



(86) Date de dépôt PCT/PCT Filing Date: 2004/05/11
(87) Date publication PCT/PCT Publication Date: 2004/11/18
(45) Date de délivrance/Issue Date: 2014/07/22
(85) Entrée phase nationale/National Entry: 2005/11/10
(86) N° demande PCT/PCT Application No.: GB 2004/001997
(87) N° publication PCT/PCT Publication No.: 2004/099153
(30) Priorité/Priority: 2003/05/12 (GB0310856.0)

(51) Cl.Int./Int.Cl. *C07D 223/28* (2006.01)
(72) Inventeur/Inventor:
LEARMONTH, DAVID ALEXANDER, PT
(73) Propriétaire/Owner:
BIAL-PORTELA & CA, S.A., PT
(74) Agent: SIM & MCBURNEY

(54) Titre : PROCEDE DE RACEMISATION DE (S)-(+)- ET (R)-(-)-10,11-DIHYDRO-10-HYDROXY-5H-DIBENZ/B,F/AZEPINE-5-CARBOXAMIDE, ET LEURS MELANGES ENRICHIS OPTIQUEMENT
(54) Title: METHOD FOR RACEMISATION OF (S)-(+)- AND (R)-(-)-10,11-DIHYDRO-10-HYDROXY-5H-DIBENZ/B,F/AZEPINE-5-CARBOXAMIDE AND OPTICALLY ENRICHED MIXTURES THEREOF

(57) **Abrégé/Abstract:**

A high-yielding method and a useful intermediate, 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII) is disclosed. Also disclosed are methods for the racemisation of optically pure or optically enriched mixtures of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) to racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III).



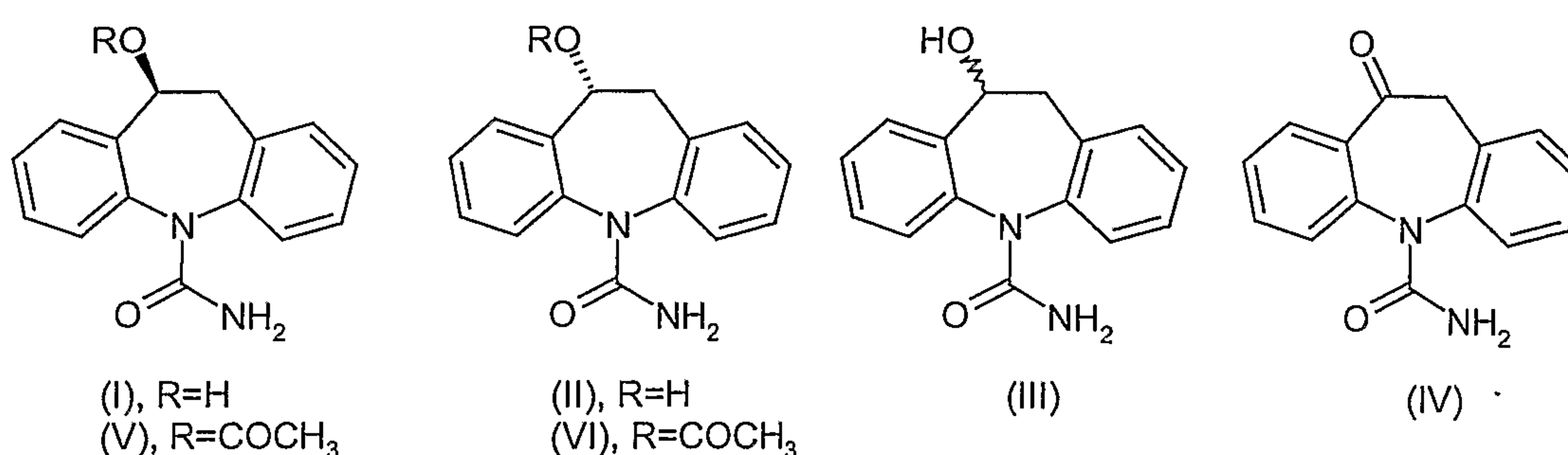
Abstract

Method for racemisation of (S)-(+)- and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide and optically enriched mixtures thereof

5 A high-yielding method and a useful intermediate, 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII) is disclosed. Also disclosed are methods for the racemisation of optically pure or optically enriched mixtures of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) to racemic
10 ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III).

Method for racemisation of (S)-(+)- and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide and optically enriched mixtures thereof

- 5 This invention relates to a method for the racemisation of optically pure or optically enriched mixtures of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (compounds of formulas (I) and (II).
- 10 Racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide of formula (III), is a known substance which has been shown to possess anti-convulsant activity (Schutz, H. et al., Xenobiotica, 16, 769-778 (1986)), and was found to be the principal metabolite of the established anti-epileptic drug oxcarbazepine (formula IV). In addition to its anti-convulsant activity, racemic alcohol (III) can be readily synthesised in
- 15 high yield by reduction of oxcarbazepine (IV), and thus serves as a useful intermediate for the preparation of optically pure (S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (formula V) and (R)-(+)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (formula VI), two more recently disclosed, single-enantiomer anti-epileptic drugs demonstrating improved biological properties (Benes, J.
- 20 et al., J. Med. Chem., 42, 2582-2587 (1999)). The (S)-(-)-enantiomer (V) in particular has been shown to display a very favourable anti-convulsant profile.



