(12) STANDARD PATENT (11) Application No. **AU 2006281449 B2**
(19) AUSTRALIAN PATENT OFFICE

(54) Title
Method for producing betamimetics

(51) International Patent Classification(s)
C07D 265/36 (2006.01) ***C07C 233/13*** (2006.01)
C07C 205/45 (2006.01) ***C07C 233/18*** (2006.01)
C07C 211/45 (2006.01)

(21) Application No: **2006281449** (22) Date of Filing: **2006.08.10**

(87) WIPO No: **WO07/020227**

(30) Priority Data

(31) Number	(32) Date	(33) Country
05107470.6	**2005.08.15**	**EP**

(43) Publication Date: **2007.02.22**
(44) Accepted Journal Date: **2013.01.31**

(71) Applicant(s)
Boehringer Ingelheim International GmbH

(72) Inventor(s)
Duran, Adil;Rall, Werner;Ries, Uwe;Leuter, Zeno A.;Krueger, Thomas;Schnaubelt, Juergen;Soyka, Rainer

(74) Agent / Attorney
Davies Collison Cave, Level 15 1 Nicholson Street, MELBOURNE, VIC, 3000

(56) Related Art
WO 2004/087142
TIMBERLAKE, J.W. et al., Journal of Organic Chemistry, 1981, vol. 46, pages 2082-2089
BABIN, D. et al., Tetrahedron, 1981, vol. 37, pages 325-332
DE 1144713
YASUDA, M. et al., Journal of Organic Chemistry, 2003, vol. 68, pages 7618-7624
BUU-HOI, N.P. et al., Journal of Organic Chemistry, 1958, vol. 23, pages 42-45
US 4460581
AU 2005243469

(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
22. Februar 2007 (22.02.2007)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2007/020227 A1

(51) Internationale Patentklassifikation:
C07D 265/36 (2006.01) *C07C 233/18* (2006.01)
C07C 205/45 (2006.01) *C07C 233/13* (2006.01)
C07C 211/45 (2006.01)

(21) Internationales Aktenzeichen: PCT/EP2006/065217

(22) Internationales Anmeldedatum:
10. August 2006 (10.08.2006)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
05107470.6 15. August 2005 (15.08.2005) EP

(71) Anmelder *(für alle Bestimmungsstaaten mit Ausnahme von DE, US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Str. 173, 55216 Ingelheim am Rhein (DE).

(71) Anmelder *(nur für DE)*: **BOEHRINGER INGELHEIM PHARMA GMBH & CO. KG** [DE/DE]; Binger Str. 173, 55216 Ingelheim am Rhein (DE).

(72) Erfinder; und
(75) Erfinder/Anmelder *(nur für US)*: **KRUEGER, Thomas** [DE/DE]; Blumenstrasse 16, 88353 Kissleg (DE). **RIES, Uwe** [DE/DE]; Tannenstr. 31, 88400 Biberach (DE). **SCHNAUBELT, Juergen** [DE/DE]; Ulmer-Steigesch 7, 88447 Oberhoefen/Warthausen (DE). **RALL, Werner** [DE/DE]; Beethovenstr. 33, 88441 Mittelbiberach (DE). **LEUTER, Zeno A.** [DE/DE]; Johann v. Schnitzer Str. 22, 88250 Weingarten (DE). **DURAN, Adil** [DE/DE]; Kastanienweg 8, 88400 Rissegg (DE). **SOYKA, Rainer** [DE/DE]; Geschwister-Scholl-Str. 43, 88400 Biberach (DE).

(74) Anwälte: HAMMANN, Heinz usw.; Binger Str. 173, 55216 Ingelheim am Rhein (DE).

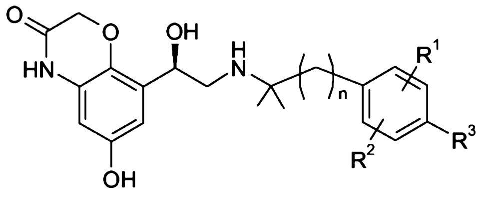
(81) Bestimmungsstaaten *(soweit nicht anders angegeben, für jede verfügbare nationale Schutzrechtsart)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(soweit nicht anders angegeben, für jede verfügbare regionale Schutzrechtsart)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *mit internationalem Recherchenbericht*

(54) Title: METHOD FOR PRODUCING BETAMIMETICS

(54) Bezeichnung: VERFAHREN ZUR HERSTELLUNG VON BETAMIMETIKA



(1)

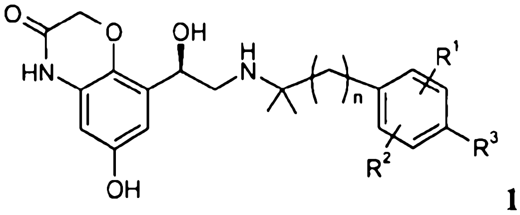
(57) Abstract: The invention relates to a method for producing betamimetics of formula (I), in which n represents 1 or 2; R^1 represents hydrogen, halogen, C_{1-4} alkyl or O-C_{1-4} alkyl; R^2 represents hydrogen, halogen, C_{1-4} alkyl or O-C_{1-4} alkyl, and; R^3 represents hydrogen, C_{1-4} alkyl, OH, halogen, O-C_{1-4} alkyl, O-C_{1-4} alkylene-COOH, O-C_{1-4} alkylene-COO-C_{1-4}-alkyl.

(57) Zusammenfassung: Die vorliegende Erfindung betrifft ein Verfahren zur Herstellung von Betamimetika der Formel (1), worin n 1 oder 2; R^1 Wasserstoff, Halogen, C_{1-4}-Alkyl oder O-C_{1-4}-Alkyl; R^2 Wasserstoff, Halogen, C_{1-4}-Alkyl oder O-C_{1-4}-Alkyl; R^3 Wasserstoff, C_{1-4}-Alkyl, OH, Halogen, O-C_{1-4}-Alkyl, O-C_{1-4}-Alkylen-COOH, O-C_{1-4}-Alkylen-COO-C_{1-4}-Alkyl; bedeuten.

WO 2007/020227 A1

PROCESS FOR THE MANUFACTURING OF BETAMIMETICS

The present invention relates to a process for preparing betamimetics of formula **1**,



1

wherein

n denotes 1 or 2;

R^1 denotes hydrogen, halogen, C_{1-4}-alkyl or O-C_{1-4}-alkyl;

R^2 denotes hydrogen, halogen, C_{1-4}-alkyl or O-C_{1-4}-alkyl;

R^3 denotes hydrogen, C_{1-4}-alkyl, OH, halogen, O-C_{1-4}-alkyl, O-C_{1-4}-alkylene-COOH, O-C_{1-4}-alkylene-COO-C_{1-4}-alkyl.

BACKGROUND TO THE INVENTION

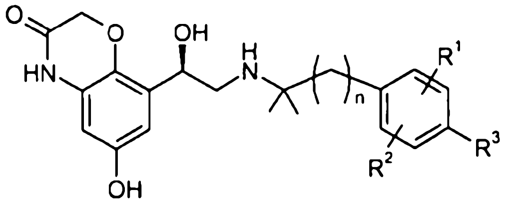
Betamimetics (ß-adrenergic substances) are known from the prior art. For example reference may be made in this respect to the disclosure of US 4,460,581, which proposes betamimetics for the treatment of a range of diseases.

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. 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 regularly taking the drug at certain times of the day.

