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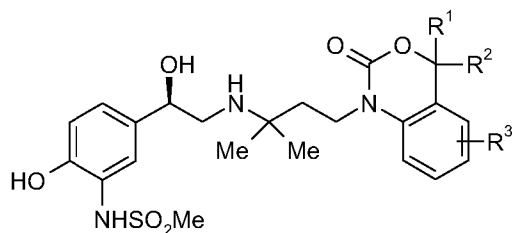
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(54) Title: PROCESS FOR THE PREPARATION OF BETAMIMETIC BENZOXAZINONE DERIVATIVES



(1)

(57) Abstract: The invention relates to a process for the manufacturing of organic compounds useful for treatment and prevention of respiratory diseases of general Formula (1) and salts thereof, wherein, R^1 and R^2 each independently mean H, halogen or C_{1-4} -alkyl or R^1 and R^2 are together have the meaning of C_{1-6} -alkylene; and R^3 denotes H, Halogen, OH, C_{1-4} -alkyl or O- C_{1-4} -alkyl.

PROCESS FOR THE PREPARATION OF BETAMIMETIC BENZOXAZINONE DERIVATIVES

5 Betamimetics (β -adrenergic substances) are known from the prior art. Reference may be made, for example, to the disclosures of US 4,460,581 or EP 43940, which proposes betamimetics for the treatment of a variety of complaints.

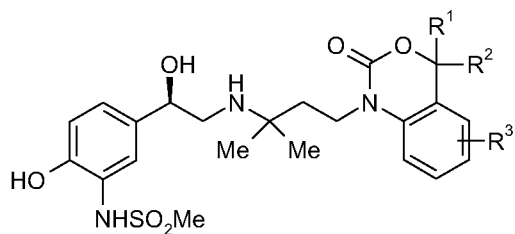
10 For drug treatment of diseases it is often desirable to prepare medicaments with a longer duration of activity. As a rule, this ensures that the concentration of the active substance in the body needed to achieve the therapeutic effect is guaranteed for a longer period without the need to re-administer the drug at frequent intervals. Moreover, giving an active substance at longer time intervals contributes to the well-being of the patient to a high degree.

15 It is particularly desirable to prepare a pharmaceutical composition which can be used therapeutically by administration once a day (single dose). The use of a drug once a day has the advantage that the patient can become accustomed relatively quickly to taking the drug regularly at certain times of the day.

20 The aim of the present invention is therefore to provide a process for the manufacturing of betamimetics which have a therapeutic benefit in the treatment of COPD and are characterised by a longer duration of activity and can thus be used to prepare pharmaceutical compositions with a longer duration of activity. A particular aim of the invention is to prepare betamimetics which, by virtue of their long-lasting effect, can be
25 used to prepare a drug for administration once a day for treating COPD.

SHORT DESCRIPTION OF THE INVENTION

30 The invention relates to a process for the manufacturing of organic compounds useful for treatment and prevention of respiratory diseases of general formula 1

**1**

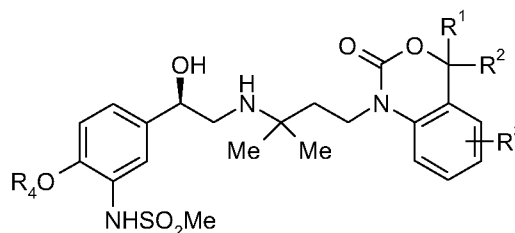
and pharmaceutically acceptable salts thereof, wherein,

R^1 and R^2 each independently mean H, halogen or C_{1-4} -alkyl or R^1 and R^2 are

5 together have the meaning of C_{1-6} -alkylene; and

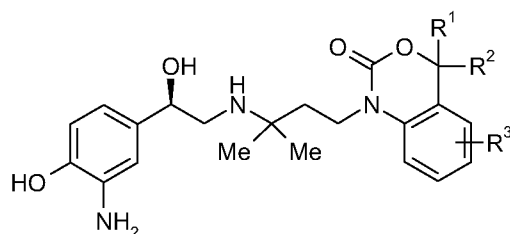
R^3 denotes H, halogen, OH, C_{1-4} -alkyl or $O-C_{1-4}$ -alkyl.

This invention further relates to optically pure intermediates for the synthesis of **1** and a process for their preparation. Accordingly, the invention relates in one aspect to a process
10 for preparing compounds of formula **1** deprotecting compounds of formula **2**

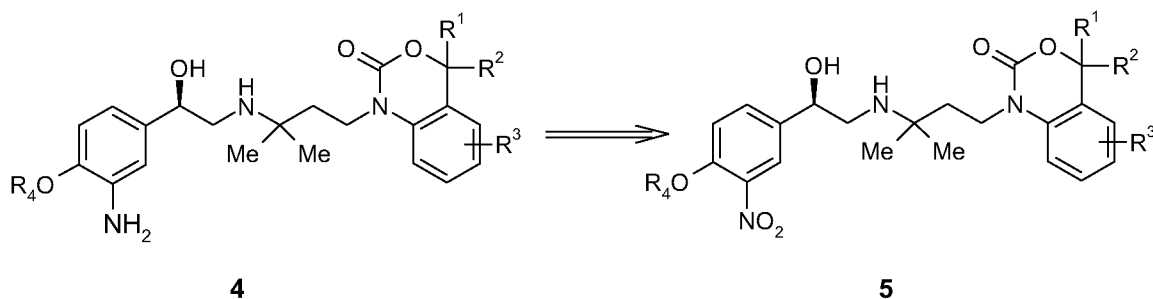
**2**

and salts thereof, wherein R^1 , R^2 and R^3 are defined as above and R^4 is selected from a group consisting of benzyl, diphenylmethyl or trityl, each optionally substituted at if
15 available an aryl group or an aliphatic carbon atom.

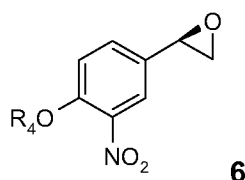
Alternatively, compounds of formula **1** are obtained by mesylation of compounds of formula **3**

**3**

20 Compounds **2** can be prepared upon mesylation of compounds **4**. In turn, compounds **4** are prepared reducing compounds of formula **5**

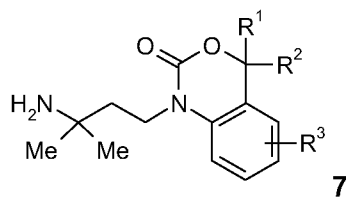


and compounds **3** are obtained by reduction of compounds **5**. Compounds **5** are prepared by reacting optically pure compounds of formula **6**

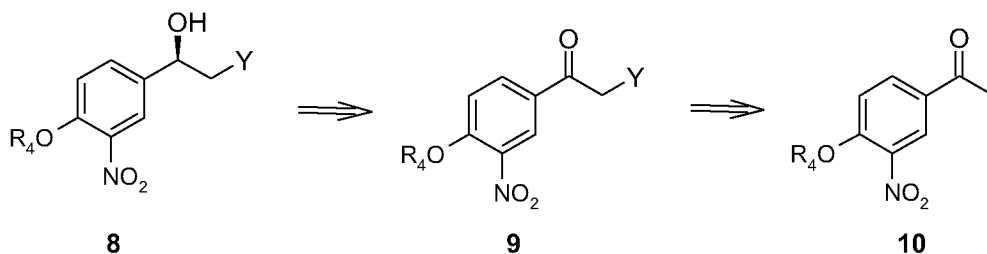


5

wherein R^4 has the above given meaning, with compounds of formula **7**



or a salt thereof, wherein R^1 , R^2 and R^3 have the above given meaning. In another aspect, the present invention provides optically pure compounds of formula **8**, and a process for their preparation which comprises asymmetric reduction of compounds of formula **9**, in turn obtained from compounds **10**.

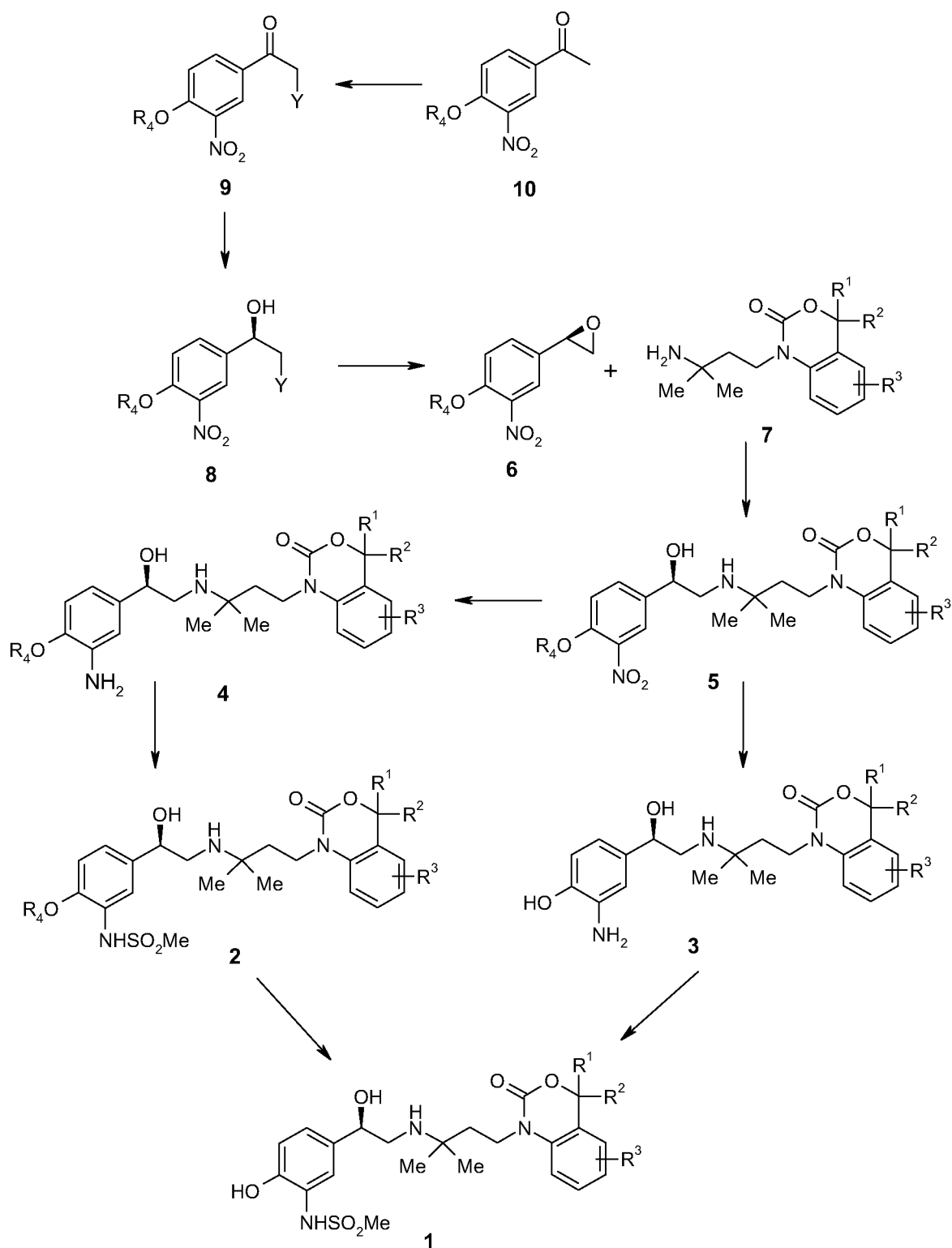


where R^4 is a hydroxy-protecting group as hereinbefore described, and Y is a chlorine or a sulfonyloxy based leaving group. Suitable examples include mesyloxy, tosyloxy, benzensulfonyl or trifluoromethanesulfonyloxy.