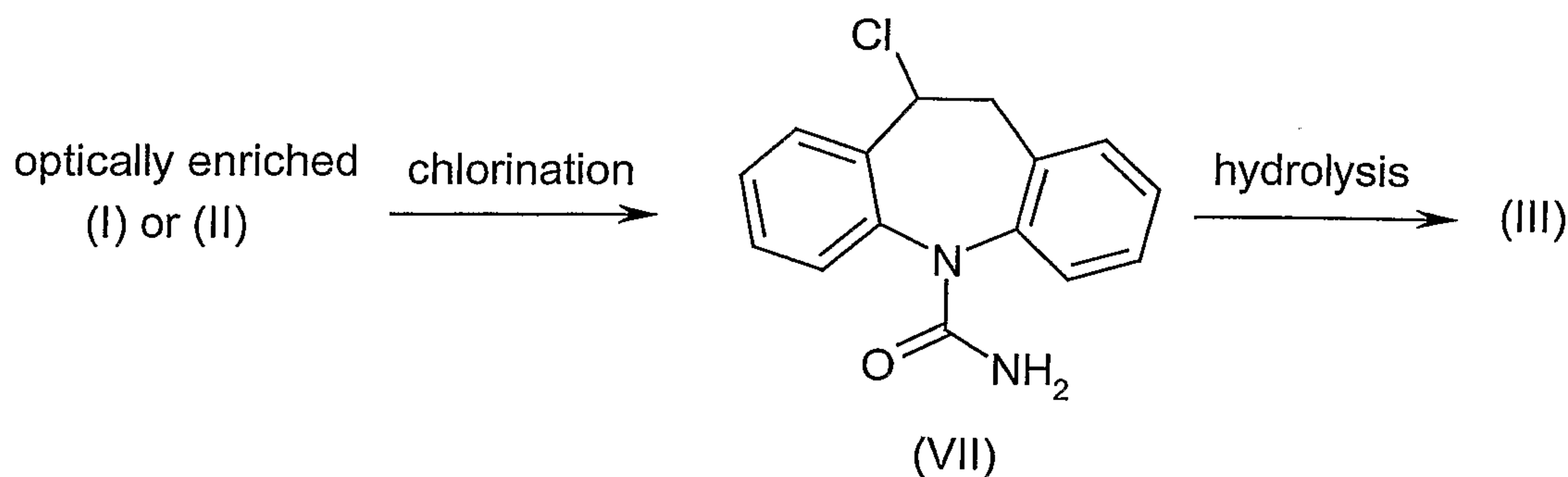
- 25 A key step in the synthesis of either of the optically pure individual acetate esters (V) or (VI) involves the resolution of racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) into its individual, optically pure stereoisomers, (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) and (R)-(-)-

10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II), which are the principal intermediates for synthesis of the optically pure acetates (V) and (VI). An improved method for this resolution was recently disclosed involving the efficient separation of diastereoisomeric tartrate half-esters of racemic ($\pm$)-10,11-dihydro-10-
5 hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) (Learmonth, D., PCT/GB02/02176).

As mentioned above, racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) can be easily prepared by simple chemical reduction of the benzylic ketone group of oxcarbazepine (IV), by the use of, for example, metal hydrides in
10 alcoholic medium. However, oxcarbazepine (IV) is an extremely expensive substance, and despite the very efficient resolution procedure (around 98% yield based on a single diastereoisomer), it should be noted that development of say only the (S)-(-)-acetate (V) would mean the loss of approximately 50% of very expensive material. It would thus be highly desirable to have a method of recycling this unwanted, but very expensive (R)-(-)
15)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) which can be recovered from the resolution mixture. This recycling could be envisaged to involve a racemisation procedure, whereby the recovered but unwanted optically enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide enantiomer (II) is converted into racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-
20 carboxamide (III) for re-introduction into the resolution cycle. The racemisation procedure should preferably involve the use of cheap, readily available solvents and reagents, and be operationally simple while affording good yields of pure, completely racemised product. However, in the case of alcohols (I) and (II), racemisation under standard acidic or basic conditions is unusually complicated, principally due to the very
25 facile elimination of water from the molecules of (I) and (II), which leads exclusively to a dehydrated olefinic product of negligible interest for the synthesis of either (V) or (VI).

It has now been surprisingly found however that racemisation can be readily achieved via a straightforward process, which involves the reaction of optically enriched
30 (enantiomeric excesses in the range from 1 to 99.5%) (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) or (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) with a standard chlorinating agent under suitable substitution conditions which furnishes an intermediate benzylic chloride, 10-

