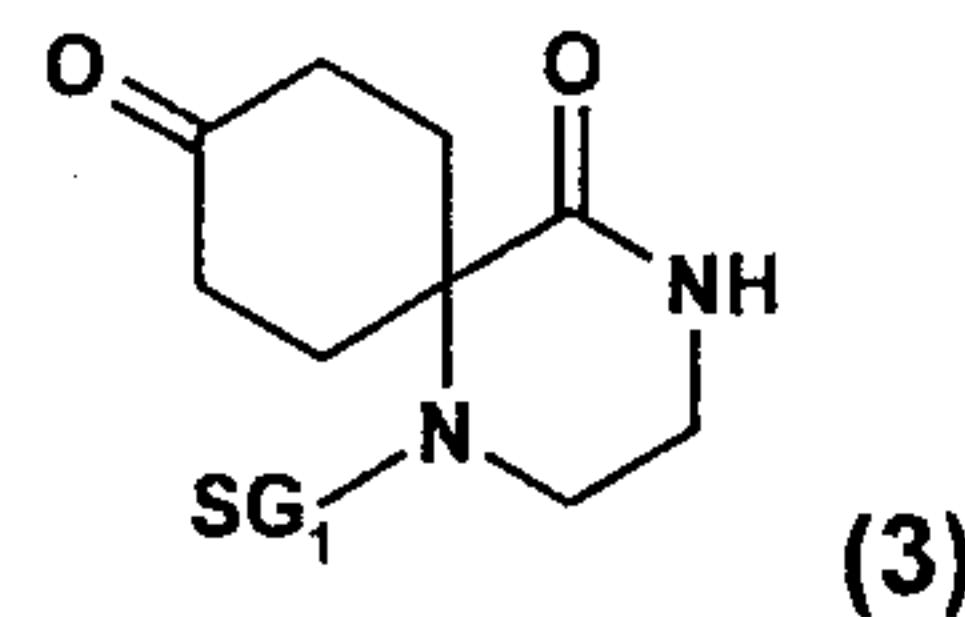
to form a compound of formula (2)



20

and

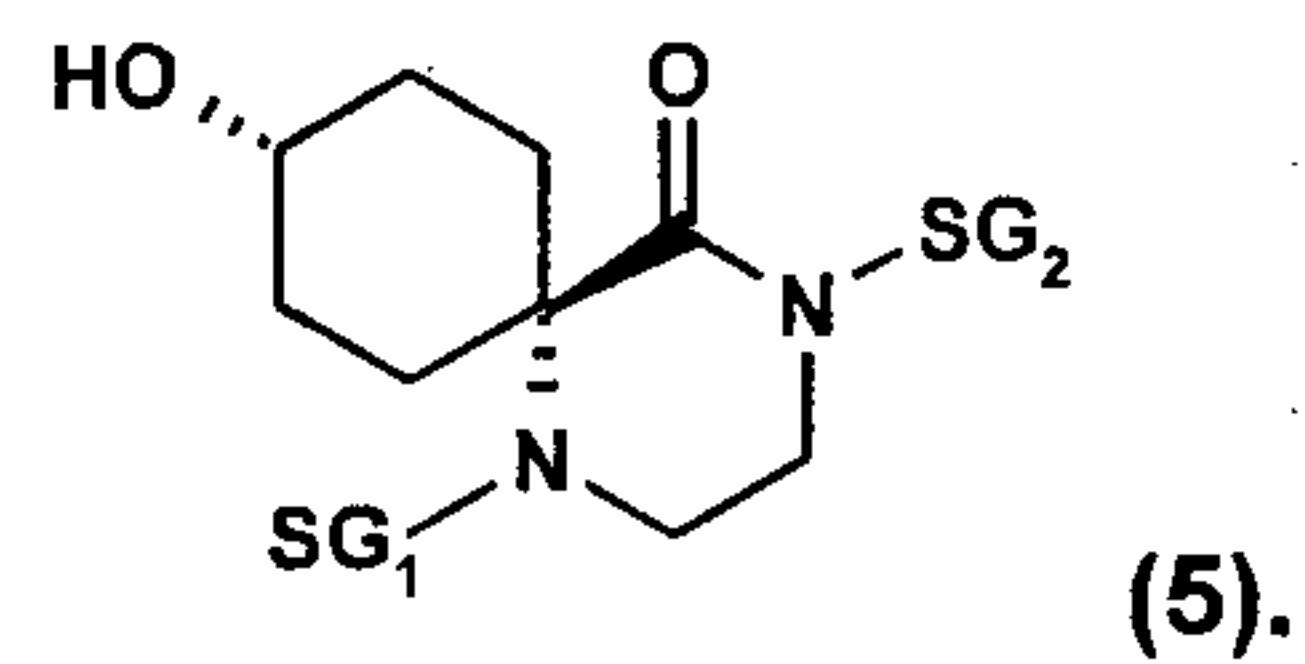
(B) denotes the reaction of the compound of formula (2) to form a compound of formula (3)



while process steps (A), (B), (C) and (D) are carried out successively in the order stated.

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Also preferred is a process for the stereoselective preparation of the compound of formula (5), optionally in the form of the tautomers thereof,



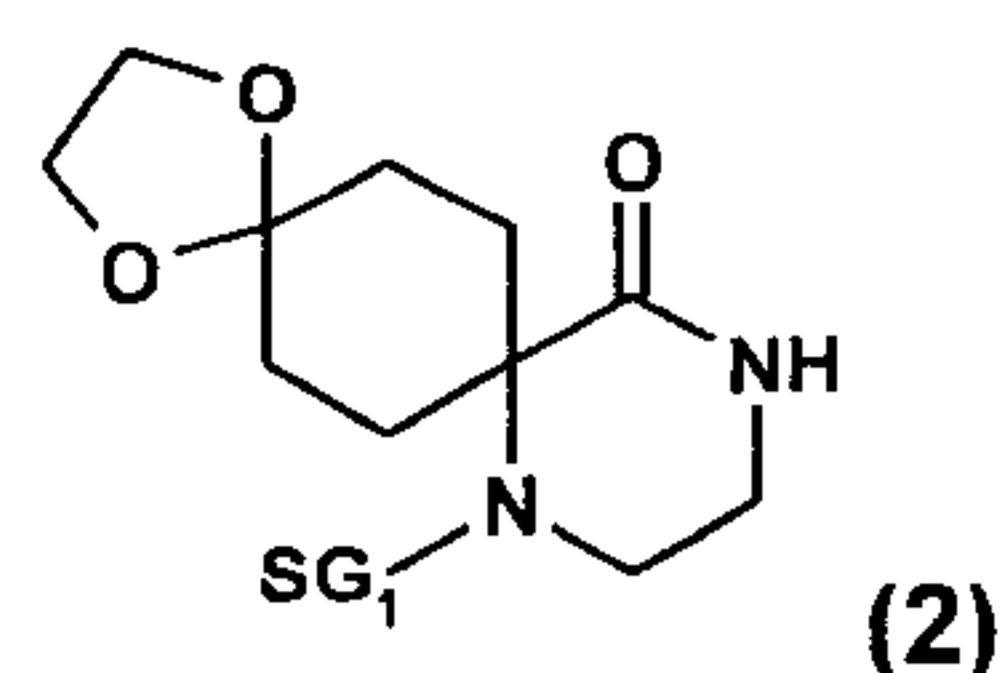
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characterised in that

**SG<sub>1</sub>** denotes trifluoroacetyl, and

**SG<sub>2</sub>** denotes tert.-butoxycarbonyl.

15 The invention further relates to an intermediate of formula (2), optionally in the form of the tautomers or salts thereof

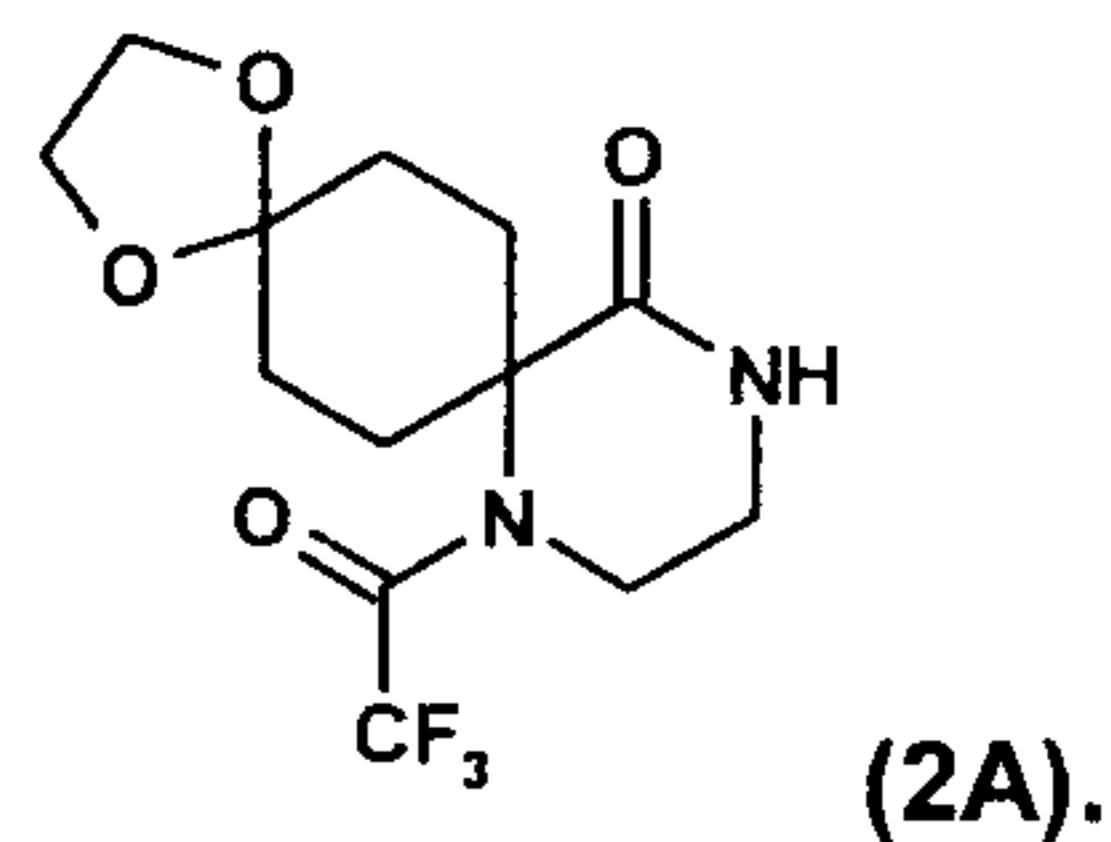


wherein,

20 **SG<sub>1</sub>** denotes a protective group selected from among trifluoroacetyl, acetyl, benzoyl and pivaloyl.