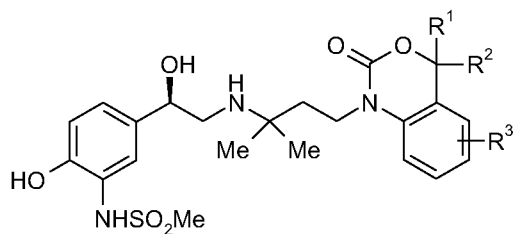
DETAILED DESCRIPTION OF THE INVENTION

In one aspect the present invention relates to a practical and efficient process for the
5 preparation of organic compounds of formula **1** as optically pure isomers. This method is
particularly advantageous because it utilizes precursors of high crystallinity and
enantiomeric purity that are readily obtained by asymmetric reduction techniques of
readily available starting materials. The stereochemical integrity is maintained in the
subsequent steps of the synthesis, which comprises crystalline or otherwise easily
10 isolable intermediates and proceeds as illustrated in Scheme 1.

Scheme 1



Therefore the invention relates to a process for manufacturing compounds of formula 1

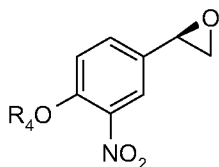
**1**

or a salt thereof, wherein

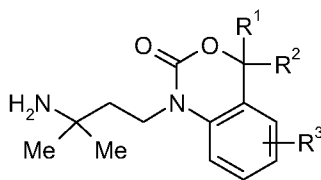
R^1 and R^2 each independently mean H, halogen or C_{1-4} -alkyl or R^1 and R^2 are together have the meaning of C_{1-6} -alkylene; and

R^3 denotes H, halogen, OH, C_{1-4} -alkyl or O- C_{1-4} -alkyl;

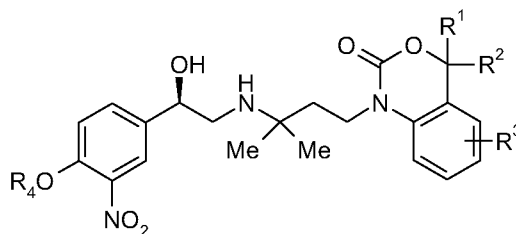
characterized in that, a compound of formula **6**

**6**

wherein R^4 is selected from the group consisting of benzyl, diphenylmethyl or trityl, each optionally substituted at if available an aryl group or an aliphatic carbon atom is reacted with a compound of formula **7**

**7**

or a salt thereof, wherein R^1 , R^2 and R^3 have the above given meaning, to a compound of formula **5**, or a salt thereof.

**5**

whereas compounds of formula **1** are obtained by reduction of the nitro group to an amine group, mesylation of this amine group and cleavage of the protecting group during the reduction step or after the mesylation step.

5

Preferred is a process wherein

R^1 and R^2 each independently mean H, F, Cl, methyl, ethyl, propyl, butyl or R^1 and R^2 are together have the meaning of ethylene, propylene, butylene or pentylene;

- 10 R^3 denotes H, F, Cl, OH, methyl, ethyl, methoxy or ethoxy; and
 R^4 is selected from the group consisting of benzyl or diphenylmethyl, each optionally substituted at if available an aryl group or an aliphatic carbon atom, with a group selected from F, Cl, Br, Me, Et, OMe, OEt or O-ⁱPr.

15 Particularly preferred is process wherein

R^1 and R^2 each independently mean H, methyl, ethyl, propyl or R^1 and R^2 are together have the meaning of ethylene, propylene, butylene or pentylene;

R^3 denotes H, F, OH, methyl or methoxy; and

- 20 R^4 denotes benzyl optionally substituted at the aryl group or the aliphatic carbon atom with a group selected from F, Cl, Br, Me, Et, OMe, OEt or O-ⁱPr.

Particularly preferred is process for manufacturing compounds of formula **1a-1h**:

- 25 **1a**: N-(5-{2-[1,1-Dimethyl-3-(2-oxo-4,4-dipropyl-4H-benzo[d][1,3]oxazin-1-yl)-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide
1b: N-[5-(2-{1,1-Dimethyl-3-[spiro(cyclohexan-1,4'-2H-3',1'-benzoxazin)-2'-oxo-1-yl]-propylamino}-1-hydroxy-ethyl)-2-hydroxy-phenyl]-methanesulfonamide
1c: N-[5-(2-{1,1-Dimethyl-3-[spiro(cyclopropyl-1,4'-2H-3',1'-benzoxazin)-2'-oxo-1-yl]-propylamino}-1-hydroxy-ethyl)-2-hydroxy-phenyl]-methanesulfonamide
 30 **1d**: N-(5-{2-[3-(4,4-Diethyl-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide
1e: N-(5-{2-[3-(4,4-Diethyl-6-fluoro-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide

1f: N-(5-{2-[3-(4,4-Diethyl-7-fluoro-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide

1g: N-(5-{2-[3-(4,4-Diethyl-8-methoxy-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide

5 **1h:** N-(5-{2-[3-(4,4-Diethyl-6-methoxy-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide

- Preferred is the process wherein a compound of formula **6** is reacted with a compound of formula **7** in the presence of a suitable solvent. Preferred are organic solvents,
10 especially preferred are suitable solvents selected from the group consisting of alcohols, ketones, aldehydes, ethers or aromatic solvents, particularly preferred are ethanol, propanol, butanol and tetrahydrofuran, or mixtures thereof.
- The reacted stoichiometric ratio of compounds **6** and **7** is preferably between 1:1 and 1:5, particular preferred are ratios from 1:1; 1:1,05; 1:1,1; 1:1,15; 1:1,2; 1:1,25.
- 15 • The reaction is preferably conducted at increased temperatures, preferably above 40°C, more preferably above 60°C, most preferred at reflux of the solvent or of the solvents mixture with or without continuous removal of the solvent
- The preferred reaction time is between 1 and 48 h, more preferably 3 and 24 h, in particular 5 and 8 h.
- 20 • After the coupling reaction the product of formula **5** is isolated directly from the reaction mixture as a salt upon addition of a solution of an appropriate acid, preferably chosen among oxalic, fumaric, maleic, methanesulfonic, hydrochloric, hydrobromic or hydroiodic acid, most preferably oxalic acid, in a suitable solvent (e.g. ethanol, propanol or butanol, methyl-t-butylether, acetonitrile).
- 25 • In another aspect of the invention the free base of compounds of formula **5** can be obtained from basic, aqueous solutions or suspensions of the corresponding salts upon extractive aqueous work up with an appropriate organic solvent (e.g. methyl-t-butylether, methyltetrahydrofuran, ethyl acetate, isopropylacetate, toluene).
- Alternatively, the coupling reaction could be performed by using a salt of compound **7**
30 (e.g. hydrochloride, hydrobromide) and liberating the corresponding base in situ by the action of an appropriate base (e.g. tBuOK, tBuONa) which generates insoluble salts, that can be removed by filtration prior to addition of epoxide **6**.

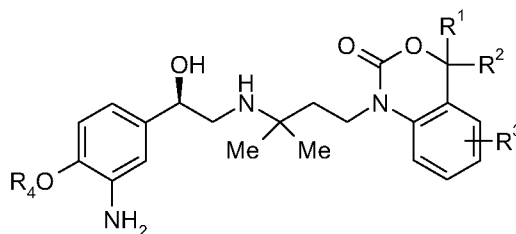
The compound of formula **1** is obtained from compound of formula **5** via a reduction and a mesylation step and cleavage of the protecting group during the reduction step or after the mesylation step.

5

In a preferred embodiment of the invention the compound of formula **5**, or a salt thereof, is:

- hydrogenated via hydrogen pressure in a suitable organic solvent, preferably tetrahydrofuran, toluene, alcoholic solvents or mixtures thereof, in the presence of a catalyst tolerating ether bonds, e.g. PtO₂, Raney-Nickel, Rh/C. The preferred pressure of hydrogen is between 30 and 70 psi, preferably 40 to 60 psi, in particular 45 to 55 psi. The preferred reaction time is between 1 and 2 h, preferably 1,2 and 1,8 h, in particular 1,4 to 1,6 h.
- The intermediate product of formula **4**

15

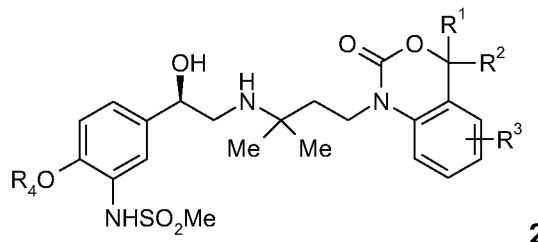
**4**

or a salt thereof, wherein R¹, R², R³ and R⁴ are defined as in claim 1 to 3, is obtained by filtering off the catalyst and removing the solvent.

- Thereafter the compound of formula **4** is reacted with methanesulfonylchloride in the presence of a suitable base, preferably an organic base, e.g. pyridine, picoline, triethylamine, in an appropriate solvent, e.g. tetrahydrofuran, acetonitrile, toluene.
- The stoichiometric ratio of compound **4** and methanesulfonylchloride is preferably between 1:1 and 1:2, particular preferred are ratios from 1:1; 1:1,1; 1:1,2; 1:1,3; 1:1,4; 1:1,5.
- The stoichiometric ratio of compound **4** and pyridine is preferably between 1:1 and 1:4, particular preferred are ratios from 1:1; 1:1,1; 1:1,2; 1:1,3; 1:1,4; 1:1,5; 1:1,6; 1:1,7; 1:1,8; 1:1,9; 1:2; 1:2,1; 1:2,2; 1:2,3; 1:2,4; 1:2,5; 1:2,6; 1:2,7; 1:2,8; 1:2,9; 1:3.
- The preferred reaction time is between 10 and 20 h, more preferably 12 and 18 h.