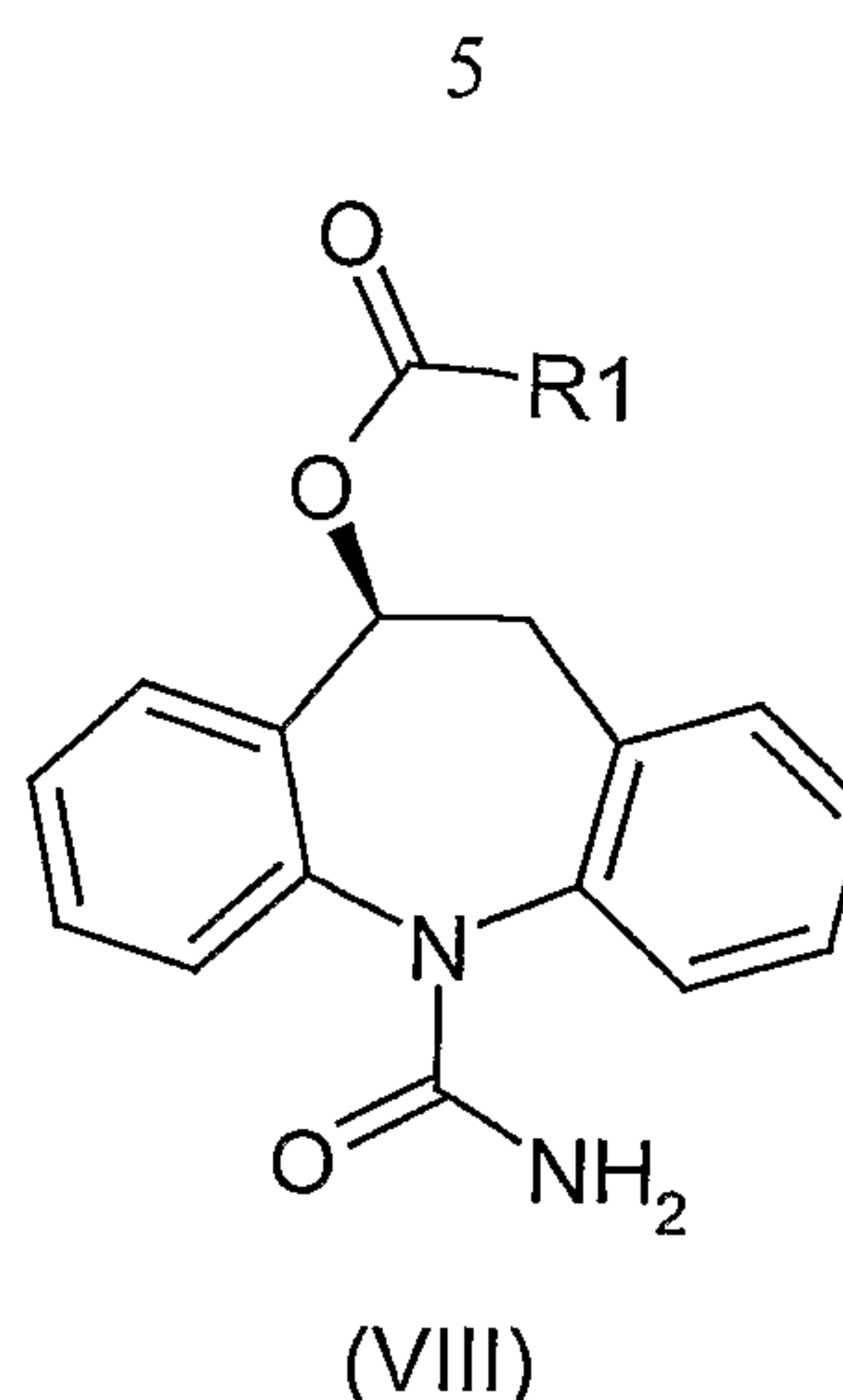
chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (formula VII), which is sufficiently stable and can be easily isolated and, if preferred, purified by standard techniques or be used directly without isolation and purification. This 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII) very conveniently undergoes hydrolysis under simple reaction conditions to provide racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) in both high yield and very good purity giving the method of the present invention according to the following synthetic scheme:



10

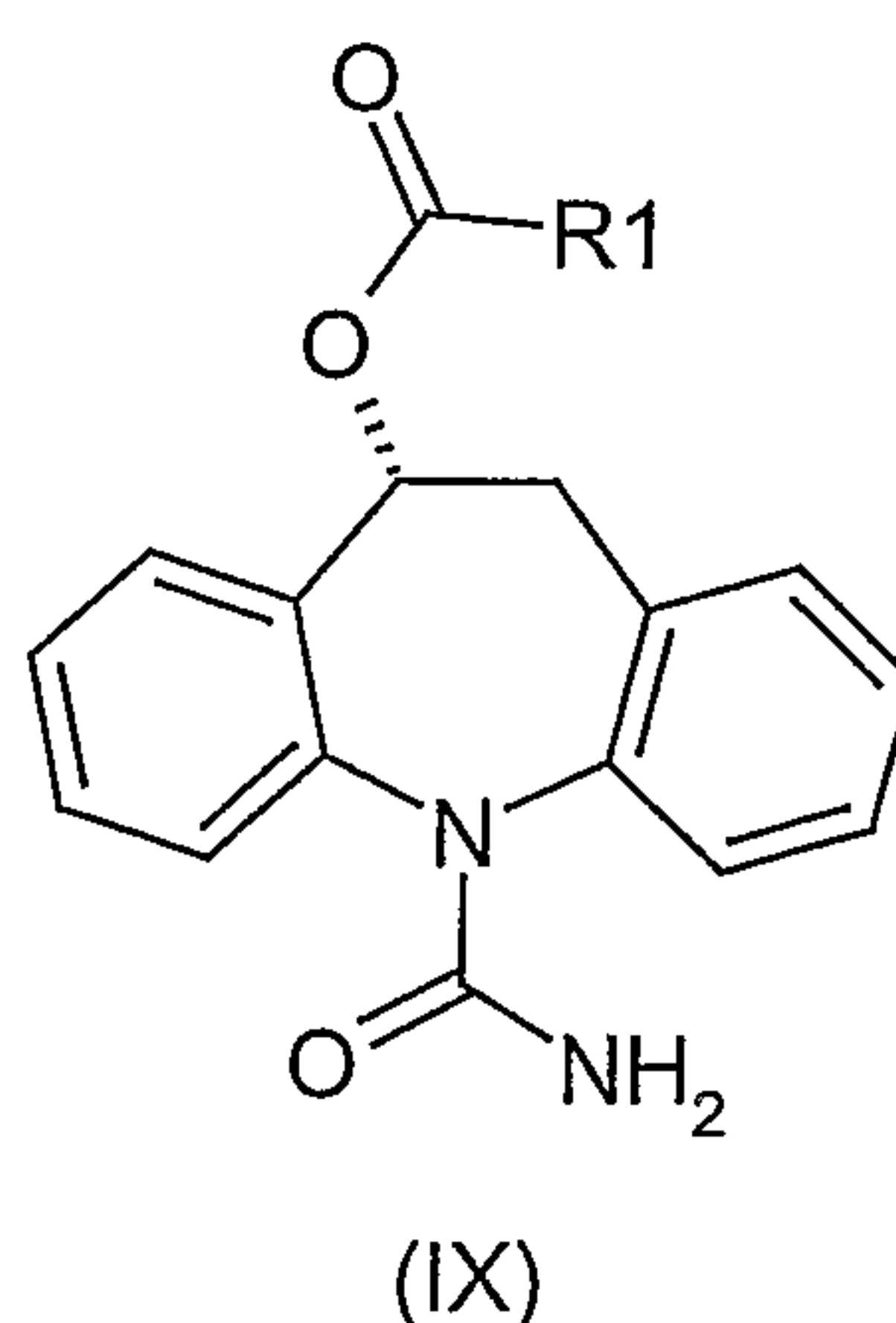
According to the present invention, the benzylic alcohol functionality of optically pure or enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) or (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) undergoes substitution by chlorine via reaction with a suitable chlorinating reagent, such as, for example, inorganic or organic acid halides including thionyl chloride, oxalyl chloride, 15 sulfuryl chloride, phosphorus pentachloride, phosphorus trichloride, phosphorus oxychloride and the like. The chlorinating reagent can be used in a 1.02-2 molar ratio with respect to the optically enriched alcohol (I) or (II), preferably in the range 1.05-1.2. The reaction is carried out in a solvent, which is inert under the reaction conditions, 20 such as, for example, dichloromethane, chloroform, carbon tetrachloride, chlorobenzene and the like. The reaction can be carried out over a wide range of temperatures, from -78°C to the boiling point of the solvent used, preferably in the range 0°C - 25°C . The compound of formula (VII) can be easily isolated from the reaction mixture by procedures familiar to those skilled in the art and if preferred, can 25 be further purified by slurring or recrystallisation from suitable solvents, such as, for example, esters including ethyl acetate or ketones including acetone and methyl ethyl ketone.