The aim of the present invention is therefore to provide a method of producing betamimetics which on the one hand confer a therapeutic benefit in the treatment of COPD or asthma and are also 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 used to prepare a drug for administration once a day for treating COPD or asthma. A further objective of the invention, apart from those mentioned above, is to prepare betamimetics which are not only exceptionally potent but are also characterised by a high degree of selectivity with respect to the β_2-adrenoceptor.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for preparing a compound of formula **1**,



1

wherein

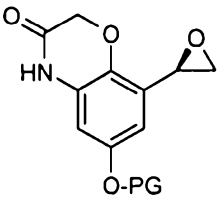
n denotes 1 or 2;

R^1 denotes hydrogen, halogen, C_{1-4}-alkyl or O-C_{1-4}-alkyl;

R^2 denotes hydrogen, halogen, C_{1-4}-alkyl or O-C_{1-4}-alkyl;

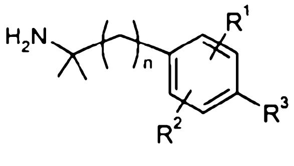
R^3 denotes hydrogen, C_{1-4}-alkyl, OH, halogen, O-C_{1-4}-alkyl, O-C_{1-4}-alkylene-COOH, O-C_{1-4}-alkylene-COO-C_{1-4}-alkyl,

characterised in that a compound of formula **1a**,



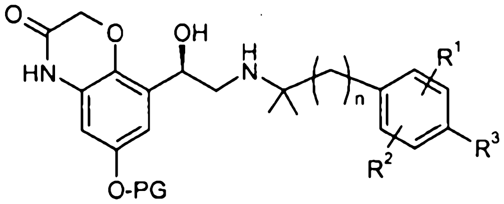
1a

wherein PG represents a protective group, is reacted with a compound of formula **1b**,



1b

wherein R^1, R^2, R^3 and n have the meaning given above, in an organic solvent to yield a compound of formula **1c**,



1c

wherein R^1, R^2, R^3, n and PG have the meanings given above, and the compound of formula **1** is obtained therefrom by cleaving the protective group PG.

The above process is preferably used to prepare compounds of formula **1**, wherein

n denotes 1 or 2;
R^1 denotes hydrogen, halogen or C_{1-4}-alkyl;
R^2 denotes hydrogen, halogen or C_{1-4}-alkyl;
R^3 denotes hydrogen, C_{1-4}-alkyl, OH, halogen, O-C_{1-4}-alkyl, O-C_{1-4}-alkylene-COOH or O-C_{1-4}-alkylene-COO-C_{1-4}-alkyl.

The above process is preferably used to prepare compounds of formula **1**, wherein

n denotes 1 or 2;
R^1 denotes hydrogen, fluorine, chlorine, methyl or ethyl;

R^2 denotes hydrogen, fluorine, chlorine, methyl or ethyl;

R^3 denotes hydrogen, C_{1-4}-alkyl, OH, fluorine, chlorine, bromine, O-C_{1-4}-alkyl, O-C_{1-4}-alkylene-COOH, O-C_{1-4}-alkylene-COO-C_{1-4}-alkyl.

The above process is preferably used to prepare compounds of formula **1**, wherein

n denotes 1 or 2;

R^1 denotes hydrogen, methyl or ethyl;

R^2 denotes hydrogen, methyl or ethyl;

R^3 denotes hydrogen, methyl, ethyl, OH, methoxy, ethoxy, O-CH_2-COOH, O-CH_2-COO-methyl or O-CH_2-COO-ethyl.

The above process is preferably used to prepare compounds of formula **1**, wherein

n denotes 1 or 2;

R^1 denotes hydrogen or methyl;

R^2 denotes hydrogen or methyl;

R^3 denotes hydrogen, methyl, OH, methoxy, O-CH_2-COOH or O-CH_2-COO-ethyl.

In the process according to the invention a compound of formula **1a** is reacted with a compound of formula **1b** in a suitable solvent. Suitable solvents which may be used are organic solvents, while particularly preferred solvents are selected from among tetrahydrofuran, toluene, ethanol, *n*-propanol, *n*-butanol, *n*-butylacetate, dimethylformamide, methoxyethanol, ethyleneglycol and dioxane. According to the invention particularly preferred solvents are *n*-propanol, tetrahydrofuran and dioxane, while dioxane and *n*-propanol are of particular importance.

Based on the compound **1a** used it is preferable according to the invention to use at least stoichiometric amounts of compound **1b**. Compound **1b** may optionally also be used in excess, for example in amounts of up to 3 equivalents, preferably up to 2.5 equivalents, particularly preferably about 1 to 2, optionally 1 to 1.5 equivalents based on the compound **1a** used.

The reaction is preferably carried out at elevated temperature, preferably at a temperature above 40°C, particularly preferably at a temperature above 50°C. Particularly preferably, the reaction mixture is heated to the boiling temperature of the solvent used.

At this temperature the reaction is then carried out over a period of about 1 to 72 hours, preferably 10 to 60 hours, particularly preferably 20 to 50 hours.

Once the reaction has ended the solvent is eliminated and the residue remaining is taken up in an organic polar solvent, preferably a C_{1-8}-alcohol or C_{3-8}-ester, particularly preferably in ethanol or ethyl acetate, and filtered. The filtrate is acidified, preferably with an inorganic acid, particularly preferably with hydrochloric acid and after a period of about 10 minutes to 12 hours, preferably 20 minutes to 6 hours, particularly preferably 30 minutes to 3 hours, the product is filtered off.

The protective group PG is preferably cleaved from compounds of formula **1a** by hydrogenation in a suitable solvent. Examples of suitable solvents include organic solvents, preferably organic, polar solvents, particularly preferred solvents are selected from among tetrahydrofuran, various C_{3-8}-esters and C_{1-8}-alcohols. Preferably, according to the invention, the solvents used are tetrahydrofuran, ethanol and methanol, while ethanol and methanol are of particular significance.

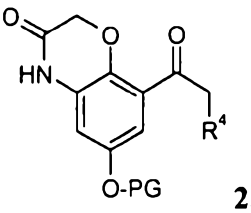
The hydrogenation in the process according to the invention preferably uses catalysts in the presence of hydrogen. Preferred catalysts are suitable transition metal catalysts, preferably heterogeneous transition metal catalysts, particularly preferably palladium-containing catalysts, particularly a palladium-charcoal mixture.

The hydrogenation is preferably carried out in the presence of an excess of hydrogen. The latter is provided according to the invention by a hydrogen pressure of 1 bar to 10 bar, preferably between 2 and 7 bar, particularly preferably between 2.5 and 4.5 bar.

Preferably the hydrogenation is carried out at elevated temperature, preferably from 25 to 70°C, particularly preferably from 30 to 60°C, particularly from 35 to 50°C. After the reaction has ended the catalyst is removed, preferably by filtration.

Then the solvent is eliminated and the product is recrystallised from a suitable organic solvent, preferably a C_{1-8}-alcohol or a mixture of C_{1-8}-alcohols, particularly preferably from a mixture of methanol and an alcohol selected from among *i*-propanol, *n*-propanol and ethanol.

In a preferred process according to the invention the compound of formula **1a** is prepared by reacting a compound of formula **2a**,



2a

wherein PG has the meaning given in claim 1 and R^4 denotes halogen, preferably bromine or chlorine.

In the process according to the invention a compound of formula **2a** is reacted in a suitable solvent with DIP chloride (diisopinocampheylchloroborane). Suitable solvents are preferably organic solvents. Preferred solvents are selected from among diethyl ether, *tert*-butyl-methylether 2-methyltetrahydrofuran, tetrahydrofuran, toluene and dioxane. Particularly preferably according to the invention the solvents used are *tert*-butyl-methylether, tetrahydrofuran and dioxane, of which dioxane and tetrahydrofuran are of particular importance.

The DIP chloride may be used in pure form or in the form of a solution, preferably in an inert organic solvent, particularly preferably an aliphatic solvent, particularly pentane, hexane, heptane or octane.

The DIP chloride is added at reduced temperature in the reaction medium, the temperature preferably being below 0°C, particularly preferably below -10°C; more particularly the addition is carried out at -20 to -40°C.

The DIP chloride is added over a period of 10 min to 6 hours, preferably 30 min to 4 hours, particularly preferably 1 to 3 hours. In particular, the addition takes place over a period of 70 to 110 min.

Based on the compound **2a** used, according to the invention at least stoichiometric amounts of DIP chloride are preferably used. The DIP chloride may optionally also be used in excess, for example in amounts of up to 3 equivalents, preferably 2.5 equivalents, particularly preferably 1.5 to 2.5 equivalents based on the compound **2a** used.

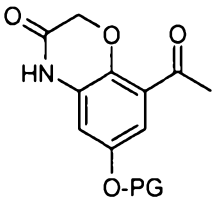
After the DIP chloride has been added the reaction mixture is stirred over a period of 10 min to 4 hours, preferably 30 min to 3 hours, particularly preferably 40 to 80 min; in particular, the reaction mixture is stirred for another 50 to 70 min after the addition has ended. During this time the reaction mixture is adjusted to a temperature of -20 to 20°C, particularly preferably from -10 to 10°C, particularly from -5 to 5°C.