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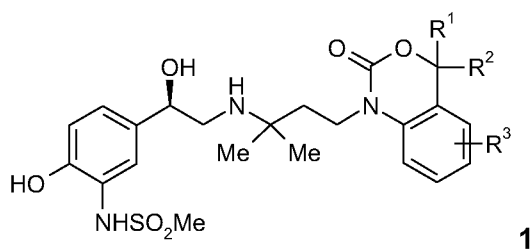
- The reaction is preferably conducted at moderate temperatures, preferably between 10 and 30°C, more preferably between 15 and 25°C, most preferably at room temperature.
- After the reaction, the solvent is removed and the remaining product of formula **2**



5

wherein R^1 , R^2 , R^3 and R^4 are defined as in claim 1 to 3, is purified as an organic solution (e.g. ethyl acetate, butyl acetate, methylisobutyl ketone, toluene, methyl-t-butylether) via extractive aqueous work up.

- A subsequent hydrogenation of **2** in a suitable organic solvent, preferably a mixture of inert solvents, e.g. MeOH, EtOH, toluene, tetrahydrofuran, and 1-2 equivalents of an acid (e.g. HCl, HBr, methanesulfonic acid), in the presence of a catalyst, e.g. Pd/C, Pd(OH)₂/C, Pd/CaCO₃, Raney-Nickel, delivers compounds **1**. The preferred pressure of hydrogen is between 30 and 70 psi, preferably 40 to 60 psi, in particular 45 to 55 psi. The preferred reaction time is between 0.5 and 6 h, preferably 1 and 4 h, in particular 2 to 3 h.
- Products of formula **1**

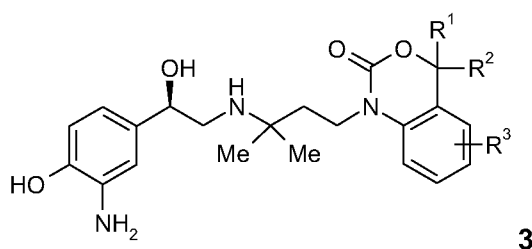


- or a salt thereof, wherein R^1 , R^2 and R^3 are defined as in claim 1 to 3, are obtained by filtering off the catalyst, removing the solvent and crystallizing from a suitable solvent, e.g. acetonitrile, tetrahydrofuran, ethanol, i-propanol, water or a mixture thereof. Preferably compounds **1** are obtained as a salt e.g. a hydrochloride or hydrobromide.

25

In another embodiment of the invention compounds of formula **5**, or a salt thereof, are:

- hydrogenated via hydrogen pressure in a suitable organic solvent, (e.g. methanol, ethanol, tetrahydrofuran) in the presence of a catalyst, e.g. Pd/C, Pd(OH)₂/C, Pd/CaCO₃, Raney-Nickel. The preferred pressure of hydrogen is between 30 and 70 psi, preferably 40 to 60 psi, in particular 45 to 55 psi. The preferred reaction time is between 1 and 5 h, preferably 2 and 3 h.
- Products of formula **3**



10

or a salt thereof, wherein R¹, R² and R³ are defined as in claim 1 to 3, are obtained by filtering off the catalyst, removing the solvent and crystallizing from an appropriate solvent (e.g. EtOAc, dichloromethane, toluene or mixtures thereof).

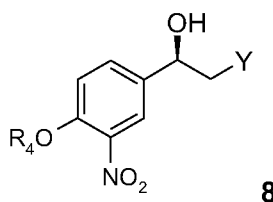
- Thereafter compounds of formula **3** or a salt thereof, are reacted with methansulfonylchloride in the presence of a suitable base, preferably an organic base (e.g. pyridine, picoline, triethylamine) and a suitable organic solvent (e.g. acetonitrile, tetrahydrofuran, N,N-dimethylformamide or mixtures thereof).
- The stoichiometric ratio of compound **3** and methansulfonylchloride is preferably between 1:1 and 1:4, particular preferred are ratios from 1:1; 1:1,1; 1:1,2; 1:1,3; 1:1,4; 1:1,5; 1:1,6; 1:1,7; 1:1,8; 1:1,9; 1:2; 1:2,1; 1:2,2; 1:2,3; 1:2,4; 1:2,5; 1:2,6; 1:2,7; 1:2,8; 1:2,9; 1:3.
- The stoichiometric ratio of compound **4** and pyridine is preferably between 1:1 and 1:4, particular preferred are ratios from 1:1; 1:1,1; 1:1,2; 1:1,3; 1:1,4; 1:1,5; 1:1,6; 1:1,7; 1:1,8; 1:1,9; 1:2; 1:2,1; 1:2,2; 1:2,3; 1:2,4; 1:2,5; 1:2,6; 1:2,7; 1:2,8; 1:2,9; 1:3; 1:3,1; 1:3,2; 1:3,3; 1:3,4; 1:3,5; 1:3,6; 1:3,7; 1:3,8; 1:3,9; 1:4.
- The preferred reaction time is between 0.5 and 6 h, more preferably 1 and 5 h, most preferred is a reaction time between 2 and 4 h.
- The reaction is preferably conducted at moderate temperatures, preferably between 10 and 70°C, more preferably between 20 and 45°C.

25

- After the reaction is complete, a reacting solvent (e.g. methanol, ethanol, aqueous ammonia) is added, the mixture is concentrated and the product of formula **1** is recovered by crystallization from a suitable aqueous solvent mixture (e.g. acetonitrile, tetrahydrofuran, N,N-dimethylformamide, or mixtures thereof) at a controlled pH value.
- 5 • The preferred pH value of the above mentioned mixture is between 5 and 9, more preferably 6 and 8, particular preferred are pH value of 7,0; 7,1; 7,2; 7,3; 7,5; 7,6; 7,7.
- The product **1** can be further purified via recrystallisation as a salt (e.g. hydrochloride, hydrobromide, maleate, fumarate, oxalate, acetate, methansulfonic acid) from a suitable solvent (e.g. acetonitrile, tetrahydrofuran, ethanol, i-propanol, water or mixture
10 thereof) containing the respective acid.
- The reduction of the free bases of compounds **5** can also be performed as described above and in the presence of 1 to 1.5 equivalents of an appropriate strong acid,
15 preferably chosen among hydrochloric, methanesulfonic, hydrobromic, hydroiodic or sulfuric acid, most preferably hydrochloric acid, in solvent suitable for the subsequent mesylation step (e.g tetrahydrofuran, methyl-t-butylether, methyltetrahydrofuran, ethyl acetate, isopropylacetate , toluene, acetonitrile).
- The subsequent mesylation step is then performed by filtering off the catalyst, diluting
20 with an appropriate organic solvent (e.g. acetonitrile, tetrahydrofuran, N,N-dimethylformamide) and adding a suitable base, preferably an organic base (e.g. pyridine, picoline, triethylamine) followed by addition of methansulfonylchloride.
- The stoichiometric ratio of compound **3** and methansulfonylchloride is preferably between 1:0.9 and 1:1.2, particular preferred are ratios from 1:1; 1:1,05; 1:1,1.
- 25 • The stoichiometric ratio of compound **4** and pyridine is preferably between 1:1 and 1:4, particular preferred are ratios from 1:1; 1:1,1; 1:1,2; 1:1,3; 1:1,4; 1:1,5; 1:1,6; 1:1,7; 1:1,8; 1:1,9; 1:2; 1:2,1; 1:2,2; 1:2,3; 1:2,4; 1:2,5; 1:2,6; 1:2,7; 1:2,8; 1:2,9; 1:3; 1:3,1; 1:3,2; 1:3,3; 1:3,4; 1:3,5; 1:3,6; 1:3,7; 1:3,8; 1:3,9; 1:4.
- The preferred reaction time is between 0.5 and 6 h, more preferably 1 and 3 h.
- 30 • The mesylation reaction is preferably conducted at moderate temperatures, preferably between 0 and 45°C.
- The work up procedure, the isolation and the purification of compound **1** is performed as described above.

- Alternatively, the free base of compounds of formula **3** can be obtained from basic, aqueous solutions or suspensions of the corresponding salts upon extractive aqueous work up with an appropriate organic solvent (e.g methyl-t-butylether, methyltetrahydrofuran, ethyl acetate, isopropylacetate , toluene).
- Thereafter, compounds of formula **3**, isolated after evaporation of the solvent or solutions of compounds of formula **3**, are treated with 1-1.5 equivalents of an appropriate strong acid, preferably chosen among hydrochloric, methanesulfonic, hydrobromic, hydroiodic or sulfuric acid, most preferably hydrochloric acid, and reacted with methansulfonylchloride in the presence of a suitable base, preferably an organic base (e.g. pyridine, picoline, triethylamine) and if necessary an additional suitable organic solvent (e.g. acetonitrile, tetrahydrofuran, N,N-dimethylformamide or mixtures thereof).
- The stoichiometric ratio of compound **3** and methansulfonylchloride is preferably between 1:0.9 and 1:1.2, particular preferred are ratios from 1:1; 1:1,05; 1:1,1.
- The stoichiometric ratio of compound **4** and pyridine is preferably between 1:1 and 1:4, particular preferred are ratios from 1:1; 1:1,1; 1:1,2; 1:1,3; 1:1,4; 1:1,5; 1:1,6; 1:1,7; 1:1,8; 1:1,9; 1:2; 1:2,1; 1:2,2; 1:2,3; 1:2,4; 1:2,5; 1:2,6; 1:2,7; 1:2,8; 1:2,9; 1:3; 1:3,1; 1:3,2; 1:3,3; 1:3,4; 1:3,5; 1:3,6; 1:3,7; 1:3,8; 1:3,9; 1:4.
- The preferred reaction time is between 0.5 and 6 h, more preferably 1 and 4 h.
- The reaction is preferably conducted at moderate temperatures, preferably between -5 and 45°C, more preferably between 0 and 25°C.
- The work up procedure, the isolation and the purification of compound **1** is performed as described above.

Furthermore the above described process is preferred, wherein the compound of formula **6** is obtained by reacting a compound of formula **8**.

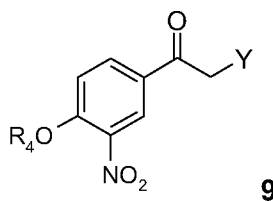


wherein R⁴ is defined as in claim 1 to 3, and Y is chlorine or a sulfonyloxy based leaving group. Suitable examples include mesyloxy, tosyloxy, benzensulfonyl or trifluoromethanesulfonyloxy. Particularly preferred is the process wherein Y is chlorine.