- According to the present invention, hydrolysis can be carried out by stirring the intermediate benzylic chloro derivative of formula (VII) in neat water. The reaction can be run over a wide range of temperatures, from 5°C-100°C, preferably 15°C-30°C. Once the reaction is complete, the product of racemisation (III) can be conveniently
5 recovered in good yield and high purity by filtration or centrifugation. The product of racemisation (III) can be rapidly analysed by chiral HPLC analysis and is found to be a strictly racemic (1:1) mixture of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide, i.e. an equimolar mixture of the compounds of
10 formulas (I) and (II). If preferred, the crude racemic product of formula (III) can be further purified by slurrying or recrystallisation from a suitable solvent, such as, for example esters including ethyl acetate, ketones including acetone and methyl ethyl ketone or lower aliphatic alcohols such as methanol, ethanol and isopropanol.
- 15 Alternatively, if preferred, the reaction can be run in the presence of a solubilising, water-miscible solvent such as, for example, dioxane, tetrahydrofuran, lower aliphatic alcohols including methanol, ethanol and isopropanol, N-methyl-2-pyrrolidinone, high molecular weight polyethyleneglycols, acetone, acetonitrile, dimethylformamide and the like. The volume ratio of organic solvent to water lies in the range 1:0.5 to 1:50, and the
20 reaction can be run over a wide range of temperatures, from 5°C-100°C, preferably 20°C-60°C. Once the reaction is complete, the racemic product can be isolated by standard procedures familiar to those skilled in the art, and further purified if preferred, and analysed by chiral HPLC as described above.
- 25 According to another aspect of the invention, there is provided a method for the preparation of a compound of the general formula (VIII):



where R_1 is hydrogen, alkyl, halogenalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aryl, or pyridyl; the term alkyl means a straight or branched hydrocarbon chain containing from 1 to 18 carbon atoms; the term halogen means fluorine, chlorine, bromine or iodine; the term cycloalkyl means an alicyclic saturated group with 3 to 6 carbon atoms; and the term aryl means an unsubstituted phenyl group or phenyl substituted by alkoxy, halogen or nitro group, said method comprising forming racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide from optically pure or optically enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (II) by a process as described above, then treating the racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide to produce the compound of formula (VIII).

15 According to another aspect of the invention, there is provided a method for the preparation of a compound of the general formula (IX):



where R₁ is hydrogen, alkyl, halogenalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aryl, or pyridyl; the term alkyl means a straight or branched hydrocarbon chain containing from 1 to 18 carbon atoms; the term halogen means fluorine, chlorine, bromine or iodine; the term cycloalkyl means an
5 alicyclic saturated group with 3 to 6 carbon atoms; and the term aryl means an unsubstituted phenyl group or phenyl substituted by alkoxy, halogen or nitro group, said method comprising forming racemic (±)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide from optically pure or optically enriched (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-
10 carboxamide (II) by a process as described above, then treating the racemic (±)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide to produce the compound of formula (IX).

Resolution of the recovered racemic (±)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) into its optically pure stereoisomers (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) is possible as described in more detail in our application no. PCT/GB02/02176. The compounds of formulas (VIII) and (IX) are described in
15 more detail in our US patent no. 5753646. The method can be used to produce any of the compounds disclosed in US5753646. For example, to produce (S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (V) it is possible to add acetyl chloride (or acetic anhydride) to a suspension of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-
20 carboxamide (I) and pyridine in dichloromethane, as described in example 4 of US5753646.

The compounds described in examples 4 to 17 of US5753646 can be produced by acylation using the appropriate acyl chloride or anhydride. The
30 compounds described in examples 18 to 23 can be produced using the appropriate carboxylic acid.