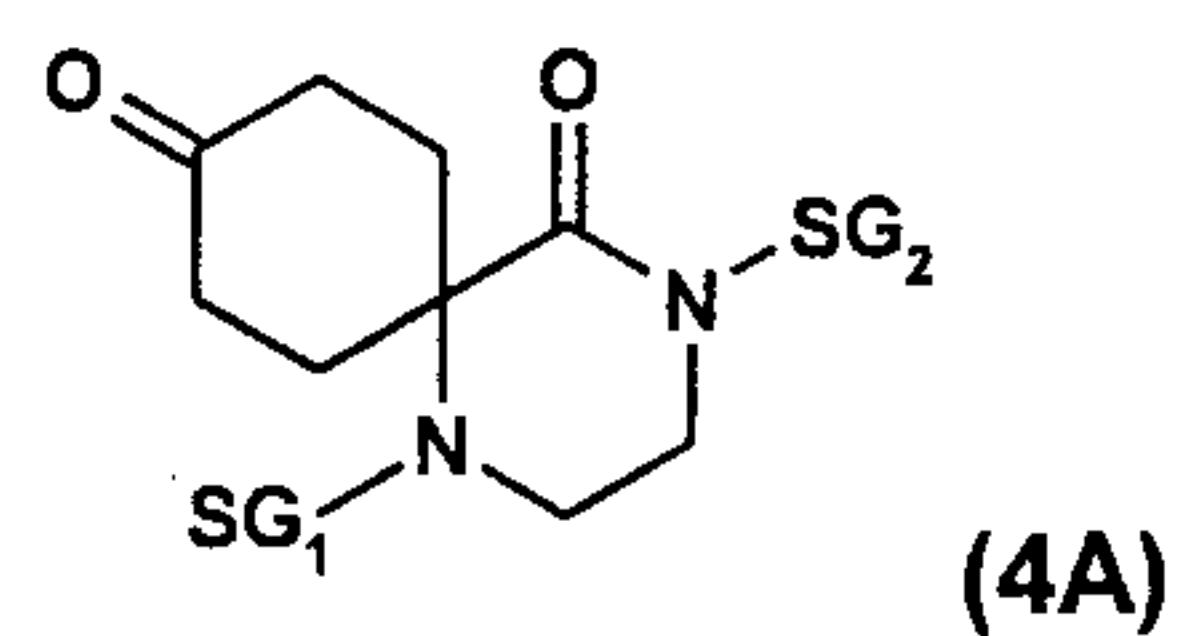
Preferred is an intermediate of formula (2A), optionally in the form of the tautomers or salts thereof,

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The invention further relates to an intermediate of formula (4), optionally in the form of the tautomers or salts thereof

5

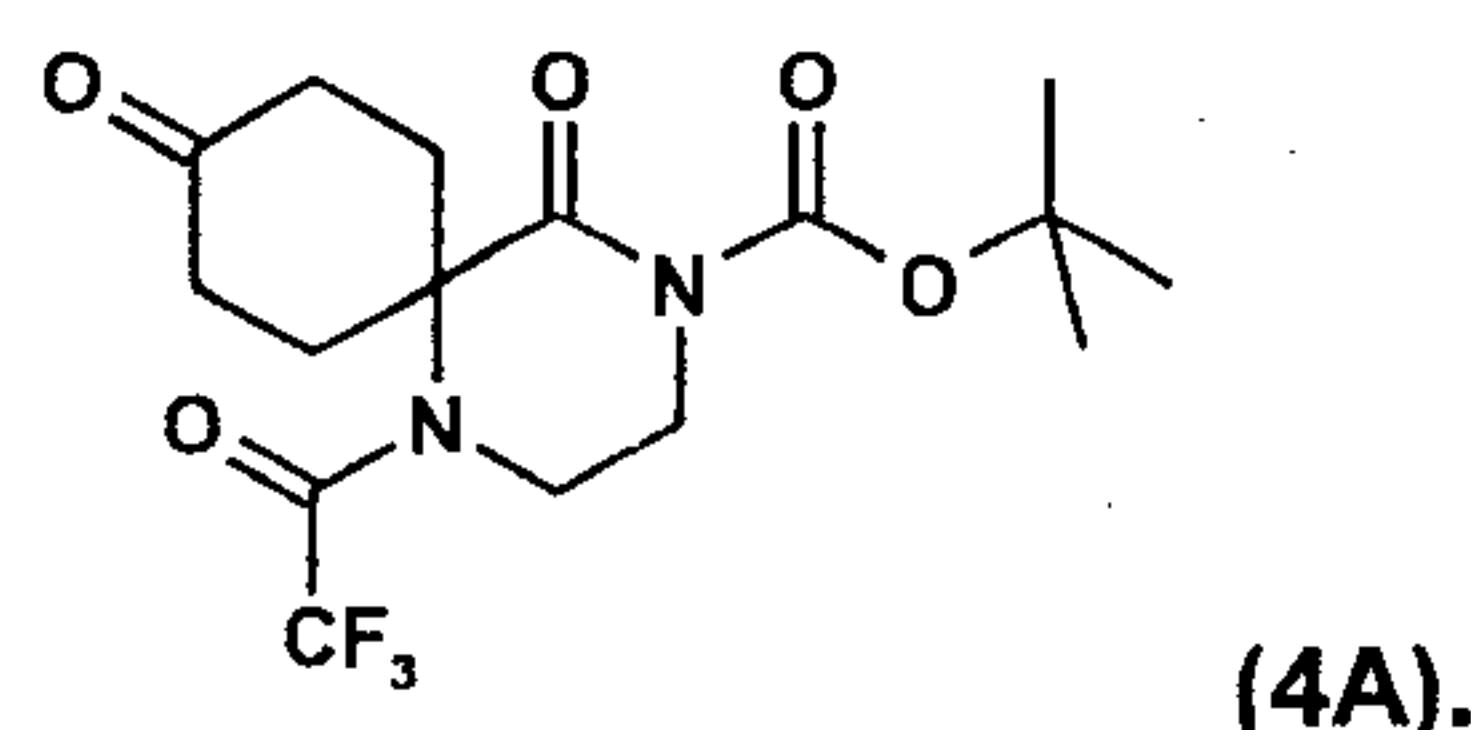


wherein

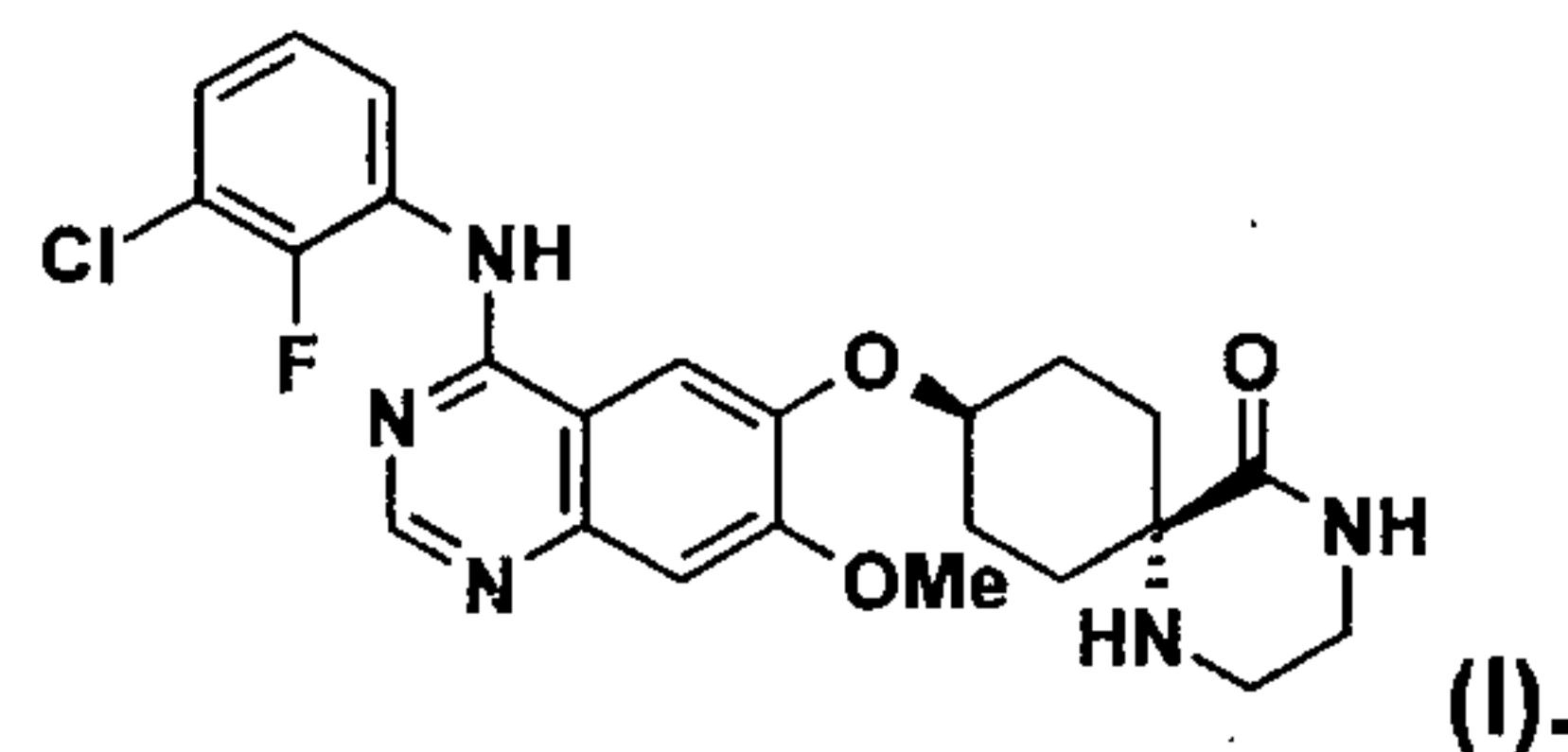
**SG<sub>1</sub>** denotes a protective group selected from among trifluoroacetyl, acetyl, benzoyl and pivaloyl, and

**SG<sub>2</sub>** denotes a protective group selected from among tert.-butoxycarbonyl, ethoxycarbonyl and methoxycarbonyl.