- 5 • Preferred is the process wherein a compound of formula **8** is reacted with a base, preferably an alkali base (e.g. NaOH, KOH, tBuOK, tBuONa, AmONa, Na₂CO₃) in the presence of a suitable solvent. Preferred is an organic solvent, especially preferred are suitable solvents selected from the group consisting of amines, alcohols, ketones, aldehydes, ether or aromatic solvents, particularly preferred are N,N-
10 dimethylformamide, ethanol, propanol and tetrahydrofuran.
- The reacted stoichiometric ratio of compounds **8** and the base is preferably between 1:1 and 1:3, particular preferred are ratios from 1:1; 1:1,1; 1:1,2; 1:1,3; 1:1,4; 1:1,5; 1:1,6; 1:1,7; 1:1,8; 1:1,9; 1:2.
- Preferably the base is added to the reaction mixture as a solution, preferably with a
15 concentration between 2 to 6 mol/L, most preferably between 3 and 5 mol/L, in particular 3,5 to 4,5 mol/L.
- The reaction is preferably conducted at moderate temperatures, preferably between 10 and 30°C, more preferably between 15 and 25°C, most preferably at room temperature.
- 20 • The preferred reaction time is between 10 and 180 min, more preferably 20 and 120 min, most preferred is a reaction time between 25 and 80 min.
- After the reaction water is added preferably together with an organic or inorganic acid (e.g. HCl, H₂SO₄, AcOH) and the product is obtained by filtration.

25

Compounds **9** can be transformed into compounds **8** with the desired configuration at the asymmetric carbon upon stereoselective reduction with borane or a borane complex in the presence of catalytic amounts of a chiral auxiliary. The reduction step is carried out under standard conditions as reviewed in E.J. Corey; C.J. Helal *Angew. Chem. Int. Ed.* **1998**, 37, 1986-2012. Therefore the above described process is preferred, wherein the compound of
30 formula **8** is obtained by reacting a compound of formula **9**.



wherein R⁴ is defined as in claim 1 to 3, and Y is as defined above.

- 5 • Preferred is the process wherein a compound of formula **9** is reacted with a mixture of a chiral auxiliar and a borane complex in the presence of a suitable solvent. Preferred is an organic solvent, especially preferred are suitable solvents selected form the group consisting of chlorinated solvents, ethers or aromatic solvents, particularly preferred are toluene and tetrahydrofuran.
- 10 • The reacted stoichiometric ratio of compounds **9** and the borane is preferably between 1:0.3 and 1:2, particular preferred are ratios from 1:0.5; 1:0,6; 1:0,7; 1:0,8; 1:0,9; 1:1; 1:1,2; 1:1,3.
- 15 • The chiral auxiliar is preferably added in an amount of 1-30% relating to the compound of formula **9**, preferred is an amount of 2-20%, more preferred 3-10%, most preferred 4-8%.
- 20 • With particularly effective chiral auxiliaries, the amount of said auxiliary can be consistently lowered. In these cases, preferred is an amount of 0.05-2%, more preferred 0.1-1%,
- 25 • Different chiral auxiliars (or their enantiomers) are disclosed by for example E.J. Corey; C.J. Helal *Angew.Chem. Int.Ed.* **1998**, 37, 1986-2012, by Y. Gao *at al.* in WO 9532937 and in *Tetrahedron Lett.* **1994**, 35, 6631-6634; by U. Kraatz in DE 3609152; by S. Itsuno and K. Ito in *J. Org. Chem.* **1984**,49, 555-557, by G. J. Quallich *et al.* in *Tetrahedron Lett.* **1993**, 34, 4145-4148, by S. Itsuno *et al.* in *J. Chem. Soc. Perkin Trans I* **1983**, 1673-1676 or by C. H. Senanayake *at al.* in *Tetrahedron Lett.* **1998**, 39, 1705-1708. Preferred is (1S,2S)-(+)-cis-1-amino-2-indanol or one of the following alternatives: (R)-2-methyl-CBS-oxazaborolidine, (R)-(+)-o-tolyl-CBS-oxazaborolidine, (R)-(+)-2-(diphenylhydroxymethyl)-pyrrolidin, (1S,2R)-(+)-2-amino-1,2-diphenylethanol, (R)-(-)-2-amino-2-phenylethanol, (R)-(+)-2-amino-3-methyl-1,1-diphenyl-1-butanol, (1S, 2S)-1-amino-1,2,3,4-tetrahydro-naphthalen-2-ol.
- 30 • The generation of the active catalyst may be well performed in situ, as originally described by U. Kraatz in DE 3609152 and by S. Itsuno *at al.* in *J.Chem.Soc. Chem.*

Commun. **1981**, 315-317 and later exemplified by G.J Quallich *at al.* in Synlett **1993**, 929 by combining the chiral auxiliary with excess borane complex in a suitable solvent selected from the group consisting of chlorinated solvents, ethers or aromatic solvents, particularly preferred are toluene and tetrahydrofuran.

- 5 • Alternatively, and for example in the case of (1S,2S)-(+)-cis-1-amino-2-indanol, (R)-(+)-2-(diphenylhydroxymethyl)-pyrrolidin, (1S,2R)-(+)-2-amino-1,2-diphenylethanol, (R)-(-)-2-amino-2-phenylethanol, (R)-(+)-2-amino-3-methyl-1,1-diphenyl-1-butanol and (1S, 2S)-1-amino-1,2,3,4-tetrahydro-naphthalen-2-ol the active catalyst is generated by first combining in a suitable solvent the above mentioned chiral auxiliaries with a
- 10 trialkylborate $B(OR')_3$ ($R' = C_{1-6}$ alkyl) to generate in situ the corresponding 1,3,2-alkoxy-oxazaborolidines, as for example described by M. Masui *at al.* in Synlett **1997**, 273-274 followed by addition of a borane complex.
- After the formation of the active catalyst a solution of the compound of general formula **9** in an appropriate solvent as described above is added to the solution of the active
- 15 catalyst and the borane complex.
- In addition other reagents or reagents classes are also known to promote stereoselective reduction of α -halogeno and α -sulfonyloxybenzophenone to the corresponding alcohol. In particular: T. Hamada; T. Torii; K. Izawa; R. Noyori; T. Ikariya *Org. Lett.* **2002**, 4, 4373-4376 or J. Chandrasekharan; P.V. Ramachandran; H.C. Brown *J. Org. Chem.* **1985**, 50, 5448-5450.
- 20 • Suitable, commercially available boranes complexes are for example: BH_3 -dimethyl sulfite, BH_3 -THF, BH_3 -4-methylmorpholine, BH_3 -N-phenylmorpholine, BH_3 -N-ethyl-N-isopropylaniline, BH_3 -N,N-diisopropylethylamine, BH_3 -triethylamine or BH_3 -N,N-diethylaniline, preferred is BH_3 -N,N-diethylaniline.
- 25 • The reaction is preferably conducted at temperatures between -5 and 80°C, more preferably between 5 and 60°C, most preferably between 10 and 45°C.
- The preferred reaction time is between 30 and 180 min, more preferably 40 and 120 min, most preferred is a reaction time between 50 and 80 min.
- If necessary, slower addition of the compound of formula **9** may also be used. The
- 30 preferred addition time is in these case between 1.5 and 16 hours, more preferably more than 2 hours, most preferred is an addition time longer than 4 hours.
- After the reaction a reacting solvent (e.g. water, methanol, ethanol, acetone) is added, the reaction mixture concentrated and the product of formula **8** is recovered via

treatment with mixtures of aqueous solutions of HCl (preferably a 0.5-1.5 mol/L solution) and organic solvents (e.g. heptane, ethyl acetate, butyl acetate, methyl-t-butylether) and recrystallised from a suitable solvent (e.g. ethanol, i-propanol, t-butanol, i-propyl ether, methyl-t-butyl ether, acetonitrile).

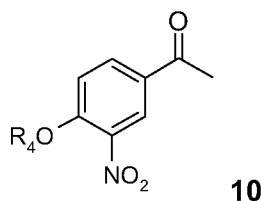
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In addition other reagents or reagents classes can be used for the same transformation. Particularly preferred methods are based on chiral ruthenium complexes (T. Hamada; T. Torii; K. Izawa; R. Noyori; T. Ikariya *Org. Lett.* **2002**, 4, 4373-4376) or chiral chloroborane (J. Chandrasekharan; P.V. Ramachandran; H.C. Brown *J. Org. Chem.* **1985**, 50, 5448-5450).

10

In the process described above, compounds **9** are obtained by chlorination or oxidation of the α -position relative to the ketone group of appropriately protected 3-substituted-4-hydroxyacetophenones **10**, wherein R^4 is as defined above. The chlorination may be carried out using conventional chlorinating agents at room or higher temperature. The oxidation can be performed using a variety of agents leading directly to the α -sulfonyloxybenzophenones (e.g. hydroxy(tosyloxy)iodobenzene, hydroxy(mesyloxy)iodobenzene J. S. Lodaya; G.F. Koser *J. Org. Chem.* **1988**, 53, 210) or to α -hydroxybenzophenones which are the precursors of α -sulfonyloxybenzophenones (e.g. $Pb(OAc)_4$, phenyliodosobenzene, $Mn(OAc)_3$). Particularly preferred is the process of chlorinating **10**. Therefore the above described process is preferred, wherein the compound of formula **9** is obtained by reacting a compound of formula **10**.

20



25

wherein R^4 is defined as in claim 1 to 3.

- Preferred is the process wherein a compound of formula **10** is reacted with a chlorinating agent in the presence of a suitable solvent. Preferred is an organic solvent, especially preferred are suitable solvents selected from the group consisting

30

of alkanes, alcohols, halogenalkanes, ketones, aldehydes, ethers or nitriles, particularly preferred are heptane, methanol, propanol, tetrahydrofuran, methyl-t-butylether, di-i-propylether, 1,2-dimethoxyethane, dioxane, acetonitrile, dichlormethane, chloroform alone or mixtures thereof, most preferred are heptane, tetrahydrofuran, methyl-t-butylether, di-i-propylether, 1,2-dimethoxyethane, dioxane, dichlormethane, chloroform alone or mixtures with methanol thereof, particular preferred are dioxane, acetonitrile or a mixture of dichlormethane and methanol.