Once the desired temperature has been reached, an at least stoichiometric amount of sodium hydroxide (NaOH), dissolved in water, is added, based on the amount of DIP chloride used. If desired the NaOH may also be used in excess, for example in amounts of up to 3 equivalents, preferably in amounts of up to 2.5 equivalents, particularly preferably 1.5 to 2.5 equivalents, based on the amount of DIP chloride used. Preferably a pH value of 12 to 14, particularly preferably 12.5 to 13.5, particularly 12.7 to 13.3 is measured in the reaction mixture after the addition of NaOH has ended.

After the desired pH has been selected, the reaction mixture is stirred over a period of 10 min to 4 hours, preferably 30 min to 3 hours, particularly preferably 40-80 min, and in particular the reaction mixture is stirred for a further 50-70 min. During this time the reaction mixture is adjusted to a temperature of 0 to 40°C, particularly preferably from 10 to 30°C, particularly from 15 to 25°C. Then the reaction mixture is adjusted to a pH of 7 to 10, particularly preferably 8 to 9, particularly 8.2 to 8.8, with an acid, preferably an inorganic acid, particularly preferably hydrochloric acid.

Finally, the product can be isolated from the reaction mixture by extraction with an organic solvent and obtained as a solid by precipitation with another suitable organic solvent.

In a preferred process according to the invention the compound of formula **2a** is prepared by reacting a compound of formula **3a**,



3a

wherein PG has the meaning given in claim 1.

In the process according to the invention a compound of formula **3a** is reacted with a halogenating reagent in a suitable solvent. Examples of suitable solvents are organic solvents. Preferred solvents are selected from among acetic acid, butyl acetate, methylene chloride, tetrahydrofuran, toluene and dioxane. Particularly preferred solvents according to the invention are tetrahydrofuran and dioxane.

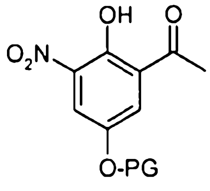
In a preferred embodiment of the invention the halogenating reagent used is a brominating reagent, particularly preferably bromine, *N*-bromosuccinimide, benzyltrimethylammonium tribromide and tetrabutylammonium tribromide. Based on the compound **3a** used, preferably at least stoichiometric amounts of halogenating reagent are used according to the invention. If required the halogenating reagent may also be used in excess, for example in amounts of up to 3 equivalents, preferably in amounts of up to 2 equivalents, particularly preferably 1 to 1.5 equivalents, based on the compound **3a** used. The halogenating reagent may be added to the reaction mixture in a solvent, preferably in an organic, polar solvent, particularly preferably in methanol, ethanol and dioxane, particularly in methanol and dioxane, or in a mixture thereof, particularly in a mixture of methanol and dioxane.

The reaction is preferably carried out at a temperature of 0 to 40°C, preferably at a temperature of 10 to 30°C, particularly preferably at a temperature of 15 to 25°C.

After the halogenating reagent has been added the reaction mixture is stirred for a period of 10 min to 6 hours, preferably 30 min to 4 hours, particularly preferably 90 to 150 min.

To isolate the product water is added to the reaction mixture, wherein the mixture is cooled to a temperature of -10°C to 10°C, preferably 0 to 10°C, particularly preferably 0 to 5°C and stirred for a period of 10 min to 4 hours, preferably 30 min to 2 hours, particularly preferably 50 to 70 min, after the addition of the water. The product may be obtained after filtration or centrifugation and drying.

In a preferred process according to the invention the compound of formula **3a** is prepared by reacting a compound of formula **4a**,



4a

wherein PG has the meaning given in claim 1.

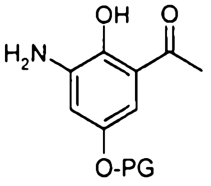
In the process according to the invention a compound of formula **4a** is hydrogenated in a suitable solvent. Examples of suitable solvents are organic solvents, preferably organic, polar solvents. Particularly preferred solvents are selected from among dimethylformamide, *N*-methylpyrrolidinone, tetrahydrofuran, 2-methyltetrahydrofuran, toluene and dioxane. According to the invention the following are particularly preferred as solvents: dimethylformamide, tetrahydrofuran, 2-methyltetrahydrofuran and dioxane, wherein dimethylformamide and 2-methyltetrahydrofuran are of particular importance.

The hydrogenation in the process according to the invention preferably uses catalysts in the presence of hydrogen. Preferred catalysts are suitable transition metal catalysts, preferably heterogeneous transition metal catalysts, particularly preferably nickel- or platinum-containing catalysts, particularly platinum oxide.

The hydrogenation is preferably carried out in the presence of an excess of hydrogen. The latter is provided according to the invention by a hydrogen pressure of 1 bar to 10 bar, preferably from 2 to 7 bar, particularly preferably from 2.5 to 4.5 bar.

Preferably the hydrogenation is carried out at a temperature from 0 to 50°C, particularly preferably from 10 to 40°C, particularly from 20 to 30°C. After the reaction has ended the catalyst is removed from the liquid phase, preferably by filtration.

The intermediate product **4a$^{\#}$** in the solution,



4a$^{\#}$

wherein PG has the meaning given in claim 1, may be isolated or further reacted directly to form a compound of formula **3a**.

In accordance with the process of the invention a base, preferably a weak base, particularly preferably a carbonate, particularly potassium carbonate, is taken and the compound of formula **4a**$^{\#}$ is added in pure form or in a solution, particularly in the form of the solution filtered off from the hydrogenation catalyst in the preceding step.

Based on the compound **4a** used, preferably at least twice the stoichiometric amount of the base is used according to the invention. The base may optionally also be used in excess, for example in amounts of up to 6 equivalents, preferably in amounts of up to 4 equivalents, particularly preferably about 3 to 3.5 equivalents, based on the compound **4a** used.

Then chloroacetyl chloride is added to the reaction mixture. The chloroacetyl chloride is added over a period of 10 min to 2 hours, preferably 15 min to 1 hour, particularly preferably 25 to 35 min.

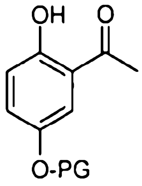
Based on the compound **4a** used, preferably at least stoichiometric amounts of the chloroacetyl chloride are used according to the invention. If required, the chloroacetyl chloride may also be used in excess, for example in amounts of up to 4 equivalents, preferably in amounts of up to 3 equivalents, particularly preferably about 1.5 to 2 equivalents, based on the compound **4a** used.

After the chloroacetyl chloride has been added the reaction mixture is stirred for a period of 10 min to 6 hours, preferably 1 to 4 hours, particularly preferably 140 to 160 min.

The reaction is preferably carried out at elevated temperature, preferably at a temperature of above 40°C, particularly preferably at a temperature of above 50°C, particularly preferably from 60°C to 70°C.

The reaction is ended by the addition of water. The compound of formula **3a** can be purified and isolated by extraction of the reaction mixture with water and subsequent recrystallisation from a suitable organic solvent. For the crystallisation it is preferable to use an aliphatic hydrocarbon, particularly preferably an aliphatic cyclic hydrocarbon, particularly cyclohexane and methylcyclohexane.

In a preferred process according to the invention, the compound of formula **4a** is prepared by reacting a compound of formula **5a**,



5a

wherein PG has the meaning given in claim 1.

In the process according to the invention a compound of formula **5a** is reacted with a nitrogenating reagent in a suitable solvent. Suitable solvents include organic solvents and acids, preferably organic protic solvents and acids. Particularly preferred solvents are acetic acid and sulphuric acid, particularly acetic acid.

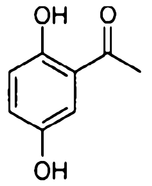
For the nitrogenation in the process according to the invention it is preferable to use 6-65% nitric acid, as well as nitronium tetrafluoroborate or acetyl nitrate. Nitric acid, particularly 65% nitric acid, is particularly preferred.

Based on the compound **5a** used, preferably at least stoichiometric amounts of the nitrogenating reagent are used according to the invention. If required the nitrogenating reagent may also be used in excess, for example in amounts of up to 2 equivalents, preferably in amounts of up to 1.5 equivalents, particularly preferably about 1 to 1.1 equivalents, based on the compound **5a** used.

After the nitrogenating reagent has been added the reaction mixture is stirred over a period of 10 min to 4 hours, preferably 20 min to 3 hours, particularly preferably 40 to 80 minutes.

Then the reaction mixture is diluted with sufficient water to precipitate the compound of formula **4a** from the solution. To complete the crystallisation stirring is continued for a further 20 min to 3 hours, preferably 30 min to 2 hours, particularly preferably 40-80 min, at a temperature of 0°C to 20°C, preferably at 5°C to 15°C, particularly preferably at 8°C to 12°C. The compound of formula **4a** may be obtained by separation from the liquid phase, preferably by filtration or centrifugation.