Using the present invention, it is therefore possible to produce the following compounds:

35 (1) 10-acetoxy-10,11-dihydro-5H-dibenz/b, f/azepine-5-carboxamide

- (2) 10-benzoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (3) 10-(4-methoxybenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (4) 10-(3-methoxybenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (5) 10-(2-methoxybenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 5 (6) 10-(4-nitrobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (7) 10-(3-nitrobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (8) 10-(2-nitrobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (9) 10-(4-chlorobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (10) 10-(3-chlorobenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 10 (11) 10-(2-acetoxybenzoyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (12) 10-propionyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (13) 10-butyryloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (14) 10-pivaloyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (15) 10-[(2-propyl)pentanoyloxy]-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 15 (16) 10-[(2-ethyl)hexanoyloxy]-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (17) 10-stearoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (18) 10-cyclopentanoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (19) 10-cyclohexanoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (20) 10-phenylacetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 20 (21) 10-(4-methoxyphenyl)acetoxy-10,11-dihydro-5H-dibenz/b,f/-azepine-5-carboxamide
- (22) 10-(3-methoxyphenyl)acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (23) 10-(4-nitrophenyl)acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 25 (24) 10-(3-nitrophenyl)acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (25) 10-nicotinoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (26) 10-isonicotinoyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (27) 10-chloroacetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (28) 10-bromoacetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- 30 (29) 10-formyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (30) 10-ethoxycarbonyloxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide
- (31) 10-(2-chloropropionyloxy)-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide

As already mentioned, the recovered racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) may be resolved into its optically pure (R)- (+)- and (S)-(-)-stereoisomers (II) and (I), whereby the desired (R)- (+)- or (S)- (-)-stereoisomers of all of the above compounds may be produced.

5

These compounds, or pharmaceutically acceptably derivatives thereof (such as salts), can be used in the preparation of pharmaceutical compositions comprising the compound itself, or the derivative, in combination with a pharmaceutically acceptable carrier. Such compositions have anticonvulsant properties and can be used in the treatment of some central and peripheral nervous system disorders, such as epilepsy.

10

The invention disclosed herein is exemplified by the following examples of preparation. It is to be understood that the invention is not to be limited to the exact details of operation, as obvious modifications and equivalents will be apparent to those skilled in the art.

15

Example 1. 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII)

20

To a stirred suspension of (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) (100g, 393.7mmol) (98.67% optical purity by chiral HPLC analysis) in dichloromethane (1000mL) cooled to 0-5°C was added thionyl chloride (56.2g, 472.4mmol) dropwise. The reaction mixture, which became a solution towards the end of addition, was allowed to stir for a further 10 minutes. A small quantity of activated charcoal was added with stirring and the reaction mixture was then filtered through a short CeliteTM pad. The filtrate was then evaporated (40°C, water-aspirator pressure) to a small residual volume. Toluene (500mL) was added, and the mixture was again evaporated (40°C, water-aspirator pressure) to leave a solid. Ethyl acetate (300mL) was added and the slurry was stirred at room temperature for one hour, whereupon the solid was removed by filtration and washed by a small volume of cold ethyl acetate.

25

30

After drying to constant weight, there was obtained 10-chloro-10, 11-dihydro-5H- dibenz/b, f/azepine-5-carboxamide (VII) as a beige solid (97.48 g, 91%) of m. p. 156-157°C.

35

Example 2. 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII)

To a stirred suspension of (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b, f/azepine-5-carboxamide (II) (4.29g, 16.89mmol) (99.2% optical purity by chiral HPLC analysis) in dichloromethane (50mL) cooled to 0-5°C was added thionyl chloride (2.22g, 18.58mmol) dropwise. The reaction mixture, which became a solution towards the end of addition, was allowed to stir for a further 10 minutes, whereupon ice/water was added. The phases were separated and the aqueous phase was extracted with a small volume of dichloromethane. The combined organic layers were washed by water and brine, then dried over anhydrous magnesium sulphate, filtered and evaporated (40°C, water-aspirator pressure) to leave a white solid. Ethyl acetate (20mL) was added and the slurry was stirred at room temperature for one hour. The solid was removed by filtration and dried until constant weight to afford 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII) as a white solid (4.22g, 92%) of m.p. 156.3- 156.6°C.

Example 3. (±)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III).

A suspension of 10-chloro-10,11-dihydro-5H-dibenz/b, f/azepine-5-carboxamide (VII) (50.0g, 183.5mmol) in de-ionised water (900mL) was stirred at room temperature for forty-eight hours. The solid was removed by filtration and washed with de-ionised water (100mL). After drying at 50°C over phosphorus pentoxide under high vacuum until constant weight, there was obtained racemic (+)-10,11-dihydro-10-hydroxy-5H-dibenz/b, f/azepine-5-carboxamide (III) as a beige solid (42.12g, 90%), of m. p. 186-188°C.

Chiral HPLC analysis of this product (LiChroCART™ 250-4 HPLC Cartridge ChiraDex™ 5µm, (Merck), Flowrate : 0.8mL/min, Mobile Phase: water/methanol 8:2, sample injected was 20µL of 0.2mg analyte/mL dissolved in the mobile phase, and UV detection at 210/254nm showed complete racemisation (1:1 mixture of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b, f/azepine-5-carboxamide (I) and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II), with retention time of (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b, f/azepine-5-carboxamide (II) at 8.39 minutes and retention

time of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) at 9.1 minutes).

Example 4. ($\pm$) 10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III)

5

A stirred suspension of 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII) (7.68g, 28.16mmol) in a mixture of dioxane (40mL) and water (40mL) was stirred at 50°C for forty minutes. The organic solvent was then removed by evaporation (40°C, water-aspirator pressure) and water (40mL) was added to the residue, which was then
10 extracted with a 10% isopropanol/dichloromethane solvent mixture. The combined organic extracts were washed with water and brine, then dried over anhydrous magnesium sulphate, filtered and evaporated (40°C, water-aspirator pressure) to leave a pale yellowish foam. Recrystallisation from a dichloromethane/isopropanol mixture afforded racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide
15 (III) as white crystals (4.92g, 69%), of m.p. 186.5-188 °C.

Chiral HPLC analysis of this product (LiChroCART 250-4 HPLC Cartridge ChiraDex 5 μ m, (Merck), Flowrate: 0.8mL/min, Mobile Phase: water/methanol 8:2, sample injected was 20 μ L of 0.2mg analyte/mL dissolved in the mobile phase, and UV detection at
20 210/254nm showed complete racemisation (1:1 mixture of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) and (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II), with retention time of (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) at 8.39 minutes and retention time of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) at
25 9.1 minutes).