- The reacted stoichiometric ratio of compounds **8** and the chlorinating agent is preferably between 1:1 and 1:2, particular preferred are ratios from 1:1; 1:1,1; 1:1,15; 1:1,2; 1:1,25; 1:1,3; 1:1,35; 1:1,4; 1:1,45; 1:1,5.
- The chlorination may be carried out using conventional chlorinating agents. Examples of the chlorinating agent may include, for example, chlorine, seleninyl chloride, hypochlorous acid, N-chlorosuccinimide, cupric chloride, quaternary ammonium polychloride preformed or generated in situ from quaternary ammonium chloride and iodo monochloride, hexachloro-2,4-cyclohexadienone, the complex of 3-chloroperbenzoic acid-hydrogen chloride-N,N-dimethylformamide or sulfuryl chloride. Specific examples are:

- Cl_2 AcOH V. Auwers *Chem. Ber.* **1926**, 59, 2899;
- Cl_2 AlCl_3 $\text{Et}_2\text{O}/\text{CCl}_4$ K. Yutaka; S. Takashi; I. Yoshio *Eur. J. Med. Chem. Chim. Ther.* **1981**, 16, 355-362;
- $\text{BnMe}_3\text{ICl}_2$ in $\text{ClCH}_2\text{CH}_2\text{Cl}/\text{MeOH}$ K. Shoji; K. Takaaki; M. Masayuki; F. Shizuo; M. Kimihiro; O. Tsuyoshi *Synthesis* **1988**, 7, 545-546 or in AcOH V. Edwin; W. Jiabing *Org. Lett.* **2000**, 2, 1031 - 1032;
- hexachloro-2,4-cyclohexadienone. G. Alain; L. Marc; G. Jean-Paul; *Synthesis* **1982**, 12, 1018-1020;

Preferred chlorinating agents are sulfuryl chloride, N-chlorosuccinimide or quaternary ammonium polychloride, most preferred is sulfuryl chloride and benzyltrimethylammonium dichloriodite isolated or generated *in situ* from benzyltrimethylammonium chloride and iodine monochloride..

- The reaction is preferably conducted at moderate temperatures, preferably between 10 and 30°C, more preferably between 15 and 25°C, most preferably at room temperature.

- The preferred reaction time is between 20 and 180 min, more preferably 50 and 130 min, most preferred is a reaction time between 80 and 100 min.
- In the case of benzyltrimethylammonium dichloriodite reaction temperatures higher than 25°C, preferably higher than 50°C and reaction times between 1 and 5h, more preferably 2 and 4 are preferred.
- After the reaction, water is added or in the case of benzyltrimethylammonium dichloriodite an aqueous solution of a reducing agent (such as for example sulfite, bisulfite, metabisulfite salts), the product is obtained by filtration and recrystallised from a suitable solvent (e.g. ethyl acetate, i-propyl ether, methyl-t-butyl ether, acetonitrile, ethanol, i-propanol).

USED TERMS AND DEFINITIONS

- The term "optionally substituted" refers to nucleus with one or more suitable substituents chosen among: halogen, C₁₋₄-alkyl, C₁₋₄-alkoxy, (fused)aryl rings. Preferred substituents are F, Cl, Br, I, Me, Et, OMe, OEt, O-Pr.

As used herein "salts" refers to derivatives of the disclosed compounds wherein the parent compound is modified by making acid or base salts thereof. Examples of salts include, but are not limited to, mineral or organic acid salts of basic residues such as amines; alkali or organic salts of acidic residues such as carboxylic acids; and the like. The "pharmaceutically acceptable salts" include the conventional non-toxic salts or the quaternary ammonium salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. For example, such conventional non-toxic salts include those derived from inorganic acids such as hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric, nitric and the like; and the salts prepared from organic acids such as acetic, propionic, succinic, glycolic, stearic, lactic, malic, tartaric, citric, ascorbic, pantoic, maleic, hydroxymaleic, phenylacetic, glutamic, benzoic, salicylic, sulfanilic, 2-acetoxybenzoic, fumaric, toluenesulfonic, methanesulfonic, ethane disulfonic, oxalic, isothionic, and the like. The salts of the present invention can be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts can be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic

solvent, or in a mixture of the two; generally, non-aqueous media like ether, ethyl acetate, ethanol, i-propanol, or acetonitrile are preferred.

The term "-C₁₋₆-alkyl" as used herein, either alone or in combination with another
5 substituent, means acyclic, straight or branched chain alkyl substituents containing from one to six carbon atoms and includes, for example, methyl, ethyl, propyl, butyl, pentyl, hexyl, 1-methylethyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl. Possibly conventional abbreviations for these groups are used e.g. Me, Et, ⁱPr or i-Pr.

10 The term "-C₁₋₆-alkylene" as used herein means a divalent alkyl substituent derived by the removal of one hydrogen atom from each end of a saturated straight or branched chain aliphatic hydrocarbon containing from one to six carbon atoms and includes, for example, -CH₂-, -CH₂CH₂-, -CH₂CH₂CH₂-, -CH₂(CH₂)₂CH₂-, -CH₂(CH₂)₃CH₂- or -CH₂(CH₂)₄CH₂-.

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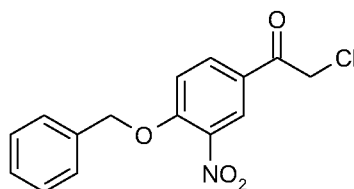
EXAMPLES

In the following is a process described suitable for the manufacturing of compounds like:

- 20 **1a:** N-(5-{2-[1,1-Dimethyl-3-(2-oxo-4,4-dipropyl-4H-benzo[d][1,3]oxazin-1-yl)-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide
- 1b:** N-[5-(2-{1,1-Dimethyl-3-[spiro(cyclohexan-1,4'-2H-3',1'-benzoxazin)-2'-oxo-1-yl]-propylamino}-1-hydroxy-ethyl)-2-hydroxy-phenyl]-methanesulfonamide
- 1c:** N-[5-(2-{1,1-Dimethyl-3-[spiro(cyclopropyl-1,4'-2H-3',1'-benzoxazin)-2'-oxo-1-yl]-propylamino}-1-hydroxy-ethyl)-2-hydroxy-phenyl]-methanesulfonamide
- 25 **1d:** N-(5-{2-[3-(4,4-Diethyl-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide
- 1e:** N-(5-{2-[3-(4,4-Diethyl-6-fluoro-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide
- 1f:** N-(5-{2-[3-(4,4-Diethyl-7-fluoro-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide
- 30 **1g:** N-(5-{2-[3-(4,4-Diethyl-8-methoxy-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide
- 1h:** N-(5-{2-[3-(4,4-Diethyl-6-methoxy-2-oxo-4H-benzo[d][1,3]oxazin-1-yl)-1,1-dimethyl-propylamino]-1-hydroxy-ethyl}-2-hydroxy-phenyl)-methanesulfonamide

Therefore R¹, R² and R³ have the meaning corresponding to those groups in examples **1a-1h**. For example if one would like to manufacture compound **1a** according to the following examples R¹ and R² would have the meaning of a propyl group and R³ would be H.

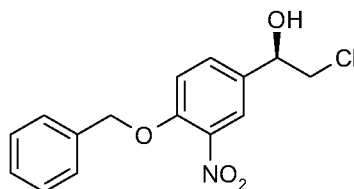
1-(4-BENZYLOXY-3-NITRO-PHENYL)-2-CHLORO-ETHANONE



210 g (0.77 mol) of 1-(4-benzyloxy-3-nitro-phenyl)-ethanone were suspended in dioxane (1.5 L) and treated over 1.5 hours with 68.3 mL (0.84 mol) of sulfuryl chloride. Water (2.4 L) was then slowly added under stirring. The precipitated solid was recovered by filtration, washed with water and crystallized from ethyl acetate. Yield: 161.0 g (68%); Mass Spectroscopy: [M+H]⁺ = 306; M.p. = 141 °C.

Alternatively, the title compound can be obtained as follows: 1.36 Kg (5.01 mol) of 1-(4-benzyloxy-3-nitro-phenyl)-ethanone and 2.40 Kg of benzyltrimethylammonium chloride (12.53 mol) were dissolved in acetic acid (5.43 L) and acetonitrile (8.2 L) at 65°C and treated with a 46% aqueous solution of iodine monochloride (4.42 Kg, 12.53 mol). The reaction mixture was stirred 2.5 hours at 65°C, then cooled to 5°C and treated with water (20.4 L) and 5% aqueous sodium bisulfite (24.1 L). The precipitated solid was recovered by filtration, washed with water and crystallized from ethyl acetate. Yield: 1.21 Kg (80.3%). [M+H]⁺ = 306.

(R)-1-(4-BENZYLOXY-3-NITRO-PHENYL)-2-CHLORO-ETHANOL



(EXAMPLE A):

5 4.5 g (30.0 mmol) of (1S,2S)-(+)-cis-1-amino-2-indanol were dissolved in dry THF (110 mL). The solution was cooled to 3°C and a solution of 51.4 g (0.31 mol) of boran-N,N-diethylaniline complex in dry THF (0.2 L) was added. After 20 minutes a solution of 183.4 g (0.60 mol) of 1-(4-benzyloxy-3-nitro-phenyl)-2-chloro-ethanone in dry THF (2.2 L) was slowly added keeping the temperature below 23°C. After one hour at this temperature the
10 reaction mixture was slowly treated with MeOH (0.22 L) and concentrated. The residual was treated with *n*-heptane (0.6 L) and HCl 1 mol/L (50 mL) and the mixture cooled to 2°C. The precipitated product was collected by filtration and crystallized from *i*-propyl alcohol (0.66 L). Yield: 154 g (83.4%); Mass Spectroscopy: $[M+H]^+ = 308$; M.p. = 94 °C; e.e. 99.6%:

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(EXAMPLE B)

A 1 M solution of (R)-2-methyl-CBS-oxazaborolidine in toluene (0.16 mL, 0.16 mmol) and 3.0 mL (16.87 mmol) of boran-N,N-diethylaniline complex were dissolved at room temperature in 7 mL of THF (water content < 0.02%). After 15 minutes the solution was
20 set to +35°C and a solution of 5.0 g (16.36 mmol) of 1-(4-benzyloxy-3-nitro-phenyl)-2-chloro-ethanone in 50 mL of THF (water content < 0.02%) was added over 5 hours at this temperature. At the end of the addition the solution was slowly treated with MeOH (10 mL) and eventually concentrated. The residual was dissolved in methyl-*t*-butylether (50 mL) and the solution washed with HCl 1 mol/L (17 mL) and brine (10 mL). The organic phase
25 was separated, dried over Na₂SO₄ and evaporated. The resulting product was crystallized from *i*-propyl alcohol (17 mL). Yield: 3.6 g (72.0%); Mass Spectroscopy: $[M+H]^+ = 308$; e.e. 100%