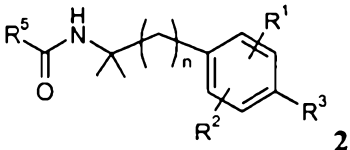
In a preferred process according to the invention, the compound of formula **5a** is prepared by reacting a compound of formula **6a**,



6a

In the process according to the invention a compound of formula **6a** is reacted in a suitable solvent with a protective group PG-A, wherein A denotes a suitable leaving group such as for example chlorine, bromine, iodine, methanesulphonyl, trifluoromethanesulphonyl or *p*-toluenesulphonyl. Preferably, a protective group is used which can be eliminated as described with reference to the cleaving of the protective group PG from compounds of formula **1a**. Particularly preferably, an optionally substituted benzyl protective group is used.

In a preferred process according to the invention, the compound of formula **1b** is prepared by reacting a compound of formula **2b**,



2b

wherein R^1, R^2, R^3 and n have the meanings given in claims 1 to 5 and

R^5 denotes Me.

In the process according to the invention a compound of formula **2b** is reacted with a strong base in a suitable solvent. Examples of suitable solvents include organic solvents; particularly preferred solvents are selected from among ethanol, 2-ethoxyethanol and ethyleneglycol or mixtures thereof. Particularly preferably, 2-ethoxyethanol or ethyleneglycol or a mixture thereof is used as the solvent according to the invention. Preferably, the mixture consists of equal parts by volume of 2-ethoxyethanol and ethyleneglycol, although a slight excess of one or other solvent is also possible.

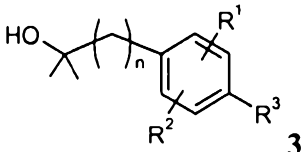
The strong base used is particularly an inorganic hydroxide, preferably an alkaline earth or alkali metal hydroxide, particularly sodium hydroxide or potassium hydroxide. According to the invention potassium hydroxide is of particular importance.

Based on the compound **2b** used, preferably at least stoichiometric amounts of the strong base are used according to the invention. If required the strong base may also be used in excess, for example in amounts of up to 8 equivalents, preferably in amounts of up to 6 equivalents, preferably about 2 to 4, particularly preferably 3.5 to 4.5 equivalents, based on the compound **2b** used.

The reaction is preferably carried out at elevated temperature, preferably at a temperature of above 100°C, particularly preferably at a temperature of above 120°C. Particularly preferably the raction mixture is heated to 140-160°C, particularly to 145-155°C.

Then for extraction the reaction mixture is diluted with a solvent and water. Solvents of particular interest are toluene, xylene, heptane, methylcyclohexane or *tert*-butyl-methylether, preferably toluene or xylene. The aqueous phase is eliminated, the organic phase is extracted with water in additional purification steps. The water may be acidic, neutral or alkaline, by the use of common additives. Preferably the organic phase is extracted once with acidified water and then with basic water. The product may be obtained from the organic phase by elimination of the solvent.

In a preferred process according to the invention, the compound of formula **2b** is prepared by reacting a compound of formula **3b**,



3b

wherein R^1, R^2, R^3 and n have the meanings given in claims 1 to 5.

In the process according to the invention a compound of formula **3b** is reacted in a suitable solvent with acetonitrile in the presence of an acid. Examples of suitable solvents are acids, preferably organic acids, while the particularly preferred solvent is acetic acid.

Based on the compound **3b** used, preferably at least stoichiometric amounts of acetonitrile are used according to the invention. Preferably the acetonitrile is used in excess, for example in amounts of up to 6 equivalents, preferably in amounts of up to 5 equivalents, particularly preferably about 2 to 4 equivalents, particularly 2.5 to 3.5 equivalents, based on the compound **3b** used.

The acid in whose presence the reaction is carried out is preferably sulphuric acid, formic acid, p-toluenesulphonic acid, methanesulphonic acid, perchloric acid or polyphosphoric acid, particularly preferably sulphuric acid.

Based on the compound **3b** used, preferably at least stoichiometric amounts of the acid are used according to the invention. If required the acid may also be used in excess, for example in amounts of up to 2 equivalents, preferably in amounts of up to 1.5 equivalents, particularly preferably about 1 to 1.1 equivalents, based on the compound **5a** used. After the acid has been added the reaction mixture is stirred for a period of 1 to 5 hours, preferably 2 to 4 hours, particularly preferably 170 to 190 min.

The reaction is preferably carried out at elevated temperature, preferably at a temperature of above 30°C, particularly preferably at a temperature of above 40°C, particularly preferably from 45°C to 60°C. Surprisingly, it has been found that in this process no undesirable cleaving of the methyl ether function takes place as might have been expected from the literature (Can. J. Chem. **56** (1978), 3054-3058).

Then the reaction mixture is transferred into a second reactor which contains a cooled mixture of solvents. Examples of suitable solvents include mixtures of polar and non-polar solvents, preferably aqueous, organic, polar and non-polar solvents. Particularly preferred solvents as components of the mixture are selected from among water, *tert*-butylmethylether, tetrahydrofuran, toluene, dioxane, hexane, cyclohexane and methylcyclohexane. According to the invention it is particularly preferable to use, as ingredients of the mixture, water, *tert*-butylmethylether, tetrahydrofuran, toluene, cyclohexane and methylcyclohexane, while a mixture of water, *tert*-butylmethylether and methylcyclohexane is of particular importance.

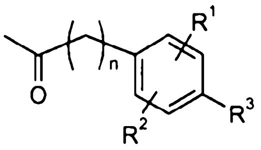
Preferably the mixture of solvents is kept at a reduced temperature, preferably at a temperature of below 20°C, particularly preferably at a temperature below 15°C, particularly preferably 0°C to 15°C.

In order to precipitate the product out of the solvent, the pH of the reaction mixture is raised, preferably into the basic range, particularly preferably from pH 8 to 12, particularly from pH 9 to 10. Preferably an ammonia solution is used to raise the pH value.

After the addition has ended and the pH has been adjusted the reaction mixture is stirred for a period of 10 min to 3 hours, preferably 20 min to 2 hours, particularly preferably 50 to 70 min.

Then the product is removed by centrifuging and washed with the above-mentioned solvents used for the reaction. A product of greater purity can be obtained by further recrystallisation, or precipitation, e.g. With C_{1-8}-alcohols and water.

In a preferred process according to the invention, the compound of formula **3b** is prepared by reacting a compound of formula **4b**,



4b

wherein R^1, R^2, R^3 and n have the meanings given in claims 1 to 5.

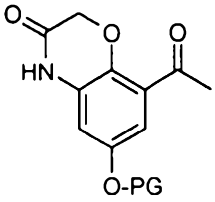
In the process according to the invention a compound of formula **4b** is subjected tio a Grignard reaction in a suitable solvent with methylmagnesium bromide. Organic solvents are suitable for use as the solvent. Preferred solvents are selected from among diethyl ether, *tert*-butyl-methylether, tetrahydrofuran, toluene and dioxane. According to the invention it is particularly preferable to use *tert*-butyl-methylether, tetrahydrofuran and toluene as solvent.

The reaction is preferably carried out at ambient temperature, preferably at a temperature of 10 to 20°C, particularly preferably at a temperature of 15 to 25°C.

After the educts have been combined the reaction mixture is stirred for a period of 10 min to 3 hours, preferably 20 min to 2 hours, particularly preferably 50 to 70 min.

To stop the reaction, water and an acid, preferably sulphuric acid, are added to the reaction mixture. After extraction of the organic phase using standard methods the product may be isolated by elimination of the solvent. The purity of the product can be increased by recrystallisation from an organic non-polar solvent, preferably *n*-heptane.

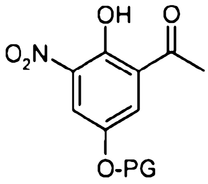
The invention further relates to the new intermediate products of formula **3a**,



3a

wherein PG has the meaning given in claim 1.

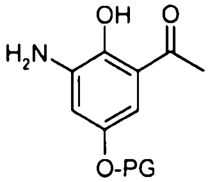
The invention further relates to the new intermediate products of formula **4a**,



4a

wherein PG has the meaning given in claim 1.