Preferred is an intermediate of formula (4A), optionally in the form of the tautomers or salts thereof.



The invention further relates to the use of the intermediates of formula (2) or (4), preferably the intermediates (2A) or (4A), optionally in the form of the tautomers or salts thereof, for preparing a compound of formula (I), optionally in the form of the tautomers or salts thereof.



The novel use of the intermediates (2) or (4), preferably of the intermediates (2A) or (4A), for preparing a compound of formula (I) may be carried out via the preparation of the 5 compound of formula (5) and the subsequent synthesis steps (G) to (L) described in WO2012104206.

Compared with the synthesis described in WO2012104206 the following advantages are obtained, particularly with a view to the large-scale industrial production of the compound (I):

- 10 a) The total yield of compound (5) starting from compound (1) is significantly increased by between 10 to 20%, for example by 15%, to 60%.
- b) Smaller amounts of acetic acid are used for the acetal splitting and the resultant larger quantities of acid waste are avoided.
- c) The use of sodium borohydride is avoided by using a less expensive heterogeneously 15 catalytic hydrogenation process.

In process steps (A), (B), (C), (D) alternative reagents, catalysts and solvents may be used, preferably selected from among the reagents, catalysts and solvents listed in Table I.1 to I.4:

20

Table I.1 Alternative solvent

process step	solvent	particularly preferred solvent
(A)	Me-THF, THF, toluene, DMF, NMP, ethyl acetate, methyl-cyclohexane, cyclohexane, $\text{CH}_2\text{Cl}_2$ and dioxane	Me-THF and methyl-cyclohexane
(B)	water, methanol, ethanol, isopropanol and dioxane	water and methanol

(C)	Me-THF, THF, DMF, NMP, acetone, acetonitrile and dioxane	acetonitrile
(D)	methanol, ethanol, isopropanol, water and ethyl acetate	ethanol

Table I.2 Alternative bases and acids

process step		bases or acids	particularly preferred bases or acids
(A)	bases	N-methylmorpholine, triethylamine, N-ethyldiisopropylamine (Hünig base), N-methylpyrrolidine and N-methylpiperidine	N-methylmorpholine
(B)	acids	acetic acid, trifluoroacetic acid, hydrochloric acid, sulphuric acid, methanesulphonic acid and p-toluenesulphonic acid	acetic acid

5

Table I.3 Alternative reagents

process step	reagents	particularly preferred reagents
(A)	trifluoroacetic anhydride, methyl trifluoroacetate, trifluoroacetyl chloride and trifluoroacetylimidazole	trifluoroacetic anhydride
(C)	di-tert-butyldicarbonate	di-tert-butyldicarbonate

Table I.4 Alternative catalysts

process step	catalysts	particularly preferred catalysts
(C)	dimethylaminopyridine (DMAP) and pyridine	DMAP
(D)	Raney nickel, platinum/charcoal, platinum dioxide, ruthenium/charcoal and rhodium/charcoal	Raney nickel

The process steps (A) to (D) described above are preferably carried out in the following temperature ranges:

5      In process step:

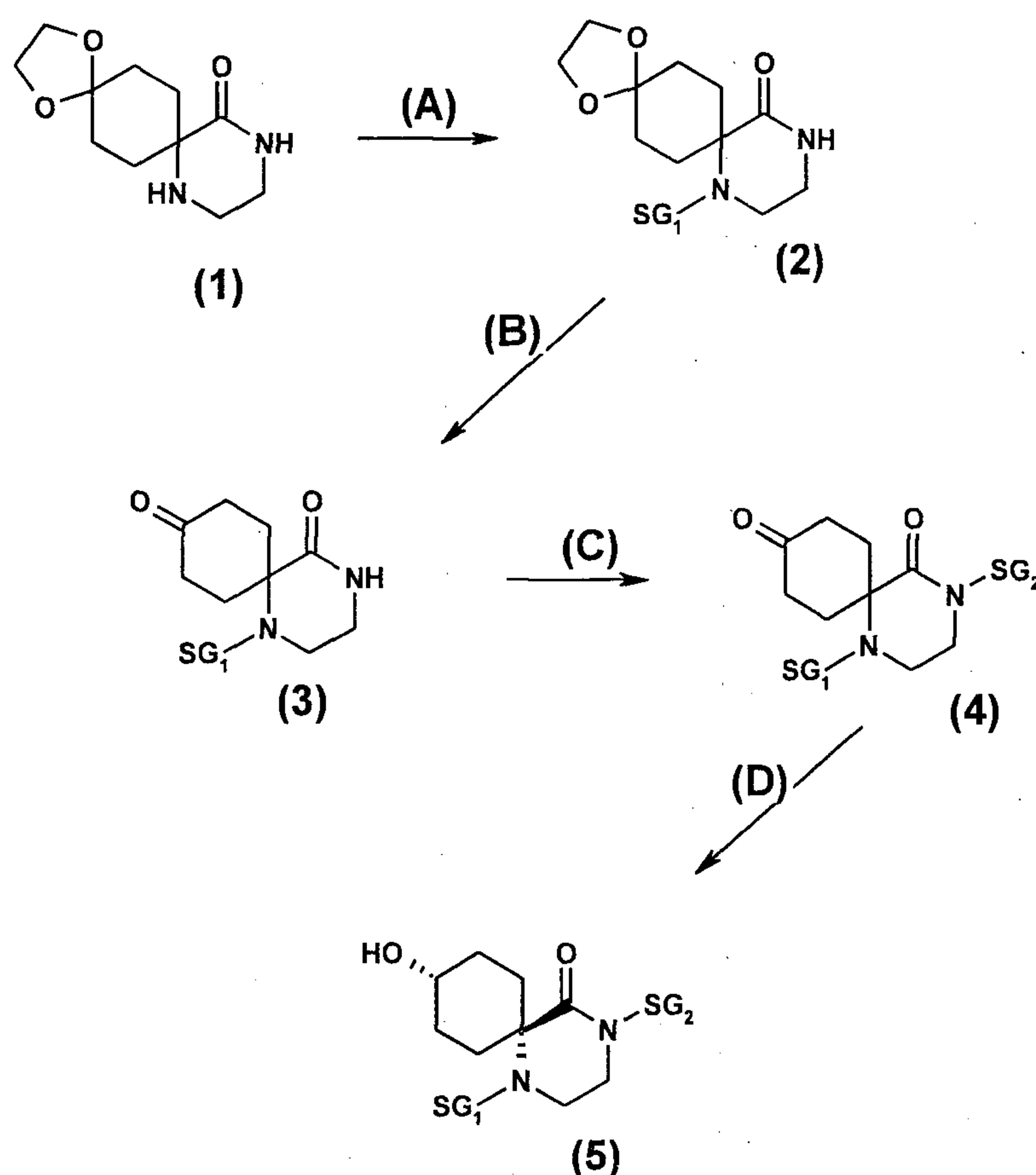
(A): preferably 0 to 70°C, particularly preferably 10 to 20°C;

(B): preferably 20 to 70°C, particularly preferably 60 to 70°C;

(C): preferably 0 to 78°C, particularly preferably 10 to 30°C;

10     (D): preferably 20 to 80°C, particularly preferably 40 to 70°C.

Scheme 1 illustrates the synthesis according to the invention. All the compounds are shown in the form of their bases.

Scheme 1 Synthesis of compound (5)

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In process step (A) the educt (1) is protected at the amine nitrogen using 2.0 to 3.0 molar equivalents of reagent in the presence of 2.2 to 3.2 molar equivalents of base. Process step (B) describes the aqueous-acidic deprotection of the ketal (2) to obtain the corresponding ketone (3) using 2.0 to 4.0 molar equivalents of acid. In the next step (C) the amide nitrogen that is still free is protected with 1.0 to 1.5 molar equivalents of reagent in the presence of 2 to 10 molar percent of catalyst. In the last step (D) catalytic stereoselective reduction of the keto group with hydrogen takes place to form the *cis*-configured alcohol (4).

In a preferred embodiment, in process step (A) the educt (1) is protected at the amine nitrogen using 2.2 molar equivalents trifluoroacetic anhydride (TFAA) in the presence of 2.4 molar equivalents N-methylmorpholine (NMM) trifluoroacetyl. Process step (B) describes the aqueous acidic deprotection of the ketal (2) to form the corresponding 5 ketone (3) using 2.8 molar equivalents acetic acid (HOAC). In the next step (C) the amide nitrogen that is still free is protected with 1.2 molar equivalents of di-tert-butyl dicarbonate in the presence of 5 molar percent of dimethylaminopyridine as carbamate. In the last step (D) catalytic stereoselective reduction of the keto group is carried out with hydrogen to obtain the *cis*-configured alcohol (4).