(EXAMPLE C)

A 1 M solution of (R)-2-methyl-CBS-oxazaborolidine in toluene (0.017 mL, 0.017 mmol) and 3.0 mL (16.87 mmol) of boran-N,N-diethylaniline complex were dissolved at room temperature in 7 mL of THF (water content < 0.02%). The solution was stirred 15 min at this temperature and set to 25°C. A solution of 5.0 g (16.36 mmol) of 1-(4-benzyloxy-3-nitro-phenyl)-2-chloro-ethanone in 50 mL of THF (water content < 0.02%) was added over 5 hours at this temperature. At the end of the addition the solution was stirred one additional hour at this temperature and then slowly treated with MeOH (10 mL) and eventually concentrated. The residual was dissolved in methyl-*t*-butylether (50 mL) and the solution washed with HCl 1 mol/L (17 mL) and brine (10 mL). The organic phase was separated, dried over Na₂SO₄ and evaporated. The resulting product was crystallized from i-propyl alcohol (17 mL). Yield: 3.6 g (71.5%); Mass Spectroscopy: [M+H]⁺ = 308; e.e. 99.7%

15 (EXAMPLE D)

(R)-(-)-2-amino-2-phenylethanol, 112 mg (0.82 mmol) and 3.0 mL (16.87 mmol) of boran-N,N-diethylaniline complex were dissolved at room temperature in 7 mL of THF (water content < 0.02%). The solution was stirred 1 hour at this temperature and set to 35°C. A solution of 5.0 g (16.36 mmol) of 1-(4-benzyloxy-3-nitro-phenyl)-2-chloro-ethanone in 50 mL of THF (water content < 0.02%) was added over 6 hours at this temperature. At the end of the addition the solution was slowly treated with MeOH (10 mL) and eventually concentrated. The residual was dissolved in methyl-*t*-butylether (50 mL) and the solution washed with HCl 1 mol/L (17 mL) and brine (10 mL). The organic phase was separated, dried over Na₂SO₄ and evaporated. The resulting product was crystallized from i-propyl alcohol (17 mL). Yield: 3.5 g (70.0%); Mass Spectroscopy: [M+H]⁺ = 308; e.e. 97.6%.

25 (EXAMPLE E)

(1S,2R)-(+)-2-amino-1,2-diphenylethanol, 174 mg (0.82 mmol) and 3.0 mL (16.87 mmol) of boran-N,N-diethylaniline complex were sequentially dissolved at room temperature in 7 mL of THF (water content < 0.02%). The solution was stirred 45 min at this temperature and set to 35°C. A solution of 5.0 g (16.36 mmol) of 1-(4-benzyloxy-3-nitro-phenyl)-2-chloro-ethanone in 50 mL of THF (water content < 0.02%) was added over 6 hours at this temperature. At the end of the addition the solution was slowly treated with MeOH (10 mL) and eventually concentrated. The residual was dissolved in methyl-*t*-butylether (50 mL)

and the solution washed with HCl 1 mol/L (17 mL) and brine (10 mL). The organic phase was separated, dried over Na₂SO₄ and evaporated. The resulting product was crystallized from i-propyl alcohol (17 mL). Yield: 3.7 g (74.0%); Mass Spectroscopy: [M+H]⁺ = 308; e.e. 99.2%.

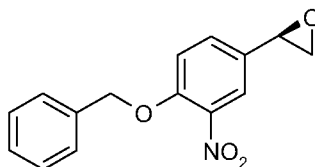
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(EXAMPLE F)

(R)-(+)-2-(diphenylhydroxymethyl)-pyrrolidin, 42 mg (0.17 mmol) and 3.0 mL (16.87 mmol) of boran-N,N-diethylaniline complex were dissolved at room temperature in 7 mL of THF (water content < 0.02%). The solution was stirred 16 hour at this temperature then set to 25°C. A solution of 5.0 g (16.36 mmol) of 1-(4-benzyloxy-3-nitro-phenyl)-2-chloro-ethanone in 50 mL of THF (water content < 0.02%) was added over 5 hours at this temperature. At the end of the addition the solution was slowly treated with MeOH (10 mL) and eventually concentrated. The residual was dissolved in methyl-*t*-butylether (50 mL) and the solution washed with HCl 1 mol/L (17 mL) and brine (17 mL). The organic phase was separated, dried over Na₂SO₄ and evaporated. The resulting product was crystallized from i-propyl alcohol (17 mL). Yield: 3.7 g (74.0%); Mass Spectroscopy: [M+H]⁺ = 308; e.e. 100%.

(EXAMPLE G)

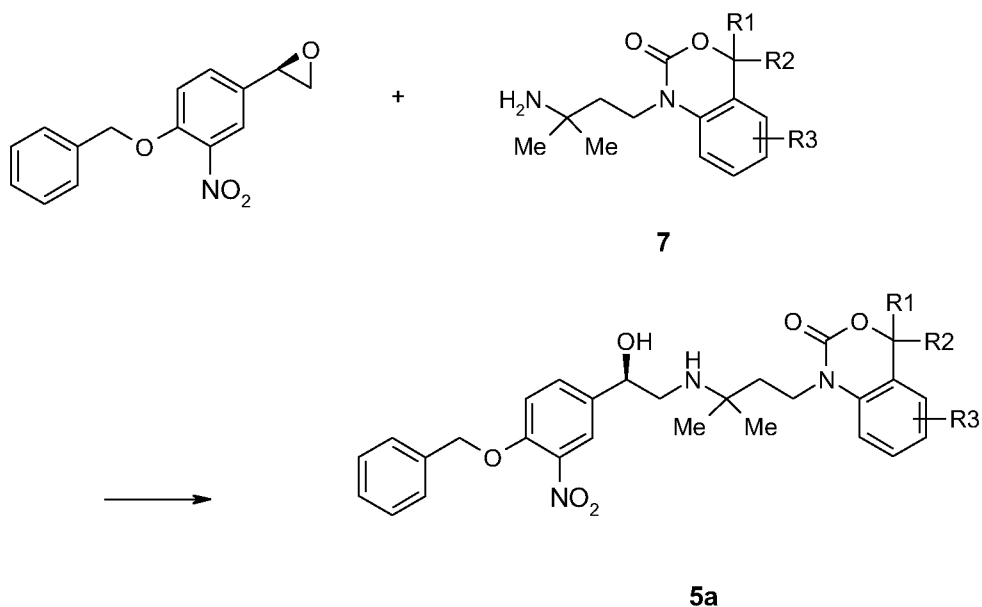
(1S,2S)-(+)-cis-1-amino-2-indanol, 76 mg (0.51 mmol) and trimethyl borate (0.070 mL, 0.63 mmol) were sequentially dissolved at 25°C in 7 mL of THF (water content < 0.02%). After 1 hour 3.0 mL (16.87 mmol) of boran-N,N-diethylaniline complex were added. The solution was stirred 15 min at this temperature then set to +35°C and a solution of 5.0 g (16.36 mmol) of 1-(4-benzyloxy-3-nitro-phenyl)-2-chloro-ethanone in 50 mL of THF (water content < 0.02%) was added over 5 hours at this temperature. At the end of the addition the solution was slowly treated with MeOH (10 mL) and eventually concentrated. The residual was dissolved in methyl-*t*-butylether (50 mL) and the solution washed with HCl 1 mol/L (17 mL) and brine (17 mL). The organic phase was separated, dried over Na₂SO₄ and evaporated. The resulting product was crystallized from i-propyl alcohol (17 mL). Yield: 3.7 g (74.0%); Mass Spectroscopy: [M+H]⁺ = 308; e.e. 99.6%.

(R)-2-(4-benzyloxy-3-nitro-phenyl)-oxirane

15 151.8 g (0.49 mol) of 1-(4-benzyloxy-3-nitro-phenyl)-2-chloro-ethanol were dissolved in THF (0.75 L) and treated dropwise with NaOH 4 mol/L 182 mL (0.73 mol). After one hour, AcOH (30 mL) was added followed by water (2.5 L). The mixture was cooled and the precipitated product was recovered by filtration and dried under vacuum at 65°C. Yield: 133.0 g (99.3%); Mass Spectroscopy: $[M+H]^+ = 272$; M.p. = 66 °C; e.e.=99.5%

10

RING OPENING OF 2-(4-benzyloxy-3-nitro-phenyl)-oxirane BY NEOPENTYL, BENZOXAZINONE BASED AMINES



15 A solution of 2-(4-benzyloxy-3-nitro-phenyl)-oxirane (1.58 Kg, 5.82 mol) in tetrahydrofuran (4.16 L) and n-BuOH (4.00 L) was added to a refluxing solution of the amine **7** (6.12 mol) in n-BuOH (19.50 L) over 5 hours with continuous removal of solvent. At the end of the addition a total of 19 L of solvent were collected. The solution was refluxed for additional 2 hours, then cooled to 94°C and treated with a solution of oxalic acid (0.525 Kg, 5.83 mol)

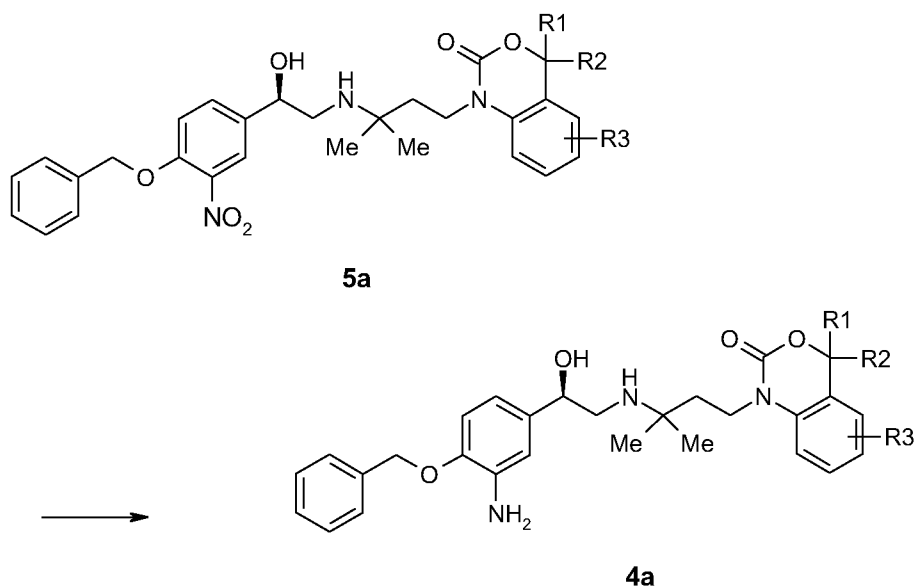
in EtOH 90% (8.90 L). Upon cooling to room temperature the oxalate of **5a** crystallized from the reaction mixture. This was recovered by filtration, washed with EtOH/TBME (2 x 1 L) and dried under vacuum at 60°C. Yield: (75.0%).