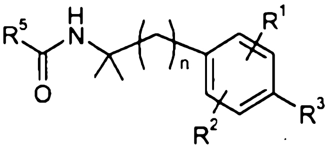
The invention further relates to the new intermediate products of formula **4a[#]**,



4a#

wherein PG has the meaning given in claim 1.

The invention further relates to the new intermediate products of formula **2b**,

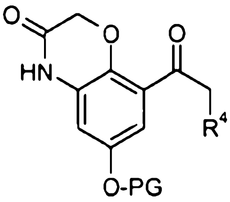


2b

wherein R^1, R^2, R^3 and n have the meanings given in claims 1 to 5 and

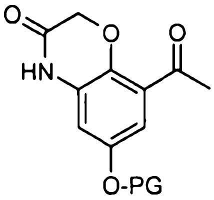
R^5 denotes Me.

The subject matter of the invention also includes a process for preparing compounds of formula **2a,**



2a

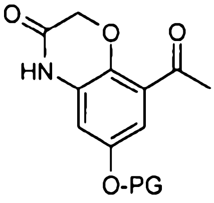
wherein PG has the meaning given in claim 1 and R^4 denotes halogen, preferably bromine or chlorine, characterised in that a compound of formula **3a,**



3a

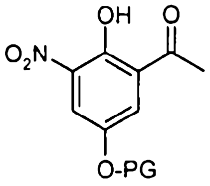
wherein PG has the meaning given in claim 1, is reacted with the halogenating reagent selected from among tetrabutylammonium tribromide, benzyltrimethylammonium dichloriodide, N-bromo-succinimide, N-chloro-succinimide, sulphuryl chloride and bromine/dioxane, preferably tetrabutylammonium tribromide or N-bromo-succinimide.

The subject matter of the invention also includes a process for preparing compounds of formula **3a,**



3a

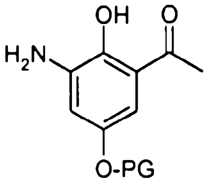
wherein PG has the meaning given in claim 1, characterised in that a compound of formula **4a**,



4a

wherein PG has the meaning given in claim 1, is subjected to catalytic hydrogenation and then reacted with chloroacetyl chloride.

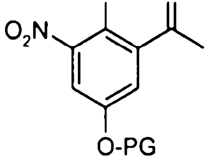
The subject matter of the invention also includes a process according to claim **16**, wherein a compound of formula **4a**[#],



4a[#]

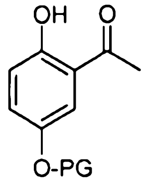
wherein PG has the meaning given in claim 1, is formed as the intermediate product of the hydrogenation.

The subject matter of the invention also includes a process for preparing compounds of formula **4a,**



4a

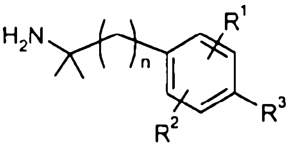
wherein PG has the meaning given in claim 1 and is characterised in that a compound of formula **5a**,



5a

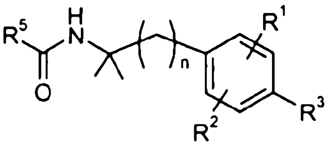
wherein PG has the meaning given in claim 1, is reacted with a nitrogenating reagent selected from among 65% nitric acid, potassium nitrate/sulphuric acid or nitronium tetrafluoroborate, preferably 65% nitric acid.

The subject matter of the invention also includes a process for preparing compounds of formula **1b**,



1b

wherein R^1, R^2, R^3 and n have the meanings given in claims 1 to 5, characterised in that a compound of formula **2b**,



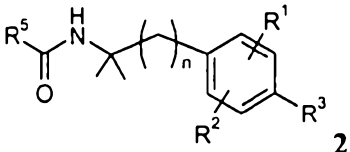
2b

wherein R^1, R^2, R^3 and n have the meanings given in claims 1 to 5 and

R^5 denotes Me,

is reacted with a base selected from among potassium hydroxide, sodium hydroxide, lithium hydroxide and caesium hydroxide, preferably potassium hydroxide or sodium hydroxide.

The subject matter of the invention also includes a process for preparing compounds of formula **2b,**

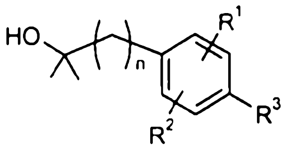


2b

wherein R^1, R^2, R^3 and n have the meanings given in claims 1 to 5 and

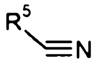
R^5 denotes Me,

characterised in that a compound of formula **3b,**



3b

wherein R^1, R^2, R^3 and n have the meanings given in claims 1 to 5, is reacted with a compound of formula



wherein R^5 has the meaning given above, in the presence of a hygroscopic reagent selected from among sulphuric acid, formic acid, p-toluenesulphonic acid, methanesulphonic acid, perchloric acid and polyphosphoric acid, preferably sulphuric acid, and is then reacted with a base selected from among aqueous solutions of ammonia, sodium hydroxide, potassium hydroxide, sodium carbonate and potassium carbonate.

TERMS AND DEFINITIONS USED

By an "organic solvent" is meant, within the scope of the invention, an organic, low-molecular substance which can dissolve other organic substances by a physical method. To be suitable the prerequisite for the solvent is that neither the dissolving substance nor the dissolved substance should be chemically altered during the dissolving process, i.e. The components of the solution should be recoverable in their original form by physical separation processes such as distillation, crystallisation, sublimation, evaporation or adsorption. For various reasons, not only the pure solvents but also mixtures that combine the dissolving properties may be used. Examples include:

- alcohols, preferably methanol, ethanol, propanol, butanol, octanol, cyclohexanol;
- glycols, preferably ethyleneglycol, diethyleneglycol;
- ethers / glycolethers, preferably diethyl ether, *tert*-butyl-methylether, dibutylether, anisol, dioxane, tetrahydrofuran, mono-, di-, tri-, polyethyleneglycol ethers;
- ketones, preferably acetone, butanone, cyclohexanone;
- esters, preferably acetic acid esters, glycolesters;
- amides and other nitrogen compounds, preferably dimethylformamide, pyridine, *N*-methylpyrrolidone, acetonitrile;
- sulphur compounds, preferably carbon disulphide, dimethylsulphoxide, sulpholane;
- nitro compounds, preferably nitrobenzene;
- halogenated hydrocarbons, preferably dichloromethane, chloroform, tetrachlormethane, tri- and tetrachloroethene, 1,2-dichloroethane, chlorofluorocarbons;
- aliphatic or alicyclic hydrocarbons, preferably benzines, petroleum ether, cyclohexane, methylcyclohexane, decaline, terpene-L.; or
- aromatic hydrocarbons, preferably benzene, toluene, *o*-xylene, *m*-xylene, *p*-xylene;

or corresponding mixtures thereof.

By the term "C_{1-4}-alkyl" (including those which are part of other groups) are meant branched and unbranched alkyl groups with 1 to 4 carbon atoms. Examples include: methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl or *tert*-butyl. In some cases the abbreviations Me, Et, *n*-Pr, *i*-Pr, *n*-Bu, *i*-Bu, *t*-Bu, etc. Are also used for the above-mentioned groups. Unless stated otherwise, the definitions propyl and butyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes *n*-propyl and *iso*-propyl, butyl includes *iso*-butyl, *sec*-butyl and *tert*-butyl etc.

By the term "C_{1-4}-alkylene" (including those which are part of other groups) are meant branched and unbranched alkylene groups with 1 to 4 carbon atoms. Examples include: methylene, ethylene, propylene, 1-methylethylene, butylene, 1-methylpropylene, 1,1-dimethylethylene or 1,2-dimethylethylene. Unless stated otherwise, the definitions propylene and butylene include all the possible isomeric forms of the groups in question with the same number of carbons. Thus, for example, propyl also includes 1-methylethylene and butylene includes 1-methylpropylene, 1,1-dimethylethylene, 1,2-dimethylethylene.