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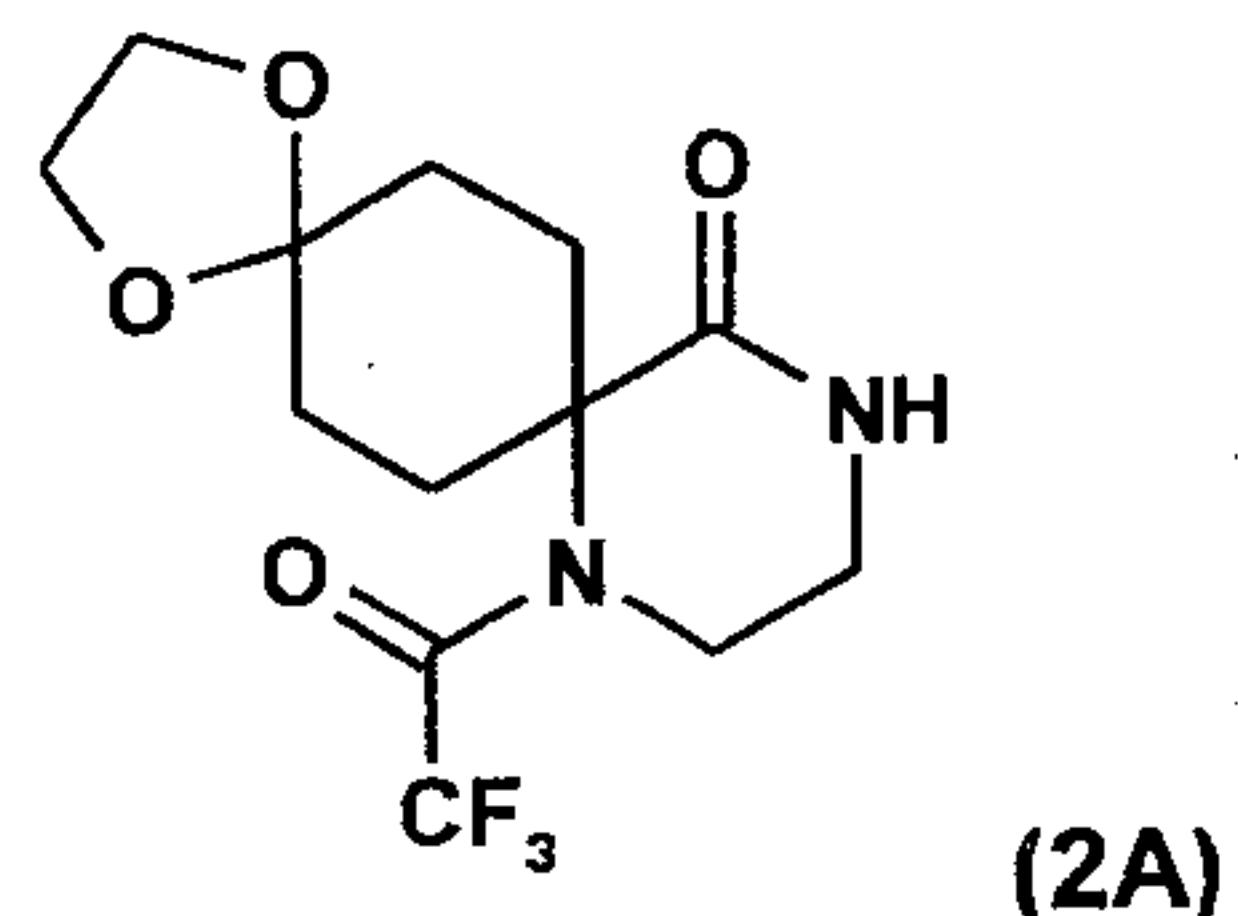
The following Examples serve to illustrate the processes carried out by way of example for preparing the compound of formula (5). These Examples are intended as an illustration of the invention without restricting it to their content.

15

Example 1

1,4-Dioxa-9-(2,2,2-trifluoro-acetyl)- 9,12-diaza-dispiro[4.2.5.2]pentadecan-13-one

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**Process step (A)**

107.2 g of N-methylmorpholine are added dropwise to 100 g 1,4-dioxa-9,12-diaza-dispiro[4.2.5.2]pentadecan-13-one in 300 ml of 2-methyltetrahydrofuran at ambient 25 temperature (RT corresponds to 20 to 25°C). Then the mixture is cooled to 6 – 10°C and 204.2 g of trifluoroacetic anhydride are added dropwise. During this addition the temperature rises to RT. After 120 min 200 ml of water and 450 ml of methylcyclohexane are added successively. After 60 min the suspension is cooled to 0°C. After 25 min the

precipitate is filtered off and washed successively with 100 ml of water and 100 ml methylcyclohexane. After drying at 50°C *in vacuo*, 137.9 g of product is obtained.

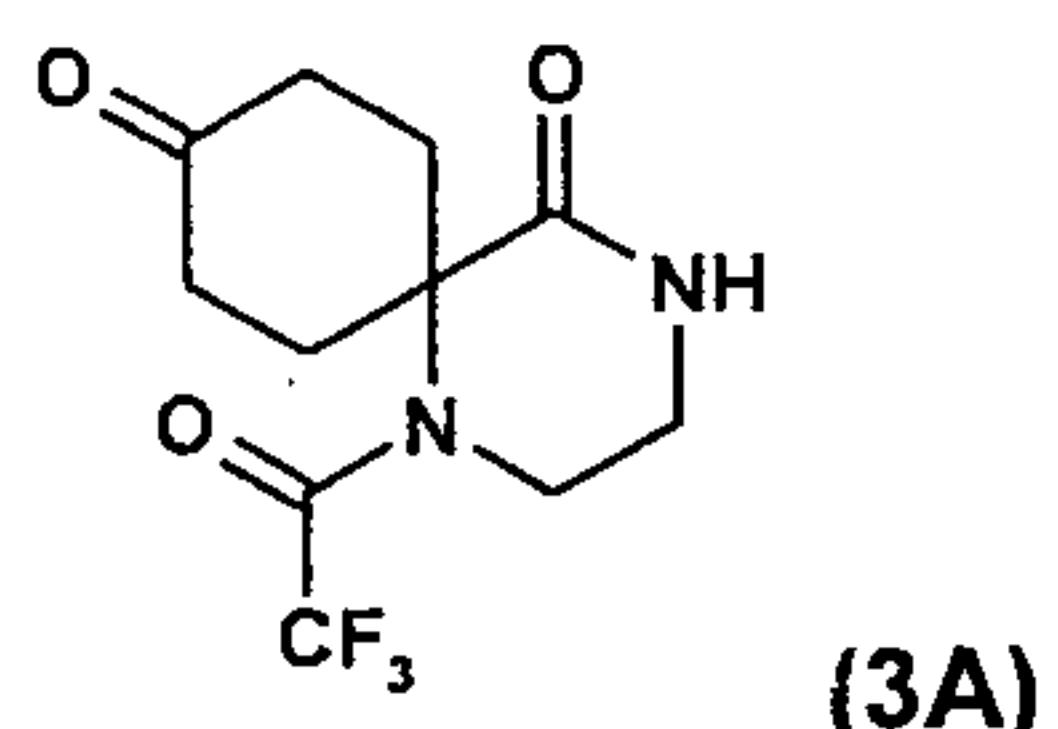
Mass spectrum (ESI<sup>+</sup>): m/z = 323 [M+H]<sup>+</sup>

M.p. 224.8°C

5

**Example 2**

1-(2,2,2-trifluoro-acetyl)- 1,4-diaza-spiro[5.5]undecane-5,9-dione



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**Process step (B)**

195 ml of water and 65 ml of acetic acid are added to 130 g of 1,4-dioxa-9-(2,2,2-trifluoro-acetyl)- 9,12-diaza-dispiro[4.2.5.2]pentadecan-13-one in 390 ml of methanol. The mixture is heated to 68°C and stirred for 120 min at this temperature. Then 325 ml of solvent are 15 distilled off. The resulting suspension is cooled to 5°C. After 30 min the precipitate is filtered off and the residue is washed with 50 ml of tert.-butylmethylether. After drying at 50°C *in vacuo*, 101.4 g of product is obtained.

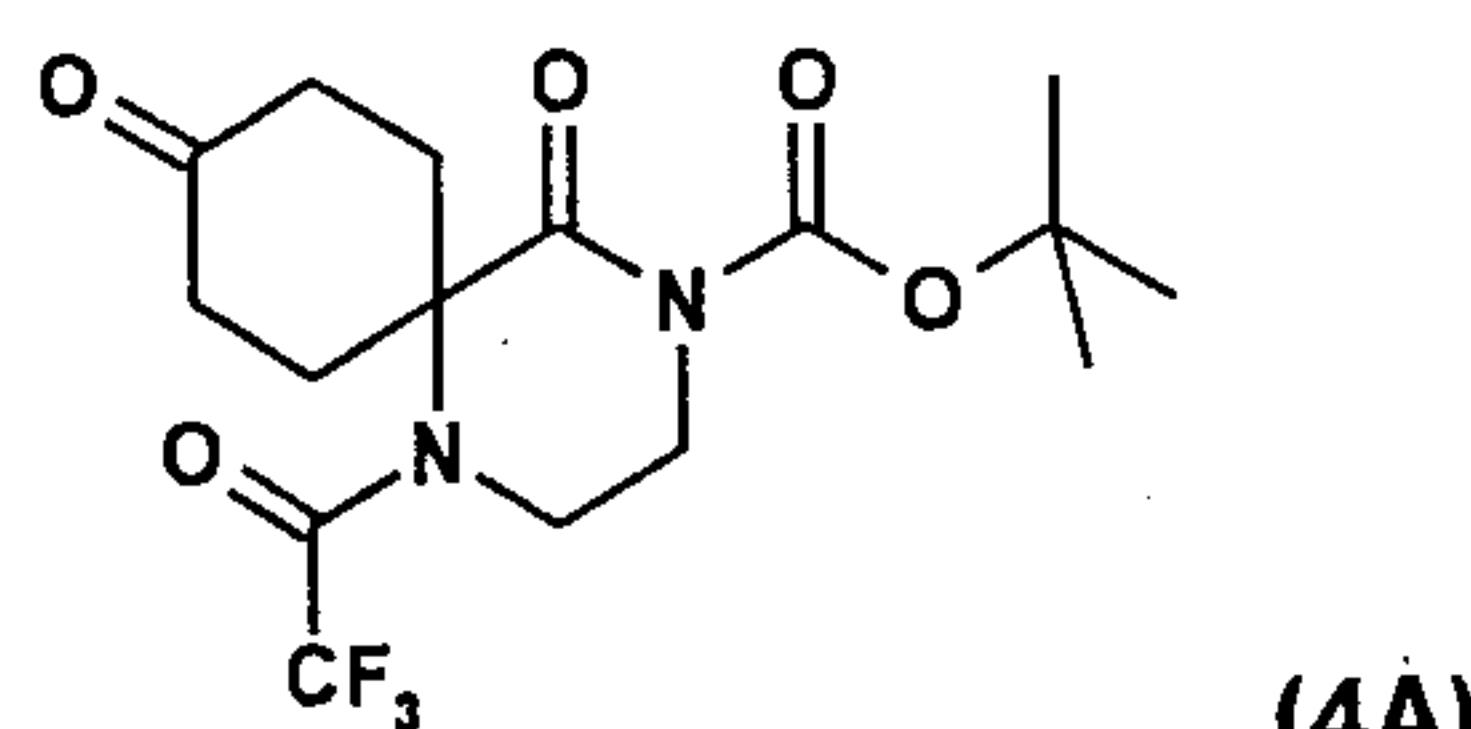
Mass spectrum (ESI<sup>+</sup>): m/z = 279 [M+H]<sup>+</sup>

M.p. 169.0°C

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**Example 3**

Tert-butyl 5,9-dioxo-1-(2,2,2-trifluoro-acetyl)-1,4-diaza-spiro[5.5]undecane-4-carboxylate



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**Process step (C)**

84.7 g of di-tert-butyldicarbonate in 90 ml acetonitrile are added dropwise to a mixture of 90 g of 1-(2,2,2-trifluoro-acetyl)-1,4-diaza-spiro[5.5]undecane-5,9-dione and 1.98 g of dimethylaminopyridine in 180 ml of acetonitrile at RT within 75 min. After 60 min 990 ml of water are added and inoculated. After 60 min the precipitate is filtered off and washed with 180 ml of water. After drying at 50°C in vacuo 113.8 g of product is obtained.