Example 5. 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII)

To a stirred suspension of (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-
30 carboxamide (II) (10g, 39.37mmol) (87% optical purity by chiral HPLC analysis) in dichloromethane (100mL) cooled to 0-5°C was added thionyl chloride (5.62g, 47.24mmol) dropwise. The reaction mixture, which became a solution towards the end of addition, was allowed to stir for a further 10 minutes, whereupon ice/water was

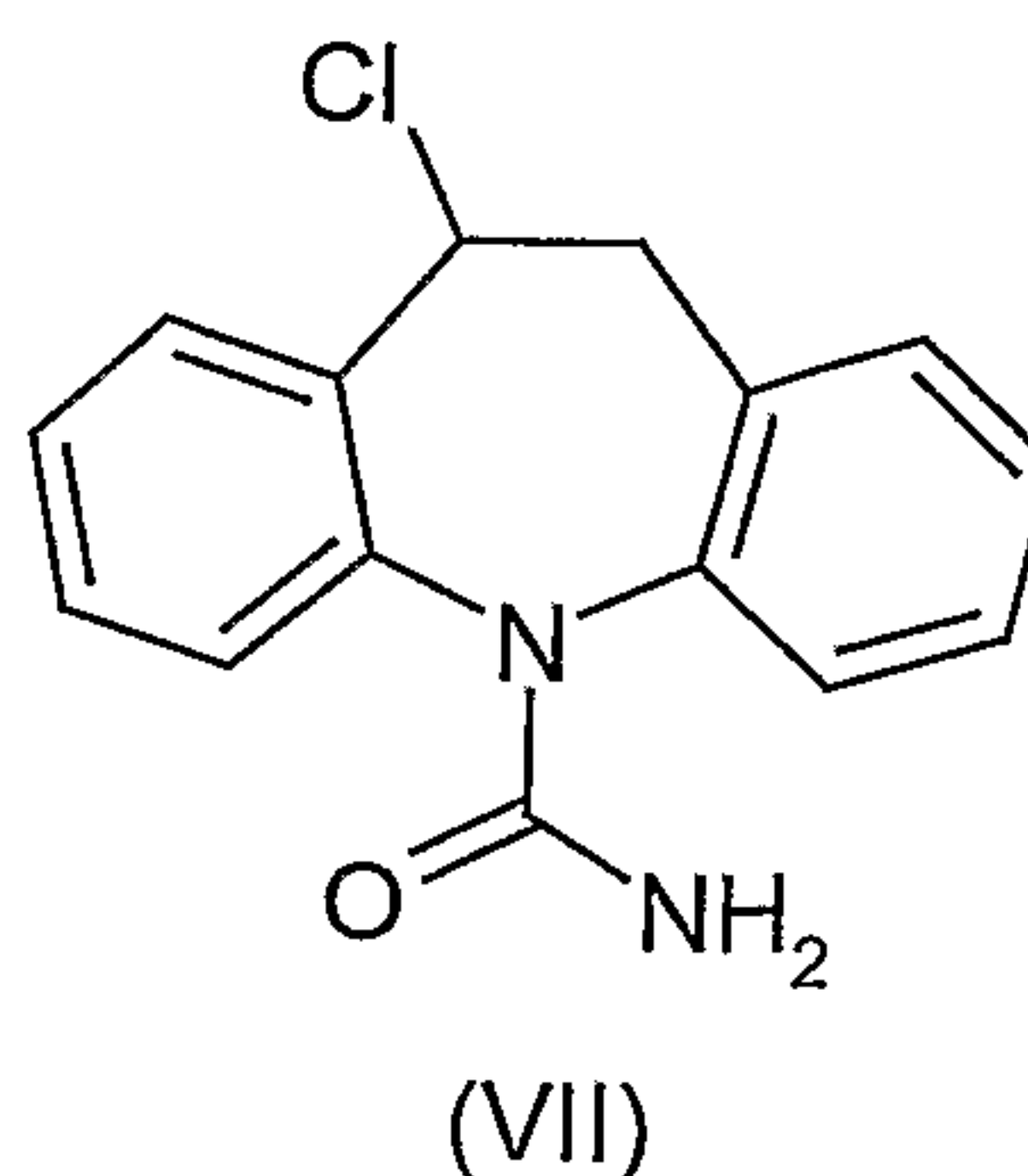
added. The phases were separated and the aqueous phase was extracted with a small volume of dichloromethane. The combined organic layers were washed by water and brine, then dried over anhydrous magnesium sulphate, then filtered and evaporated (40°C, water-aspirator pressure) to leave a white solid. Ethyl acetate (50mL) was added
5 and the slurry was stirred at room temperature for one hour. The solid was removed by filtration and dried until constant weight to afford 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII) as a white solid (9.98g, 93%) of m.p. 155-157°C.

10 This intermediate was hydrolysed as described in Example 3 to give the perfectly racemic product ($\pm$) 10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) as judged by chiral HPLC analysis

It will be appreciated that the invention described above may be modified.

Claims

1. 10-chloro-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VII)



2. A method for the manufacture of the compound (VII) as defined in claim 1, comprising reacting optically pure or optically enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II), or reacting optically pure or optically enriched (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I), with a chlorinating reagent in a substantially inert solvent to give the compound of formula (VII).