- 5 Alternatively, compounds **5a** could be prepared as follows: The chloridrate of the amine **7** (148.0 mmol) was added to a solution of potassium tert-butyrate (17.6 g, 154.0 mmol) in n-BuOH (0.5 L). After one hour the insolubles were filtered off and washed with n-BuOH (0.06L) and the resulting clear solution treated with 2-(4-benzyloxy-3-nitro-phenyl)-oxirane (40 g, 140.0 mmol). The reaction mixture was refluxed for 6 hours and then treated with a
10 solution of oxalic acid (12.7 g, 141.1 mmol) in EtOH 90% (0.2 L). Upon cooling to room temperature the oxalate of **5a** crystallized from the reaction mixture. This was recovered by filtration, washed with EtOH/TBME (2 x 100 mL) and dried under vacuum at 45°C. Yield: (64.6%).

- 15 Compounds **5a** as free bases could be recovered after basic work up and extraction with the appropriate solvent as follows:

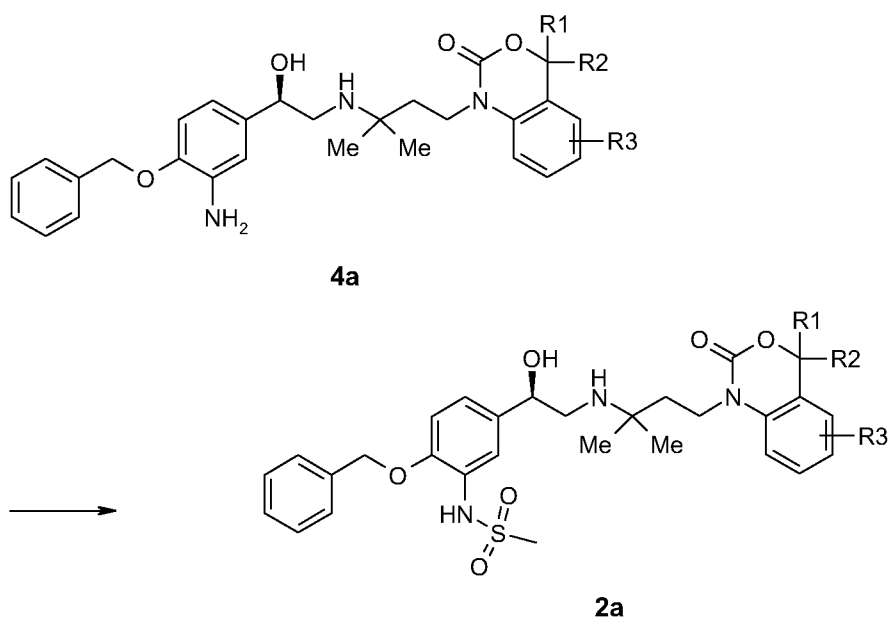
The oxalate of compound **5a** (80.0 mmol) was suspended in water (0.3 L) and methyl-t-butylether (0.25 L), 32% aqueous ammonia was added (30 mL) and the organic phase
20 was separated. The aqueous phase was extracted with methyl-t-butylether (2 x 0.1 L) and the combined extracts were washed with water (0.1 L) and brine (0.1 L) and dried (Na₂SO₄). Evaporation of the solvent gave compound **5a** as the free base.

REDUCTION OF THE NITRO FUNCTION



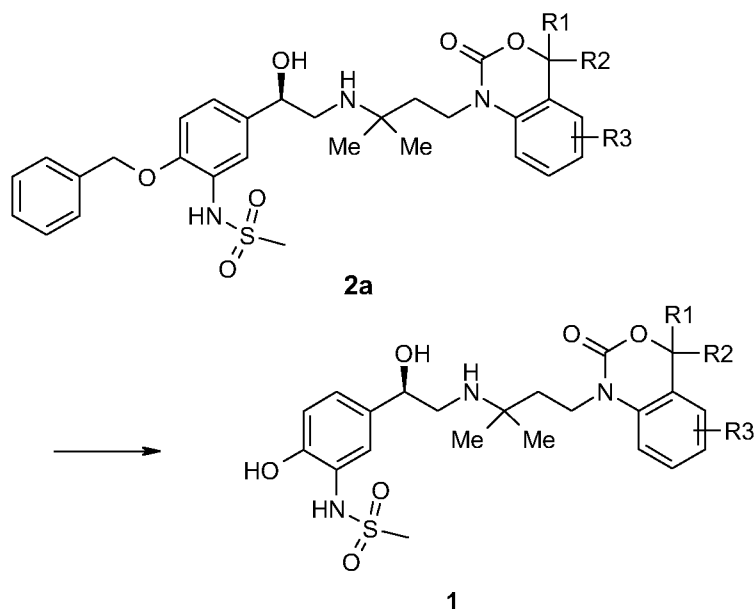
The nitro compound **5a** (free base, 13.0 mmol) was dissolved in THF (70mL)/toluene
5 (70mL) and hydrogenated at 50 psi in the presence of PtO_2 (3.5 mmol). After 1.5 hours
the catalyst was filtered off, the solvents were removed under reduced pressure to afford
the anilino compound **4a**. Yield: (96.0%).

10 MESYLATION OF THE ANILINO FUNCTION



A solution of compound **4a** (148.5 mmol) in THF (0.8 L) was treated with pyridine (24.0 mL, 298.0 mmol) followed by neat methansulfonylchloride (12.0 mL, 155.0 mmol). After 16 hours the reaction mixture was concentrated under reduced pressure and the residual material partitioned between ethyl acetate (1 L) and 1%aq NaHCO₃ (0.6 L). The organic phase was washed sequentially with water (0.5 L) and brine (0.1 L). The organic phase was dried over sodium sulfate and the solvent evaporated to afford crude sulfonamide **2a**. Yield: (93.1%).

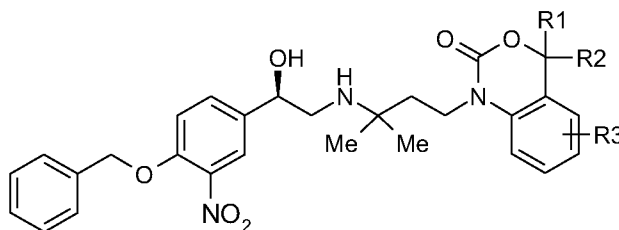
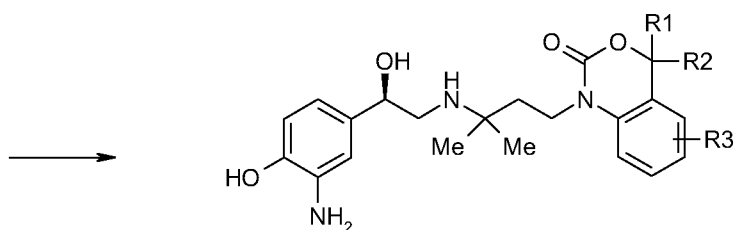
REMOVAL OF BENZYL PROTECTING GROUP



Crude sulfonamide **2a** (83.25 mmol) obtained as described above was dissolved in a mixture of MeOH (0.5 L) and 37%aq HCl (7.9 mL) and hydrogenated at 50 psi in the presence of Pd/C 10% (5.0 g). After 2 hours the catalyst was filtered off, the solvent was removed under reduced pressure and the residual crystallized from acetonitrile (580 mL) and water (1 mL) to give the hydrochloride of compound **1**. Yield: (36.2%).

Alternatively, is possible to prepare compounds **1** according to the following procedure:

REDUCTION OF THE NITRO FUNCTION AND REMOVAL OF THE BENZYL PROTECTING GROUP

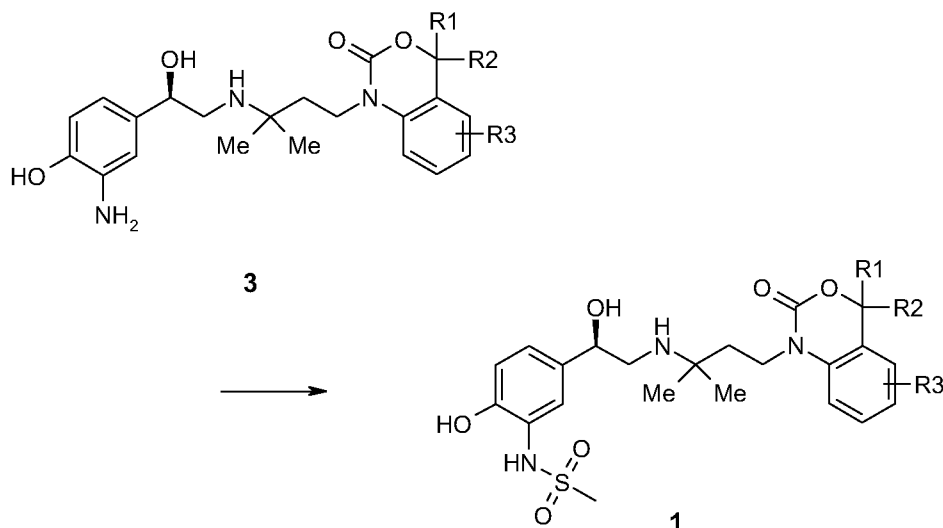
**5a****3**

5 The oxalate of nitro compound **5a** (1.11 mol) was suspended in MeOH (7.24 L) and hydrogenated at 50 psi in the presence of Pd/C 10% (36.2 g). After 2.5 hours the catalyst was filtered off and the solvent was removed under reduced pressure and the residue triturated in hot EtOAc (4.0 L) to give the oxalate of compound **3**. Yield: (99.1%).

10 If desired, compounds **3** as free bases could be recovered after basic work up and extraction with the appropriate solvent as follows:

The oxalate of compound **3** (1.69 mol) was dissolved in water (4.0 L) under an argon atmosphere. The solution was partitioned between cold water (7.2 L) and ethyl acetate (7.2 L) and 32% aqueous ammonia was added (0.61 L). The organic phase was
 15 separated, washed with water (5.4 L) and brine (0.75 L) and filtered over Na₂SO₄ (1.6 Kg) and charcoal (0.2 Kg). Evaporation of the solvent gave compound **3** as the free base.