5 Mass spectrum (ESI<sup>+</sup>): m/z = 379 [M+H]<sup>+</sup>

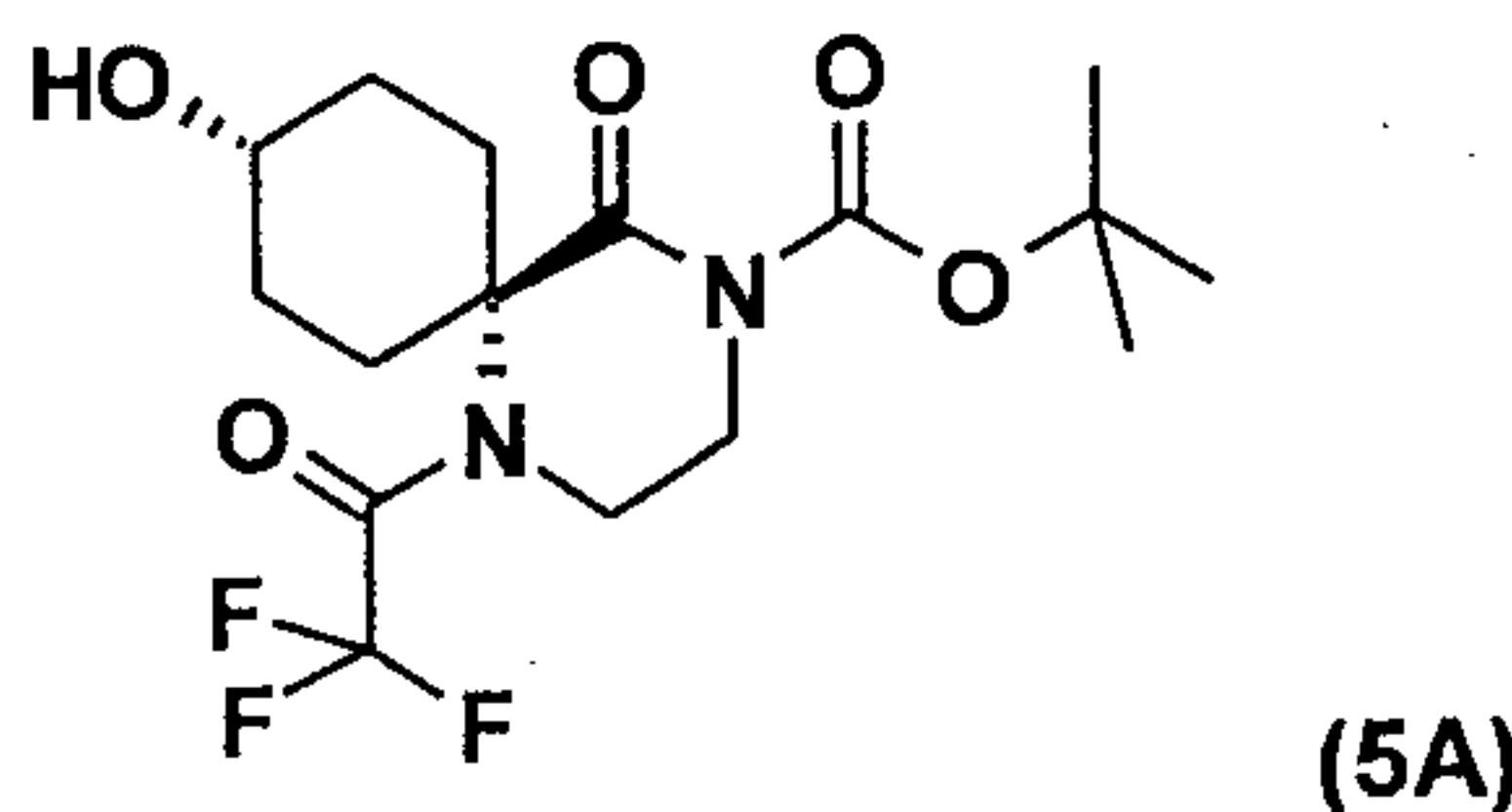
M.p. 114.9°C

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**Example 4**

Tert-butyl (cis)-9-hydroxy-5-oxo-1-(2,2,2-trifluoro-acetyl)-1,4-diaza-spiro[5.5]undecane-4-carboxylate

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**Process step (D)**

5.1 g of Raney nickel are added to 17 g of tert-butyl 5,9-dioxo-1-(2,2,2-trifluoro-acetyl)-1,4-diaza-spiro[5.5]undecane-4-carboxylate in 170 ml of ethanol. The reaction mixture is 20 hydrogenated in the autoclave for 10 hours at 60°C and 50 bar hydrogen pressure. Then the catalyst is filtered off and the filter cake is washed with 40 ml of ethanol. 165 ml of ethanol are distilled off. 374 ml of toluene are added to the residue and a further 136 ml of solvent are distilled off. The resulting solution is combined with 55 ml of water at 60°C and the phases are separated. A further 195 ml of solvent are distilled off from the organic 25 phase remaining. The resulting suspension is cooled to 2°C within 120 min. After 30 min the precipitate is filtered off and washed twice with 20 ml of toluene. After drying at 50°C in vacuo, 12.6 g of product is obtained, which still contains approx. 6% of trans-product.

Mass spectrum (ESI<sup>+</sup>): m/z = 381 [M+H]<sup>+</sup>

M.p. 163.0°C

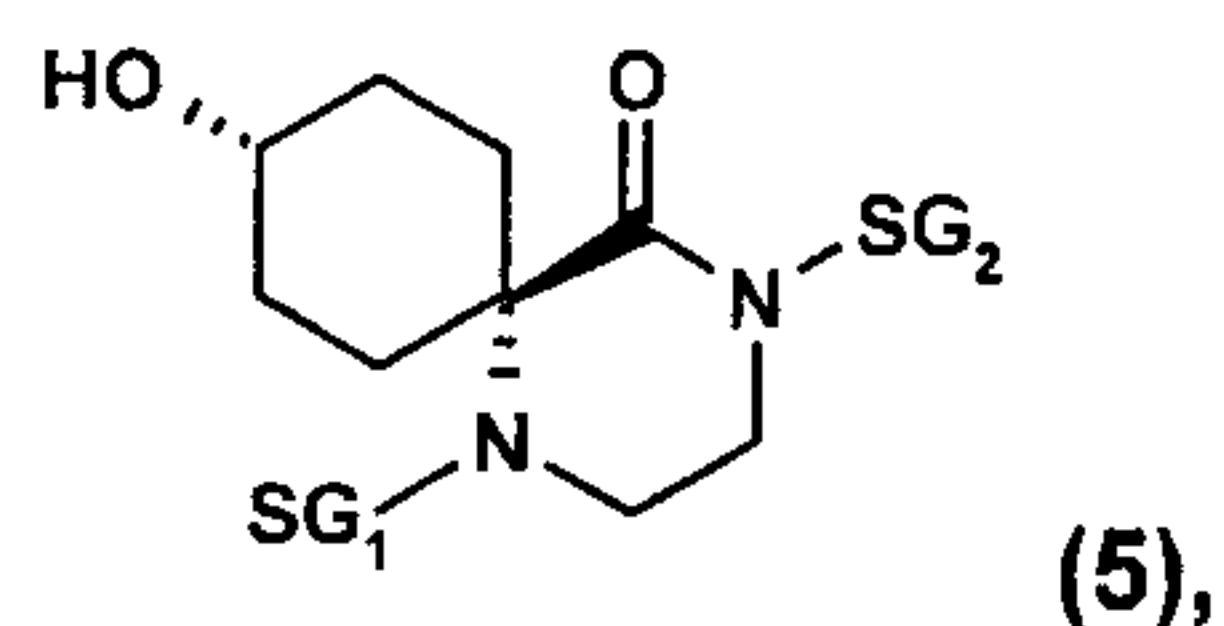
**Compilation of data**

A Waters mass spectrometer ZQ 2000 (Electrospray source) is used to compile the MS data shown.

## PATENT CLAIMS

1. Method for the stereoselective preparation of the compound of formula (5),  
optionally in the form of the tautomers thereof,

5



wherein

**SG<sub>1</sub>** denotes a protective group selected from among trifluoroacetyl, acetyl, benzoyl and pivaloyl,

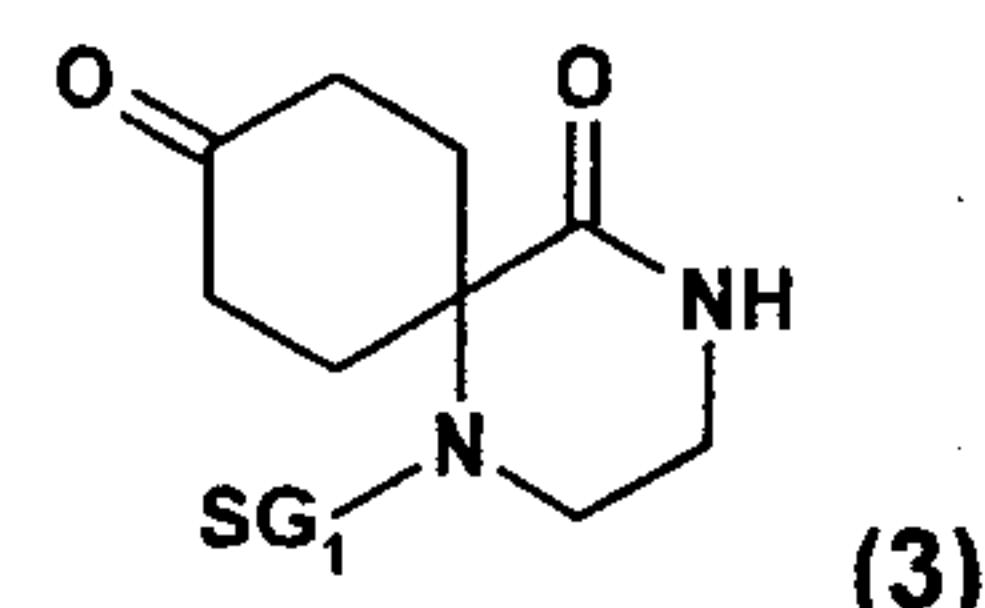
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**SG<sub>2</sub>** denotes a protective group selected from among tert.-butoxycarbonyl, ethoxycarbonyl and methoxycarbonyl,