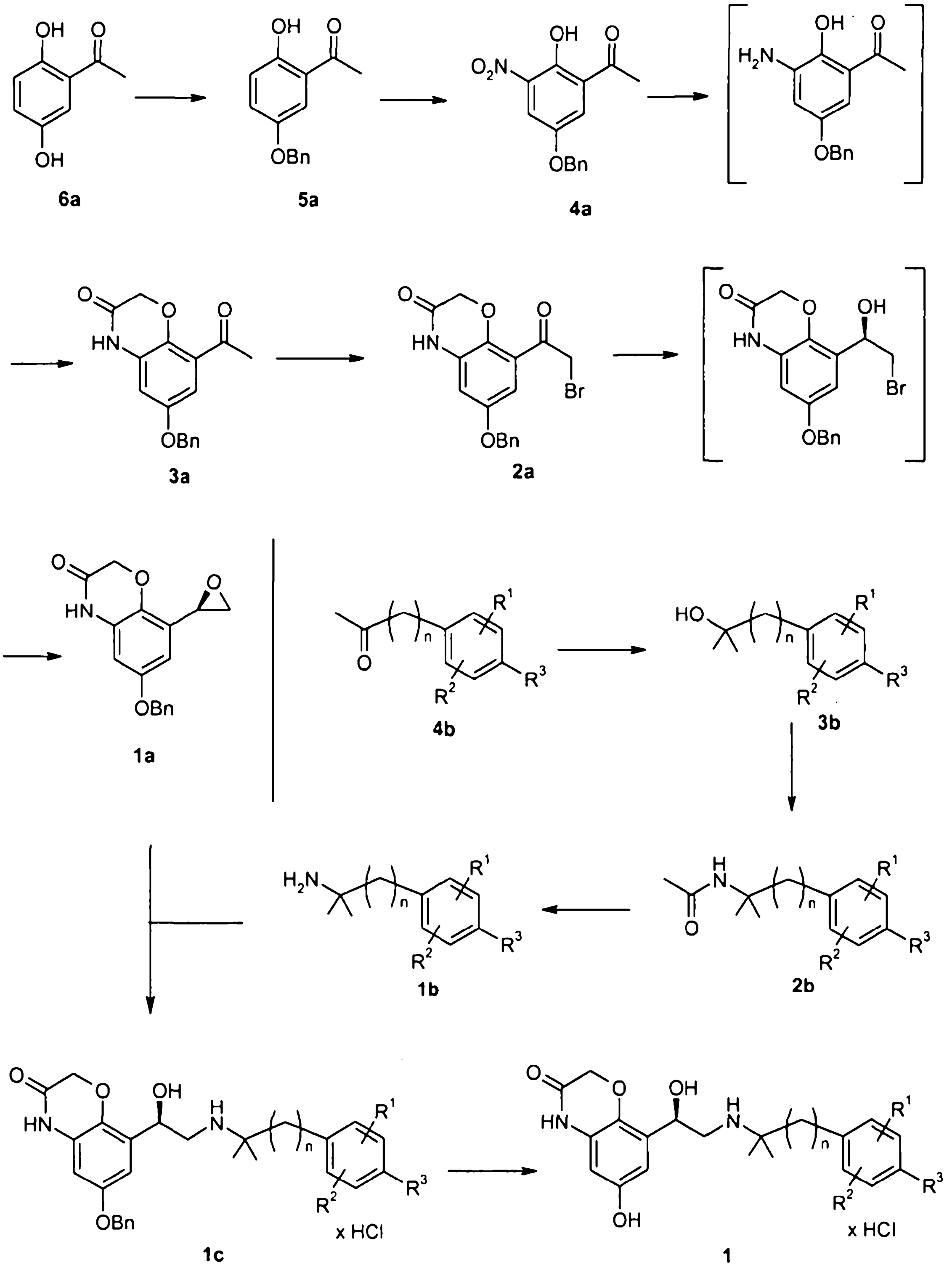
By the term "C_{1-8}-alcohol" are meant branched and unbranched alcohols with 1 to 8 carbon atoms and one or two hydroxy groups. Alcohols with 1 to 4 carbon atoms are preferred. Examples include: methanol, ethanol, *n*-propanol, *iso*-propanol, *n*-butanol, *iso*-butanol, *sec*-butanol or *tert*-butanol. In some cases the abbreviations MeOH, EtOH, *n*-PrOH, *i*-PrOH, *n*-BuOH, *i*-BuOH, *t*-BuOH, etc. Are optionally also used for the above-mentioned molecules. Unless stated otherwise, the definitions propanol, butanol, pentanol and hexanol include all the possible isomeric forms of the groups in question. Thus for example propanol includes *n*-propanol and *iso*-propanol, butanol includes *iso*-butanol, *sec*-butanol and *tert*-butanol etc.

By the term "C_{3-8}-esters" are meant branched and unbranched esters with a total of 3 to 8 carbon atoms. Esters of acetic acid with 3 to 6 carbon atoms are preferred. Examples include: methyl acetate, ethyl acetate, *n*-propyl acetate, *i*-propyl acetate or n-butyl acetate, of which ethyl acetate is preferred.

"Halogen" within the scope of the present invention denotes fluorine, chlorine, bromine or iodine. Unless stated to the contrary, fluorine, chlorine and bromine are regarded as preferred halogens.

"Protective groups" for the purposes of the present invention is a collective term for organic groups with which certain functional groups of a molecule containing a number of active centres can temporarily be protected from attack by reagents so that reactions take place only at the desired (unprotected) sites. The protective groups should be introduced selectively under mild conditions . They must be stable for the duration of the protection under all the conditions of the reactions and purifying procedures which are to be carried out ; racemisations and epimerisations must be suppressed. Protective groups should be capable of being cleaved again under mild conditions selectively and ideally in high yields. The choice of a suitable protective group, the reaction conditions (solvent, temperature, duration, etc.), and also the options for removing a protective group are known in the art (e.g. Philip Kocienski, Protecting Groups, 3rd ed. 2004, THIEME, Stuttgart, ISBN: 3131370033). Preferred protective groups are optionally substituted benzyl, diphenylmethyl, trityl, tosyl, mesyl or triflate, of which optionally substituted benzyl is particularly preferred.

EXPERIMENTAL SECTION



wherein Bn denotes benzyl and

n	may denote 1 or 2;
R^1	may denote hydrogen, halogen, C_{1-4}-alkyl or O-C_{1-4}-alkyl;
R^2	may denote hydrogen, halogen, C_{1-4}-alkyl or O-C_{1-4}-alkyl;
R^3	may denote hydrogen, C_{1-4}-alkyl, OH, halogen, O-C_{1-4}-alkyl, O-C_{1-4}-alkylene-COOH, O-C_{1-4}-alkylene-COO-C_{1-4}-alkyl.

8-[(1R)-1-hydroxy-2-[[2-aryl-1,1-dimethyl-ethyl]-amino]ethyl]-6-(phenylmethoxy)-2H-1,4-benzoxazin-3(4H)-one-hydrochloride of formula **1c**: 7.00 kg (23.54 mol) 8-(2R)-oxiranyl-6-(phenylmethoxy)-2H-1,4-benzoxazin-3(4H)-one **1a** and 34.70 mol aryl-1,1-dimethyl-ethylamine of formula **1b** are placed in 70 l 1,4-dioxane. The reactor contents are heated to 97°C and stirred for 48 hours at this temperature. Then the mixture is cooled to 40°C and 56 l of 1,4-dioxane are distilled off in vacuo. 70 l ethanol are added to the residue, it is cooled to 25°C, and 4.15 kg (34.14 mol) hydrochloric acid (30%) are added at 25°C within 15 minutes. Then the mixture is inoculated and stirred until crystallisation occurs. The resulting suspension is cooled to 20°C and stirred for a further 2 hours. The product is centrifuged, washed with 21 l of ethanol and dried in vacuo at 50°C.
Yield (**1c**): 84-90%, enantiomer purity according to HPLC: 89.5 -99.5%.

6-hydroxy-8-[(1R)-1-hydroxy-2-[[2-aryl-1,1-dimethyl-ethyl]-amino]ethyl]-2H-1,4-benzoxazin-3(4H)-one-hydrochloride of formula **1**: 19.49 mol of 8-[(1R)-1-hydroxy-2-[[2-(4-methoxyphenyl)-1,1-dimethyl-ethyl]-amino]ethyl]-6-(phenylmethoxy)-2H-1,4-benzoxazin-3(4H)-one-hydrochloride of formula **1c** are placed in the hydrogenation reactor and suspended with 40 l methanol. 500 g palladium on charcoal 10% (50% water) are suspended in 17 l methanol and added to the hydrogenation reactor. The mixture is hydrogenated at 40°C internal temperature and at 3 bar hydrogen pressure until no further uptake of hydrogen is discernible. The catalyst is filtered off and rinsed with 13.3 l methanol. 60 l of methanol are distilled off under a weak vacuum. If there is no crystal formation, the distillation residue is inoculated. Then at 50°C 30 l *i*-of propanol are metered in and within 1 hour the mixture is cooled to 0°C. At 0°C it is stirred for 1 hour, suction filtered and washed with 15 l cold *i*-propanol. The moist product is dissolved in 50 litres of methanol. The resulting solution is filtered clear and the pressure filter is rinsed with 10 litres of methanol. Then 52 l methanol are distilled off under a weak vacuum (about 500 mbar). If there is no crystal formation, the distillation residue is inoculated. Then 22.6 l *i*-propanol are metered in. The mixture is cooled to 0°C, and the suspension is stirred for 1 hour at 0°C. The suspension is suction filtered, washed with 15 litres of cold *i*-propanol and dried *in vacuo* at 50°C. Yield (**1**): 63-70%.