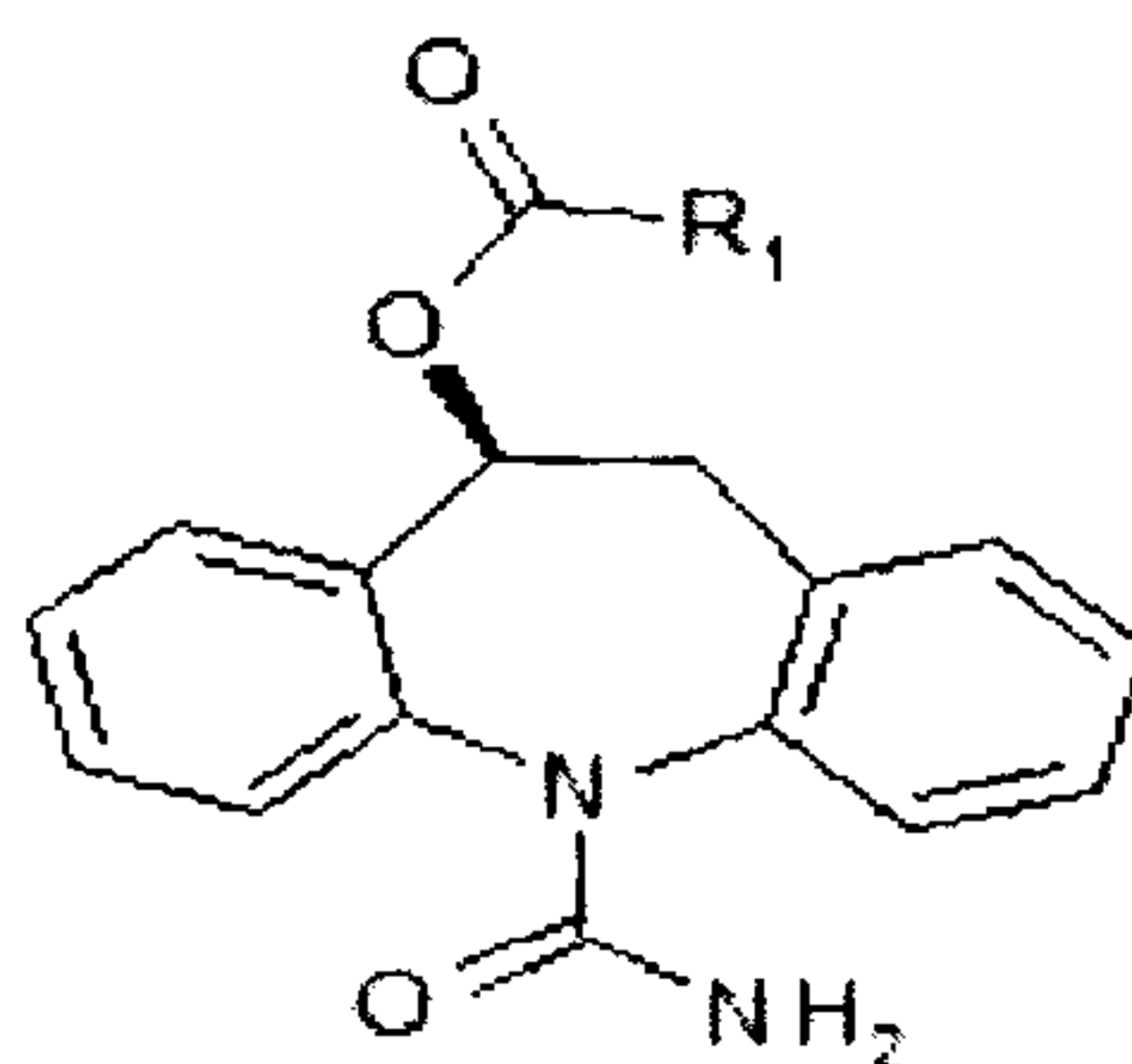
3. A method for the racemisation of optically pure or optically enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) comprising:

15

- (a) reacting optically pure or optically enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) with a chlorinating reagent in a substantially inert solvent to give the intermediate of formula (VII), and
- (b) hydrolysing the resulting intermediate of formula (VII) to give racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III).

4. A method for the racemisation of optically pure or optically enriched (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) comprising:
- 25

- (a) reacting optically pure or optically enriched (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (I) with a chlorinating reagent in a substantially inert solvent to give the intermediate of formula (VII), and
- 5 (b) hydrolysing the resulting intermediate of formula (VII) to give racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz[b,f]azepine-5-carboxamide (III).
5. A method according to claim 2, 3 or 4, wherein the chlorinating reagent is thionyl chloride, oxalyl chloride, sulfuryl chloride, phosphorus pentachloride,
10 phosphorus trichloride or phosphorus oxychloride.
6. A method according to claim 2, 3, 4 or 5, wherein the substantially inert solvent is a chlorinated aliphatic or aromatic hydrocarbon solvent.
- 15 7. A method according to any one of claims 2 to 6, wherein hydrolysis of the intermediate (VII) is carried out in neat water.
8. A method according to any one of claims 2 to 6, wherein hydrolysis of the intermediate (VII) is carried out in a water/water-miscible solvent mixture.
20
9. A method according to claim 8, wherein the water-miscible solvent is chosen from dioxane, tetrahydrofuran, methanol, ethanol, isopropanol, N-methyl-2-pyrrolidinone, high molecular weight polyethyleneglycols, acetone, acetonitrile and dimethylformamide.
- 25 10. A method for the preparation of a compound of general formula (VIII):



(VIII)

where R_1 is hydrogen, alkyl, halogenalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aryl, or pyridyl; the term alkyl means a straight or branched hydrocarbon chain containing from 1 to 18 carbon atoms; the term halogen means fluorine, chlorine, bromine or iodine; the term cycloalkyl means an alicyclic saturated group with 3 to 6 carbon atoms; and the term aryl means an unsubstituted phenyl group or phenyl substituted by alkoxy, halogen or nitro group, said method comprising:

(a) forming racemic $(\pm)$ -10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide from optically pure or optically enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) by a method according to claim 3; or

(b) forming racemic $(\pm)$ -10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide from optically pure or optically enriched (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) by a method according to claim 4;