characterised in that the method comprises reaction steps (C) and (D), where

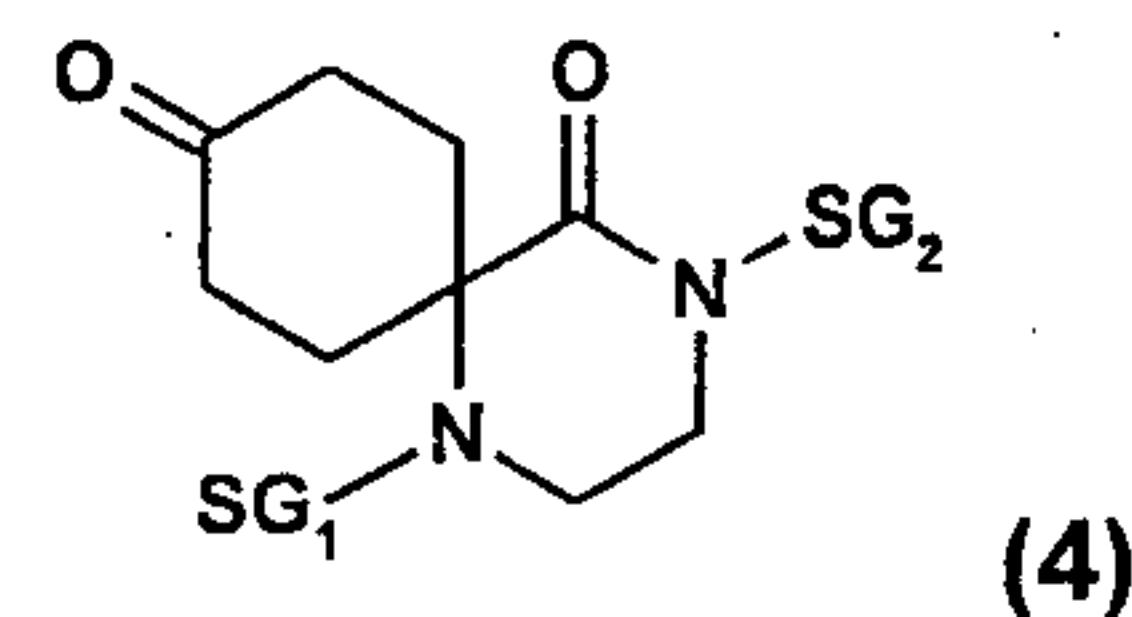
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(C) is the reaction of the compound of formula (3)



to form a compound of formula (4)

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and

(D) is the reduction of the compound of formula (4) to form a compound of formula (5),

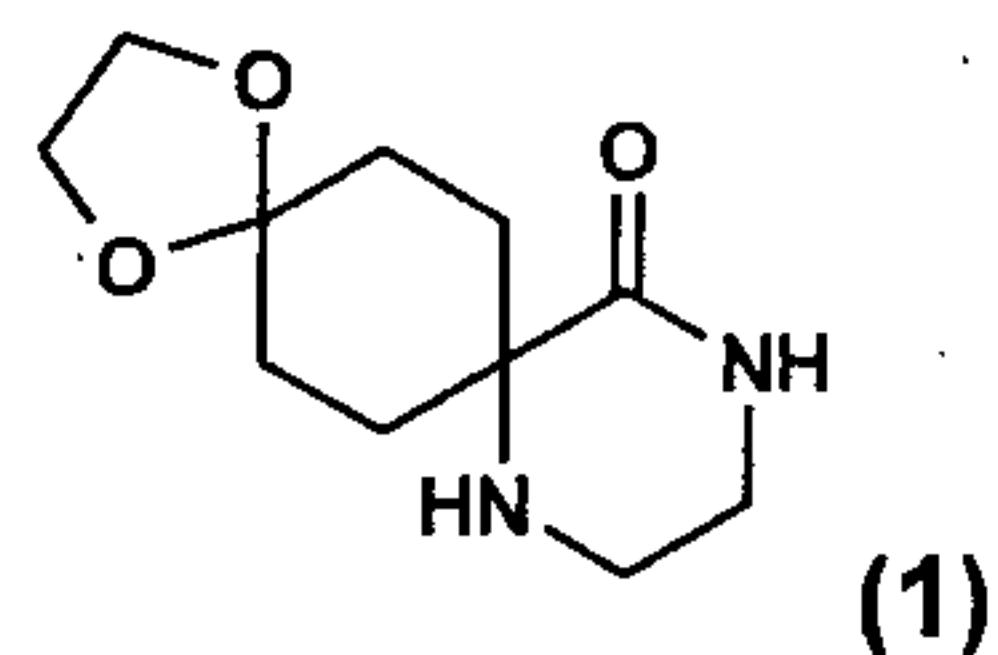
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while process steps (C) and (D) are carried out successively in the order stated.

2. Method according to claim 1, characterised in that reaction steps (C) and (D) are preceded by further reaction steps (A) and (B),  
wherein

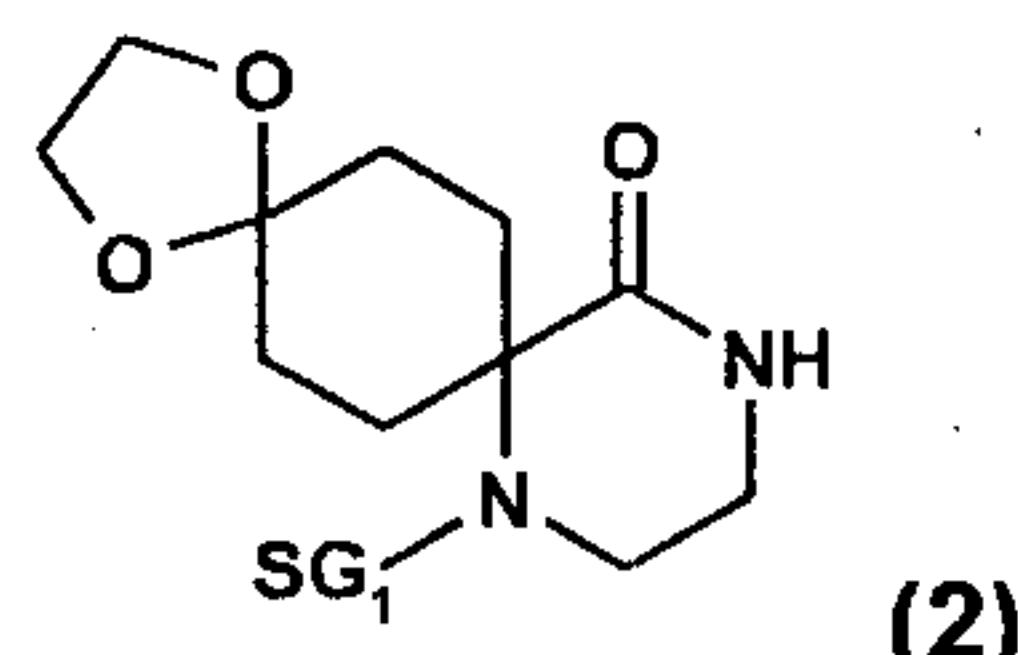
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(A) denotes the reaction of the compound of formula (1)



to form a compound of formula (2)

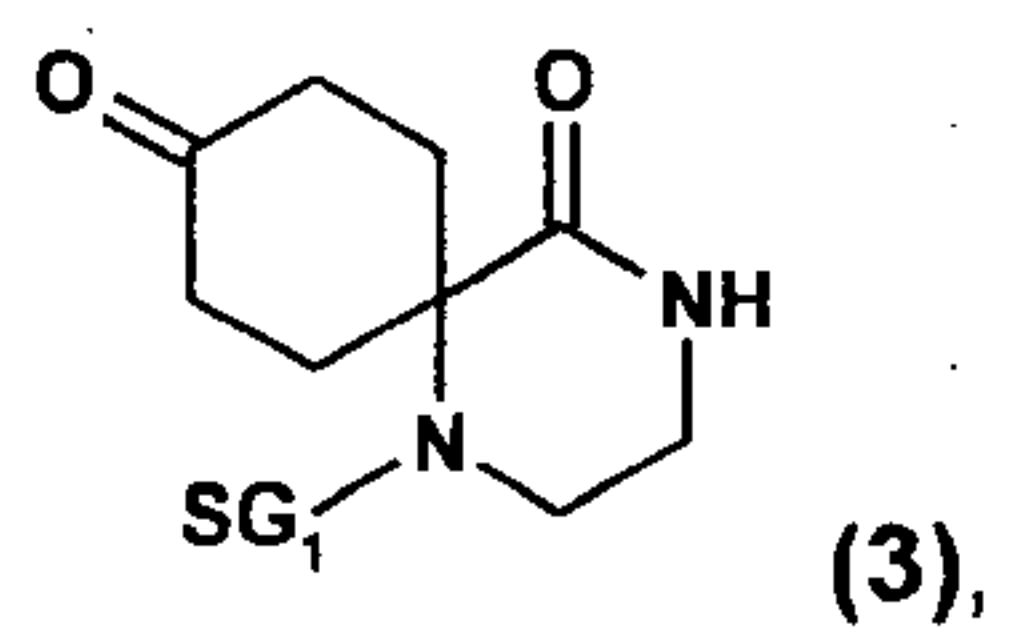
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and

(B) denotes the reaction of the compound of formula (2) to form a compound of formula (3)