20 MESYLATION OF THE ANILINO FUNCTION



The oxalate of compound **3** (2.07 mol) was dissolved in a mixture of acetonitrile (7.70 L) and tetrahydrofuran (7.70 L) and treated with pyridine (0.54 L, 6.62 mol). The reaction mixture was treated over one hour with a solution of methanesulfonyl chloride (0.32 L, 4.14 mol) in acetonitrile (1.65 L) keeping the temperature between 25 and 33°C. After a total time of 3 hours MeOH (0.2 L) was added and the reaction mixture concentrated. Water (5.5 L) and acetonitrile (0.55 L) were added and the pH set to 7.3 with saturated aqueous NaHCO₃ (10.0 L) while the product crystallized. The precipitated solid was collected by filtration, washed with water (2 x 1.5 L) and TBME (3 x 1.0 L) and dried at 60°C to give **1** as the free base. This material was transformed into the corresponding hydrochloride upon crystallization from a mixture of acetonitrile (10.7 L) and 37% aq HCl (165.6 mL). Yield: 75.7%.

15

Alternatively, compounds **1** can be obtained from the free base of compound **3** as follows: The free base of compound **3** (1.69 mol) was dissolved in a mixture of tetrahydrofuran (7.5 L) and acetonitrile (7.5 L) at 50°C. The solution was cooled to 5°C and conc. hydrochloric acid (139 mL, 1.69 mol) was added followed by pyridine (287 mL, 3.55 mol). At 3°C a solution of methanesulfonyl chloride (131 mL, 1.69 mol) in acetonitrile (0.75 L) was added over 20 min. After additional 2 hours MeOH (205 mL) was added, the temperature was set to 30°C and the reaction mixture concentrated. Water (4.25 L) and acetonitrile (1.5 L) were then added to the residue followed by saturated aqueous NaHCO₃ (2.3 L). Some crystals of **1** were added followed by additional saturated aqueous

20

NaHCO₃ (2.3 L) while the product crystallized. The precipitated solid was recovered by filtration, washed with water (2 x 1.7 L) and TBME (2 x 2.5 L) and dried at 60°C to give **1** as the free base. Yield: 87.4%.

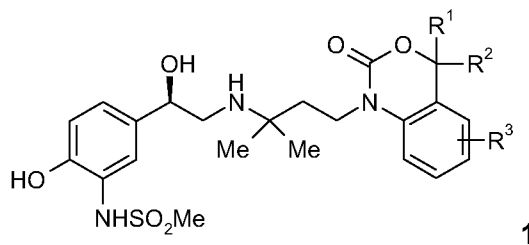
- 5 This material was transformed into the corresponding hydrochloride by suspending it in acetonitrile (9.3 L) and pyridine (11.8 g, 0.147 mol), and treating the mixture with conc. hydrochloric acid (120 mL, 1.45 mol) in acetonitrile (1.22 L). The mixture was heated to 67°C and the obtained solution filtered. Upon cooling the hydrochloride of **1** crystallized. This was recovered by filtration, washed with acetonitrile (2 x 1.6 L) and methyl-t-butyl
10 ether (2 x 1.6 L) and dried at 50°C. Yield: 77.3%.

Alternatively, compounds **1** can be obtained from the free base of compound **5a** as follows: The free base of compound **5a** (67.1 mmol) was dissolved in tetrahydrofuran (0.3
15 L), conc. hydrochloric acid (5.6 mL, 67.1 mmol) was added and the solution hydrogenated at 50 psi in the presence of Pd/C 10% (3.8 g). After 2.5 hours the catalyst was filtered off and the solution diluted with acetonitrile (0.3 L). The temperature was set to 30°C and pyridine (12.5 mL, 154.1 mmol) was added followed by addition of a solution of methanesulfonyl chloride (5.2 mL, 67.0 mol) in acetonitrile (20 mL) over 20 min. After
20 additional 45 min MeOH (8 mL) was added and the reaction mixture concentrated. Water (170 mL) and acetonitrile (60 L) were added followed by saturated aqueous NaHCO₃ (100 mL). Some crystals of **1** were added followed by additional saturated aqueous NaHCO₃ (120 mL) while the product crystallized. The precipitated solid was recovered by filtration, washed with water (2 x 80 mL) and TBME (2 x 80 mL). If desired, compound **1** could be
25 further purified by suspending it in hot ethyl acetate (350 mL)/isopropanol (50 mL) mixtures. The suspension was cooled and the solid was collected by filtration, washed with ethyl acetate (2 x 50 mL) and dried at 50°C to give **1** as the free base. Yield: 71.5%. The free base of **1** could be transformed into the corresponding hydrochloride as described above.

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WHAT WE CLAIM

1. Process for manufacturing of a compound of formula 1

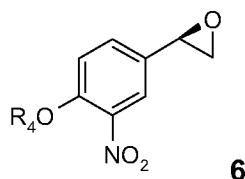


5 or a salt thereof, wherein

R^1 and R^2 each independently mean H, halogen or C_{1-4} -alkyl or R^1 and R^2 are together have the meaning of C_{1-6} -alkylene; and

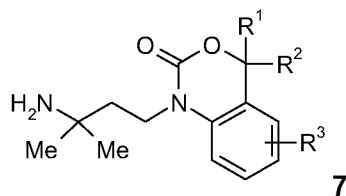
R^3 denotes H, halogen, OH, C_{1-4} -alkyl or O- C_{1-4} -alkyl;

10 characterized in that, a compound of formula 6

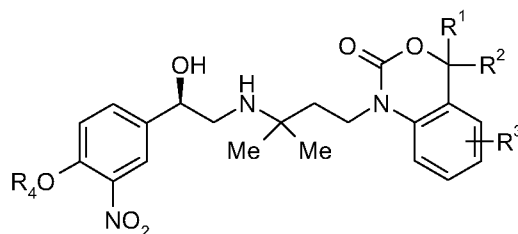


wherein R^4 is selected from the group consisting of benzyl, diphenylmethyl or trityl, each optionally substituted at if available an aryl group or an aliphatic carbon atom, is reacted

15 with a compound of formula 7



or a salt thereof, wherein R^1 , R^2 and R^3 have the above given meaning, to a compound of formula 5, or a salt thereof.

**5**

whereas compound of formula **1** is obtained by reduction of the nitro group to an amine group, mesylation of this amine group and cleavage of the protecting group during the
 5 reduction step or after the mesylation step.

2. Process according to claim 1, wherein

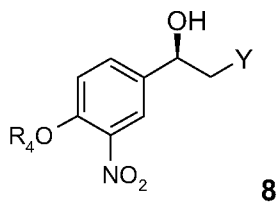
- R¹ and R²** each independently mean H, F, Cl, methyl, ethyl, propyl, butyl or **R¹ and R²**
 10 are together have the meaning of ethylene, propylene, butylene or
 pentylene;
R³ denotes H, F, Cl, OH, methyl, ethyl, methoxy or ethoxy; and
R⁴ is selected form the group consisting of benzyl or diphenylmethyl, each
 optionally substituted at if available an aryl group or an aliphatic carbon
 15 atom with a group selected form F, Cl, Br, Me, Et, OMe, OEt or O-ⁱPr.

3. Process according to claim 1, wherein

- R¹ and R²** each independently mean H, methyl, ethyl, propyl or **R¹ and R²** are together
 20 have the meaning of ethylene, propylene, butylene or pentylene;
R³ denotes H, F, OH, methyl or methoxy; and
R⁴ denotes benzyl optionally substituted at the aryl group or the aliphatic
 carbon atom with a group selected form F, Cl, Br, Me, Et, OMe, OEt or O-
ⁱPr.

25

4. Process according to one of the claims 1 to 3, wherein the compound of formula **6 is
 obtained by reacting a compound of formula **8**.**



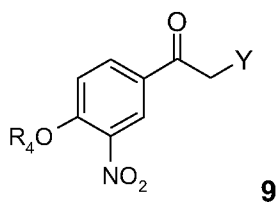
wherein R^4 is defined as in claim 1 to 3 and Y is chlorine or a sulfonyloxy based leaving group.

5

5. Process according to claim 1, wherein R^4 is defined as in claim 1 to 3 and Y is chlorine

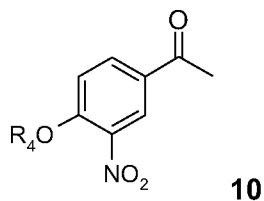
10

6. Process according to claims 4 or 5, wherein the compound of formula **8** is obtained by reacting a compound of formula **9**.



15 wherein R^4 is defined as in claim 1 to 3 and Y as in claim 4 and 5

7. Process according to claim 6, wherein the compound of formula **9** is obtained by reacting a compound of formula **10**.



20

wherein R^4 is defined as in claim 1 to 3.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/068157

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D265/18

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

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P, A	WO 2005/111005 A (BOEHRINGER INGELHEIM INT [DE]; BOEHRINGER INGELHEIM PHARMA [DE]; KONET) 24 November 2005 (2005-11-24) page 10, line 20 - page 13, line 5; compounds 1-7	1-7
Y	WO 2004/087142 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; FAIRHURST ROBIN ALEC [GB]) 14 October 2004 (2004-10-14) page 12, paragraph 2 - page 14, paragraph 4 ----- -/--	1-3

☒ 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

29 March 2007

Date of mailing of the international search report

16/04/2007

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/068157

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
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Y	HAMADA T ET AL: "Practical Synthesis of Optically Active Styrene Oxides via Reductive Transformation of 2-Chloroacetophenones with Chiral Rhodium Catalysts" ORGANIC LETTERS, AMERICAN CHEMICAL SOCIETY, US, vol. 4, no. 24, 2002, pages 4373-4376, XP002337267 ISSN: 1523-7060 the whole document -----	4-6
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Y	KOSER G F ET AL: "ONE-STEP ALPHA-TOSYLOXYLATION OF KETONES WITH O-HYDROXY(TOSYLOXY)IODOBENZENE" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY, EASTON, US, vol. 47, no. 12, 4 June 1982 (1982-06-04), pages 2487-2489, XP000653641 ISSN: 0022-3263 cited in the application the whole document -----	7

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INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2006/068157

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	ELIAS J. COREY ET AL.: "Reduction of Carbonyl Compounds with Chiral Oxazaborolidine Catalysts: A New Paradigm for Enantioselective Catalysis and a powerful New synthetic Method" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION., vol. 37, no. 15, 17 August 1998 (1998-08-17), pages 1986-2012, XP002427347 DEVCH VERLAG, WEINHEIM. cited in the application page 1989; table 1	6

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International application No

PCT/EP2006/068157

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