1-[2-hydroxy-5-(phenylmethoxy)-phenyl]-ethanone: 20 kg (131.4 mol) 2-acetyl-hydroquinone **6a** are dissolved in 150 l methylisobutylketone and combined with 19.98 kg (144.6 mol) potassium carbonate. At 60°C, 22.48 kg (131.5 mol) benzyl bromide are added. The reaction mixture is stirred for 20 hours at 60°C. The reaction mixture is cooled to 25°C and the solid is filtered off. The filtrate is washed twice with a solution of 0.96 kg (11.8 mol) sodium hydroxide solution (50%) and 60 l water at 25°C. The methylisobutylketone is largely distilled off in vacuo, and the residue is dissolved in 80 l methanol at 60°C. The solution is cooled to 0°C and stirred for 1 hour at this temperature to complete the crystallisation.

Yield (**5a**): 24.07 kg (75.6%), chemical purity according to HPLC: 99.2%.

1-[2-hydroxy-3-nitro-5-(phenylmethoxy)-phenyl]-ethanone: 10.00 kg (41.27 mol) 1-[2-hydroxy-5-(phenylmethoxy)-phenyl]-ethanone **5a** are dissolved in 50 l acetic acid. 4.40 kg (45.40 mol) nitric acid 65% are metered into this solution at 15 to 20°C. The feed vessel is rinsed with 4 l acetic acid. The reaction mixture is stirred for 1 hour. After inoculation 50 l water are added. The suspension obtained is stirred for 1 hour at 10°C to complete the crystallisation. The product is centrifuged and dried at 50°C.

Yield (**4a**): 10.34 kg (87.2%), chemical purity according to HPLC: 99.0%.

8-acetyl-6-(phenylmethoxy)-2*H*-1,4-benzoxazin-3(4*H*)-one: 15.00 kg (52.22 mol) 1-[2-hydroxy-3-nitro-5-(phenylmethoxy)-phenyl]-ethanone **4a**, 0.165 kg platinum(IV)oxide and 45 l 2-methyltetrahydrofuran are hydrogenated at 3 bar hydrogen pressure and an internal temperature of 25°C until no firther hydrogen uptake is discernible. The catalyst is filtered off and washed with 20 l of 2-methyltetrahydrofuran. 23.09 kg (167.09 mol) potassium carbonate are placed in another reactor, and the reaction mixture from the first reactor is added. It is rinsed with 22 l of 2-methyltetrahydrofuran. Then within 30 minutes 9.44 kg (83.55 mol) chloroacetyl chloride are metered into the suspension. After 2.5 hours reaction time at 65°C, 101 l water are added. The aqueous phase is separated off at 55°C. Then 34 l 2-methyltetrahydrofuran are distilled off from the organic phase in vacuo. After heating to reflux temperature, 180 l methylcyclohexane are metered in within 30 minutes at reflux temperature. The suspension obtained is cooled to 20°C and stirred for another 1 hour at this temperature to complete the crystallisation. Then the precipitate is removed by centrifuging, washed with 113 l methylcyclohexane and dried at 50°C.

Yield (**3a**): 12.70 kg (81.8%), chemical purity according to HPLC: 98.4%.

8-(bromoacetyl)-6-(phenylmethoxy)-2*H*-1,4-benzoxazin-3(4*H*)-one: 12.00 kg (40.36 mol) 8-acetyl-6-(phenylmethoxy)-2*H*-1,4-benzoxazin-3(4*H*)-one **3a** are dissolved in 108 l 1,4-dioxane. Then a solution of 24.33 kg (50.45 mol) tetrabutylammonium tribromide in 48 l of 1,4-dioxane and 12 l methanol is metered into the suspension at 20°C. The reactor contents are stirred for 2 hours at 20°C. Then 72 l water are added at 20°C within 15 minutes. After cooling to 3°C the mixture is stirred for 1 hour, centrifuged and washed with a mixture of 9 l of 1,4-dioxane and 4.5 l water. Then it is washed with 60 l water and dried in vacuo at 50°C.

Yield (**2a**): 11.29 kg (74.4%), chemical purity according to HPLC: 98.0%.

8-(2*R*)-Oxiranyl-6-(phenylmethoxy)-2*H*-1,4-benzoxazin-3(4*H*)-one: 12.00 kg (31.90 mol) 8-(bromoacetyl)-6-(phenylmethoxy)-2*H*-1,4-benzoxazin-3(4*H*)-one **2a** are dissolved in 180 l tetrahydrofuran and cooled to -30°C. 63 kg (70.18 mol) (-)-DIP chloride in hexane 65% are metered in within 1.5 hours. The reaction mixture is stirred for 1 hour and heated to 0°C. At this temperature 11.48 kg (143.54 mol) sodium hydroxide solution (50%), mixed with 36 l water, are metered in. Then the feed vessel is rinsed with 9 l water. The pH value at the end of the addition should be 13. The mixture is heated to 20°C and stirred for 1 hour. A mixture of 4.5 l (42.11 mol) industrial grade hydrochloric acid (30%) and 18.6 l water is metered in until a pH of 8.5 is achieved. After the addition of 84 l of ethyl

acetate the mixture is heated to 30°C. After phase separation half the solvent is distilled off from the organic phase, the residue is combined with 120 l *tert*-butyl-methylether, cooled to 0°C and stirred for 1 hour. The product is isolated, washed with *tert*-butylmethylether and dried in vacuo at 50°C.
Yield (**1a**): 8.06 kg (85.0%), purity of enantiomers according to HPLC: 98.3%.

Compounds of formula 3b: 24.68 kg (72.6 mol) methylmagnesium chloride (22% solution in THF) are dissolved in 35 l toluene and cooled to 16°C. At 16 - 22°C a solution of 60.9 mol arylacetone of formula **4b** and 10 l toluene is metered in and the mixture is stirred at 22°C for 1 hour. The reaction solution is metered into a mixture of 45 l water and 5.22 kg (51.1 mol) sulphuric acid at a temperature of 2-17°C. The two-phase mixture is stirred, and the aqueous phase is separated off. The organic phase is washed with a solution of 1.00 kg (11.9 mol) sodium hydrogen carbonate and 11 l water. The solvent is dissolved off completely in vacuo . The residue is dissolved in 65.5 l of *n*-heptane. After cooling to 2°C the reaction mixture is stirred for 3 hours at this temperature. Then the product is isolated, washed with 17.5 l of *n*-heptane and dried in vacuo at 25°C.
Yield (**3b**): 75-80%, chemical purity according to HPLC: 98.9-99.9%.

Compounds of formula 2b: 55.48 mol of 1-aryl-2-methyl-propan-2-ol of formula **3b** are placed in 6.83 kg (166.44 mol) acetonitrile and 13 l acetic acid and heated to 40°C. 5.66 kg (55.48 mol) sulphuric acid are metered in at 50 - 55°C. Then the mixture is stirred for 3 hours at 50°C. In a second reactor 160 l water, 20 l *tert*-butylmethylether and 21 l methylcyclohexane are cooled to 10°C. The contents of the first reactor are transferred into the second reactor. The pH of the reactor contents is adjusted to 9.5 with about 40 l of ammonia solution (25%). The suspension is cooled to 5°C and stirred for 1 hour at this temperature. The product is separated by centrifuging and washed with 30 l water as well as with a mixture of 7.5 l *tert*-butylmethylether and 7.5 l methylcyclohexane. The damp product is heated to 75°C in 25 l ethanol (96%) and at this temperature combined with 30 l water. The solution is stirred for 15 minutes at 85°C, then cooled to 2°C and stirred for 1 hour at this temperature. The product is isolated, washed with a mixture of 5 l water and 5 l ethanol (96%) and dried.