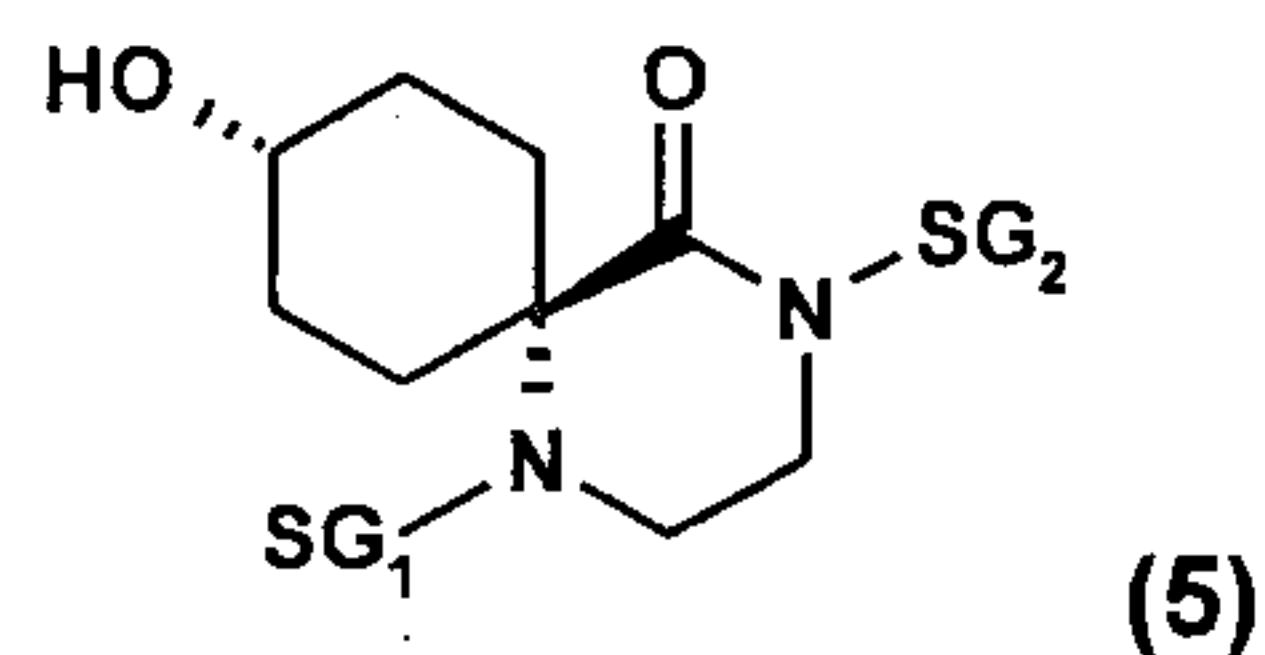
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while process steps (A), (B), (C) and (D) are carried out successively in the order stated.

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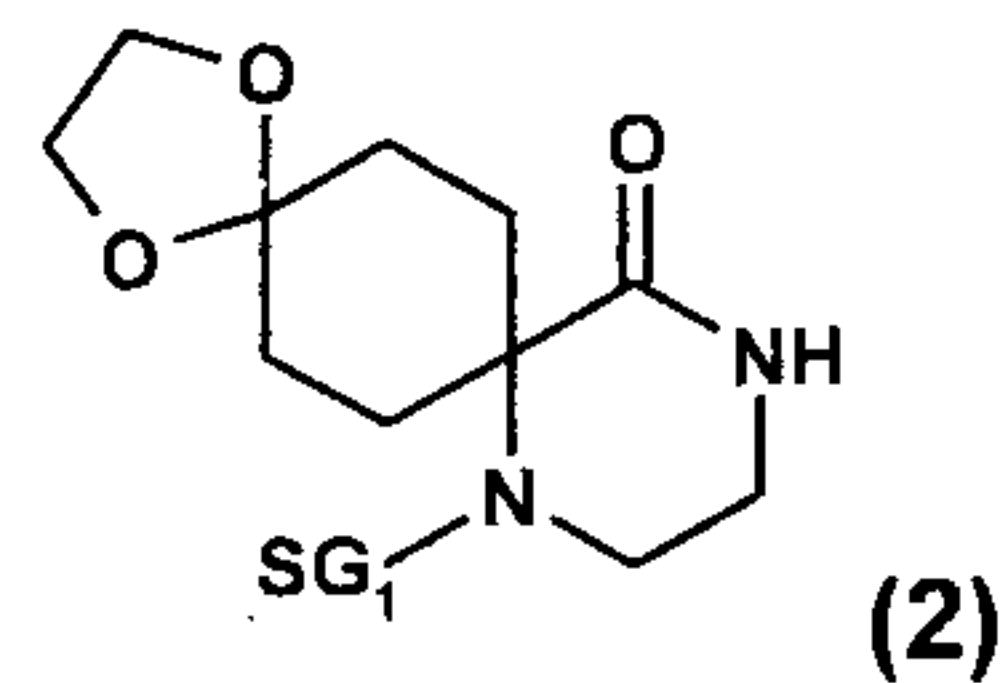
3. Method according to claim 1 or 2 for the stereoselective preparation of the compound of formula (5A), optionally in the form of the tautomers thereof,



characterised in that

5      **SG<sub>1</sub>**    denotes trifluoroacetyl, and  
**SG<sub>2</sub>**    denotes tert.-butoxycarbonyl.

4.    Intermediate of formula (2) according to claim 2, optionally in the form of the  
tautomers or salts thereof

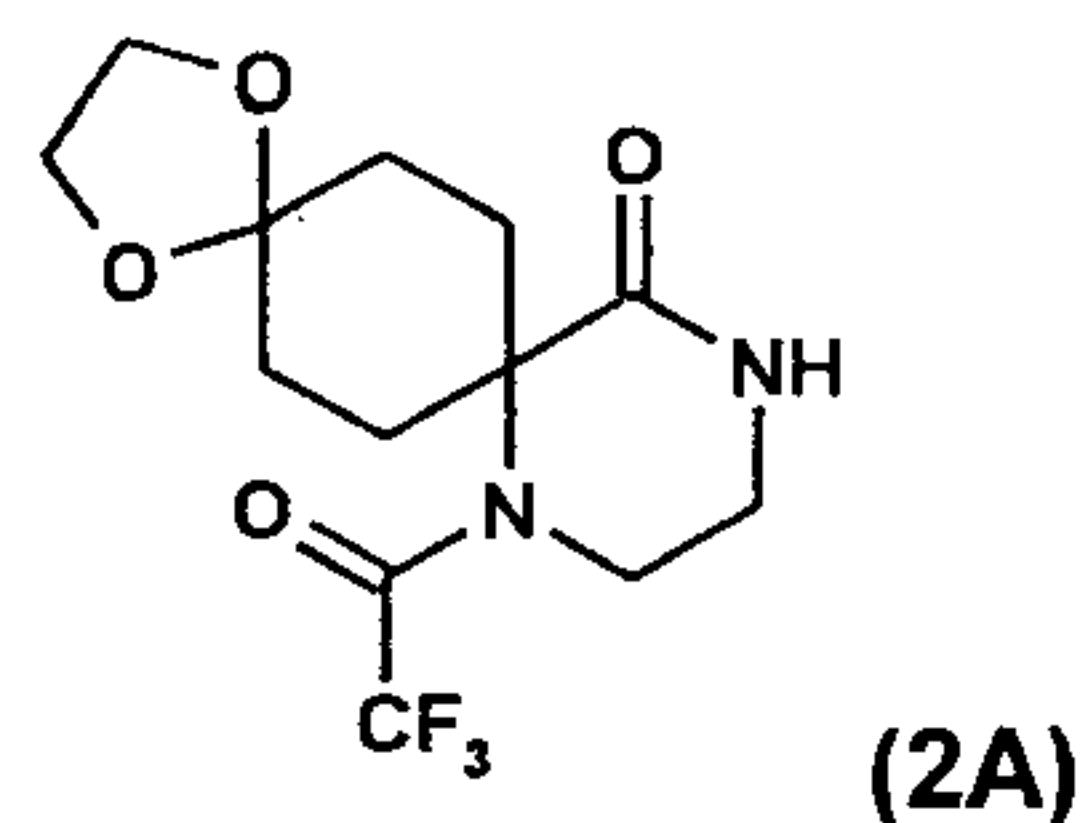


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wherein

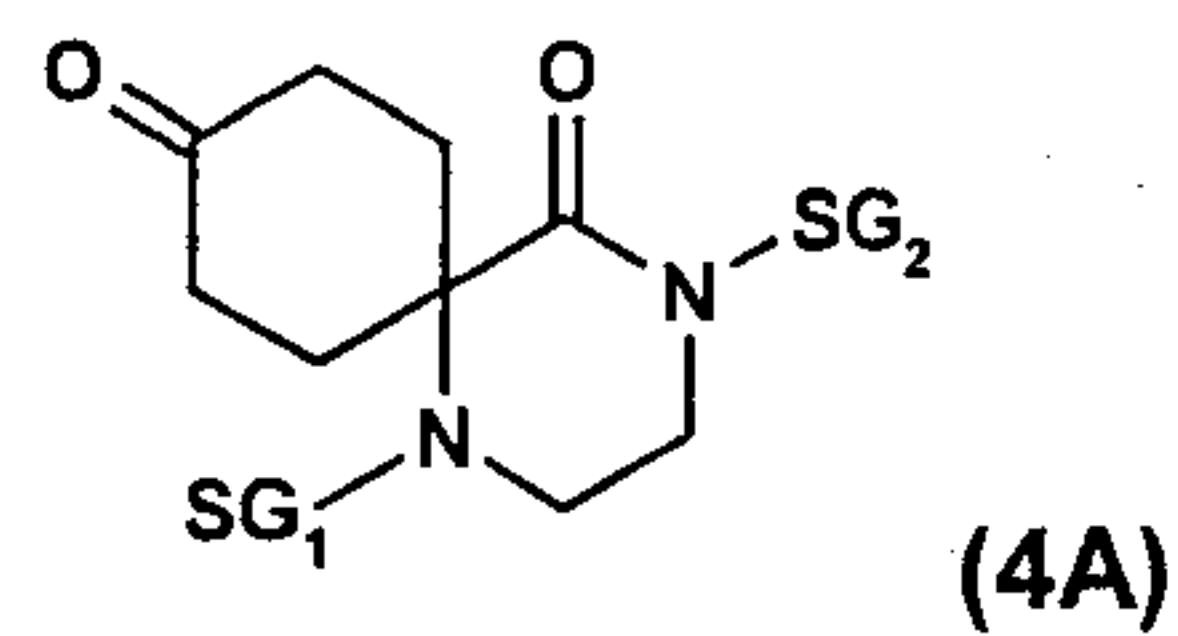
**SG<sub>1</sub>**    denotes a protective group selected from among trifluoroacetyl, acetyl,  
benzoyl and pivaloyl.