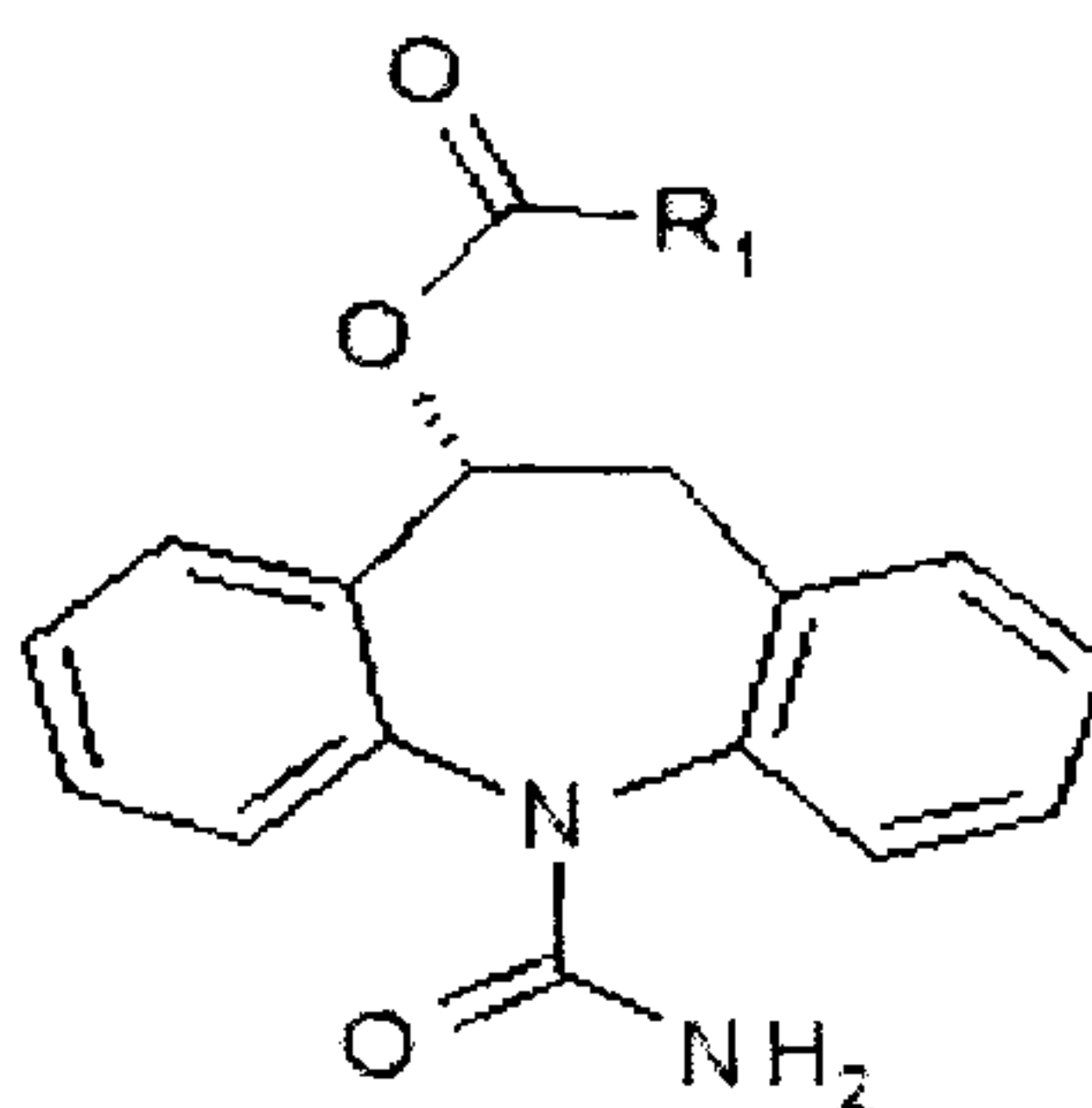
then, after step (a) or (b):

20

resolving the racemic $(\pm)$ -10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide to isolate (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) followed by acylation of the isolated enantiomer to produce the compound of formula (VIII).

25

11. A method for the preparation of a compound of general formula (IX):



(IX)

where R_1 is hydrogen, alkyl, halogenalkyl, aralkyl, cycloalkyl, cycloalkylalkyl, alkoxy, aryl, or pyridyl; the term alkyl means a straight or branched hydrocarbon chain containing from 1 to 18 carbon atoms; the term halogen means fluorine, chlorine, bromine or iodine; the term cycloalkyl means an alicyclic saturated group with 3 to 6 carbon atoms; and the term aryl means an unsubstituted phenyl group or phenyl substituted by alkoxy, halogen or nitro group, said method comprising:

10 (a) forming racemic $(\pm)$ -10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide from optically pure or optically enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) by a method according to claim 3; or

15 (b) forming racemic $(\pm)$ -10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide from optically pure or optically enriched (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) by a method according to claim 4;

then, after step (a) or (b):

20

resolving the racemic $(\pm)$ -10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide to isolate (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) followed by acylation of the isolated enantiomer to produce the compound of formula (IX).

25

12. A method for the preparation of (S)-(-)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (V) comprising forming racemic $(\pm)$ -10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) from optically pure or optically enriched (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II) by a method according to claim 3, then resolving and acylating the (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I).

30

13. A method for the preparation of (R)-(+)-10-acetoxy-10,11-dihydro-5H-dibenz/b,f/azepine-5-carboxamide (VI) comprising forming racemic ($\pm$)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (III) from optically pure or optically enriched (S)-(+)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (I) by a method according to claim 4, then resolving and acylating the (R)-(-)-10,11-dihydro-10-hydroxy-5H-dibenz/b,f/azepine-5-carboxamide (II).

14. A method according to any one of claims 10 to 13, wherein the acylation step is effected in dichloromethane in the presence of pyridine.