15    5.    Intermediate of formula (2A) according to claim 4, optionally in the form of the  
tautomers or salts thereof,



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6.    Intermediate of formula (4) according to claim 1 or 2, optionally in the form of the  
tautomers or salts thereof,



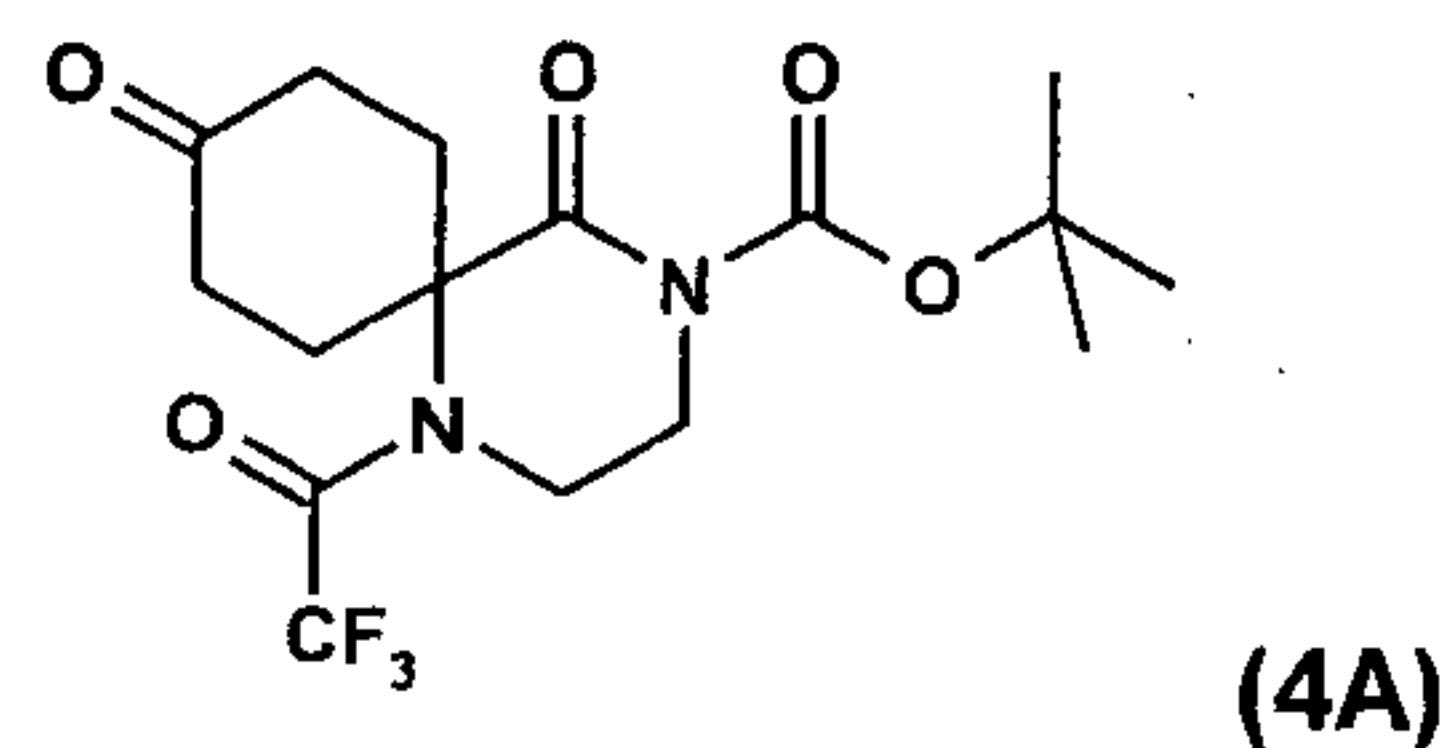
wherein

**SG<sub>1</sub>** denotes a protective group selected from among trifluoroacetyl, acetyl, benzoyl and pivaloyl, and

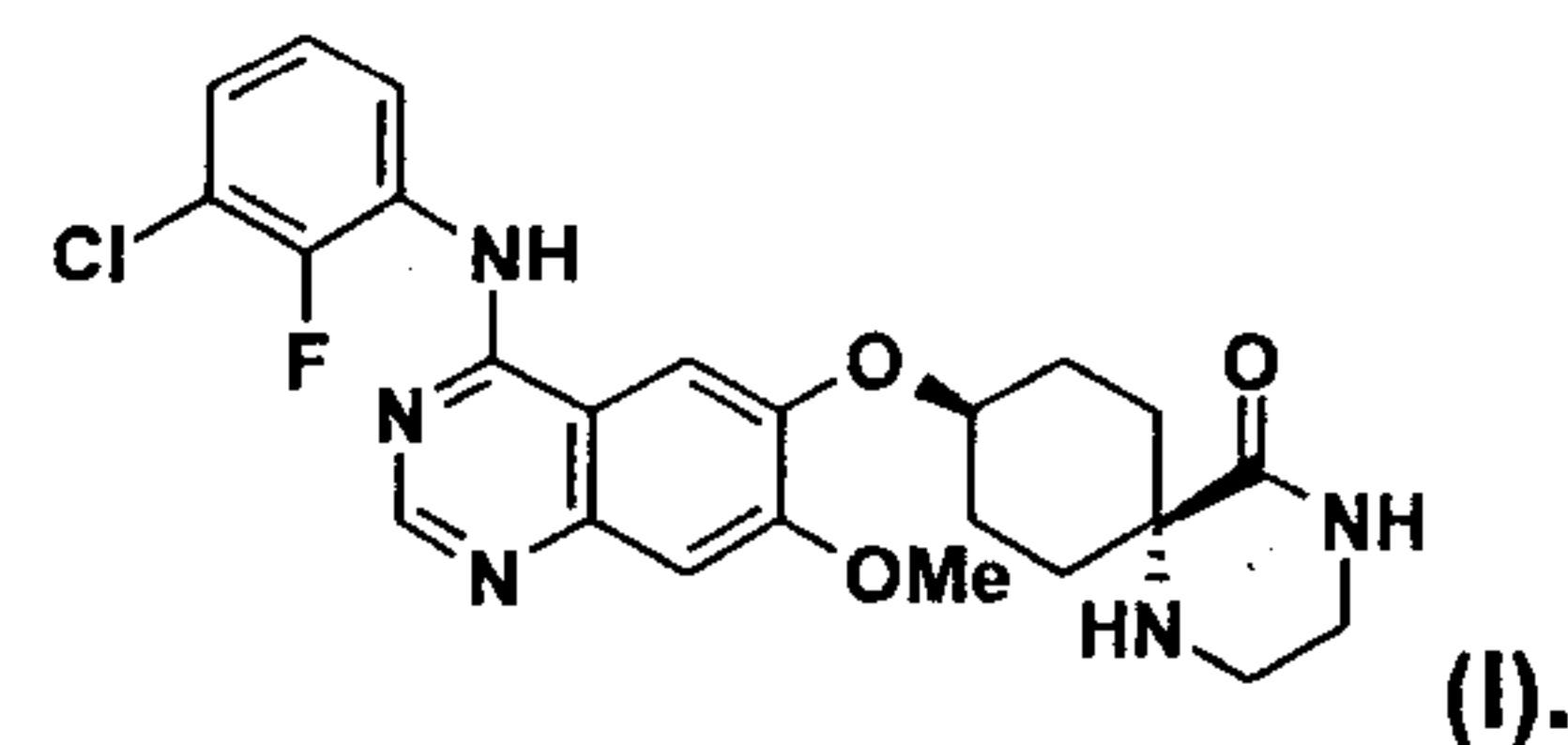
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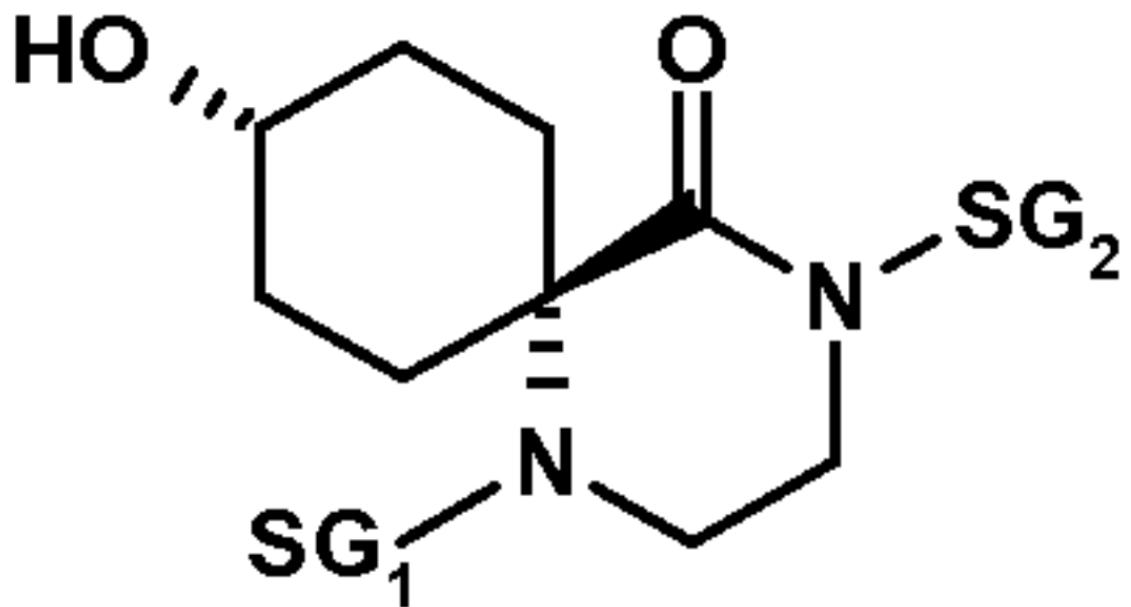
**SG<sub>2</sub>** denotes a protective group selected from among tert.-butoxycarbonyl, ethoxycarbonyl and methoxycarbonyl.

7. Intermediate of formula (4A) according to claim 6, optionally in the form of the  
10 tautomers or salts thereof.



15 8. Use of the intermediates of formula (2) or (4), optionally in the form of the  
tautomers or salts thereof, for preparing a compound of formula (I), optionally in  
the form of the tautomers or salts thereof,





(5)