Yield (**2b**): 65-71%, chemical purity according to HPLC: 98.6-99.8%.

Compounds of formula 1b: A mixture of 45.2 mol *N*-[2-aryl-1,1-dimethyl-ethyl]-acetamide of formula **2b**, 12.07 kg KOH (180.8 mol), 15 l ethoxyethanol and 15 l ethyleneglycol is heated to 150°C for 12 hours. After cooling to ambient temperature the mixture is diluted with 61 l water and 31 l toluene. The phases are separated and the organic phase is washed once more with 30 l water. The organic phase is combined with 52 l water. It is acidified with 8.91 kg hydrochloric acid (90.4 mol). After phase separation the aqueous product phase is combined with 30 l toluene and made alkaline with 9.04 kg 50% NaOH (113.0 mol) . After phase separation the organic product phase is evaporated down in vacuo to leave an oily residue.
Yield (**1b**): 69-75%, chemical purity according to HPLC: 94-96%.

In the methods described above for synthesising the compounds of formulae **3b**, **2b** and **1b** the groups R^1, R^2 and R^3 may have the following meanings, for example:

	R^1	**R^2**	**R^3**
Example 1	H	H	OMe
Example 2	2-F	H	F
Example 3	3-F	5-F	H
Example 4	H	H	OEt
Example 5	H	H	F

Analogously to the preparation methods described hereinbefore it is thus possible to obtain the *R*-forms of the following compounds of formula **1**:

- 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(2,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

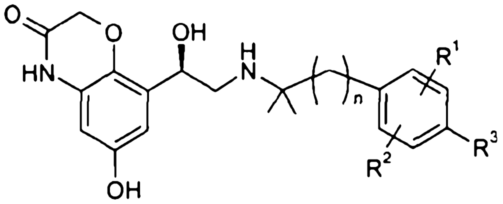
- 8-{2-[2-(3,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one.

The reference in this specification to any prior publication (or information derived from it), or to any matter which is known, is not, and should not be taken as an acknowledgment or admission or any form of suggestion that that prior publication (or information derived from it) or known matter forms part of the common general knowledge in the field of endeavour to which this specification relates.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A process for preparing a compound of formula **1**,



1

wherein

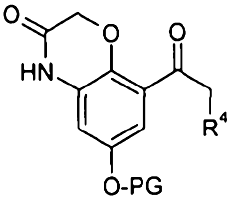
n denotes 1 or 2;

R^1 denotes hydrogen, halogen, C_{1-4}-alkyl or O-C_{1-4}-alkyl;

R^2 denotes hydrogen, halogen, C_{1-4}-alkyl or O-C_{1-4}-alkyl;

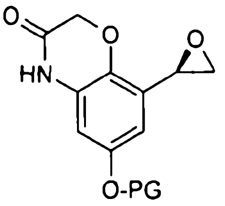
R^3 denotes hydrogen, C_{1-4}-alkyl, OH, halogen, O-C_{1-4}-alkyl, O-C_{1-4}-alkylene-COOH, O-C_{1-4}-alkylene-COO-C_{1-4}-alkyl;

wherein that a compound of formula **2a**,



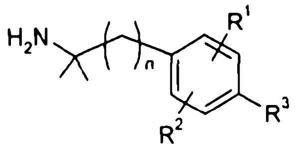
2a

wherein PG represents a protective group and R^4 denotes halogen, is reacted with DIP chloride (diisopinocampheylchloroborane) in a suitable solvent to obtain a compound of formula **1a**,



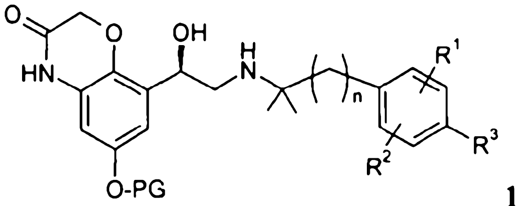
1a

wherein PG has the meaning given above, which is reacted with a compound of formula **1b**,



1b

wherein R^1, R^2, R^3 and n have the meaning given above, in an organic solvent to obtain a compound of formula **1c**,



1c

wherein R^1, R^2, R^3, n and PG have the meanings given above, and the compound of formula **1** is obtained therefrom by cleaving the protective group PG.

2. A process for preparing a compound of formula **1** according to claim 1, wherein

n denotes 1 or 2;

R^1 denotes hydrogen, halogen or C_{1-4}-alkyl;

R^2 denotes hydrogen, halogen or C_{1-4}-alkyl;

R^3 denotes hydrogen, C_{1-4}-alkyl, OH, halogen, O-C_{1-4}-alkyl, O-C_{1-4}-alkylene-COOH or O-C_{1-4}-alkylene-COO-C_{1-4}-alkyl.

3. A process for preparing a compound of formula **1** according to claim 1, wherein

n denotes 1 or 2;
R^1 denotes hydrogen, fluorine, chlorine, methyl or ethyl;
R^2 denotes hydrogen, fluorine, chlorine, methyl or ethyl;
R^3 denotes hydrogen, C_{1-4}-alkyl, OH, fluorine, chlorine, bromine, O-C_{1-4}-alkyl, O-C_{1-4}-alkylene-COOH, O-C_{1-4}-alkylene-COO-C_{1-4}-alkyl.

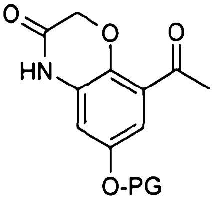
4. A process for preparing a compound of formula **1** according to claim 1, wherein

n denotes 1 or 2;
R^1 denotes hydrogen, methyl or ethyl;
R^2 denotes hydrogen, methyl or ethyl;
R^3 denotes hydrogen, methyl, ethyl, OH, methoxy, ethoxy, O-CH_2-COOH, O-CH_2-COO-methyl or O-CH_2-COO-ethyl.

5. A process for preparing a compound of formula **1** according to claim 1, wherein

n denotes 1 or 2;
R^1 denotes hydrogen or methyl;
R^2 denotes hydrogen or methyl;
R^3 denotes hydrogen, methyl, OH, methoxy, O-CH_2-COOH or O-CH_2-COO-ethyl.

6. A process according to any one of claims 1 to 5 wherein the compound of formula **2a** is prepared by reacting a compound of formula **3a**,

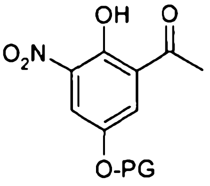


3a

wherein PG has the meaning given in claim 1, with a halogenating reagent in a suitable solvent.

7. A process according to claim 6 wherein the halogenating agent is bromine, N-bromosuccinimide, benzyl-trimethylammonium tribromide, tetrabutylammonium tribromide, N-chloro-succinimide, sulphuryl chloride or bromine/dioxane.

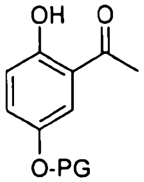
8. A process according to claim 6 or claim 7 wherein the compound of formula **3a** is prepared by hydrogenating a compound of formula **4a** in a suitable solvent,



4a

wherein PG has the meaning given in claim 1.

9. A process according to claim 8 wherein the compound of formula **4a** is prepared by reacting a compound of formula **5a**,

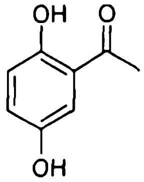


5a

wherein PG has the meaning given in claim 1, with a nitrogenating agent in a suitable solvent.

10. A process according to claim 9 wherein the nitrogenating agent is 6-65% nitric acid, acetyl nitrate, potassium nitrate/sulphuric acid or nitronium tetrafluoroborate.

11. A process according to claim 9 or claim 10 wherein the compound of formula **5a** is prepared by reacting a compound of formula **6a**,

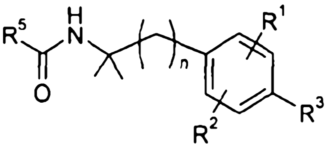


6a

in a suitable solvent with a protective group PG-A, wherein A denotes a suitable leaving group.

12. A process according to claim 11 wherein the leaving group is chlorine, bromine, iodine, methanesulphonyl, trifluoromethanesulphonyl or *p*-toluenesulphonyl.

13. A process according to any one of claims 1 to 5, wherein the compound of formula **1b** is prepared by reacting a compound of formula **2b**,



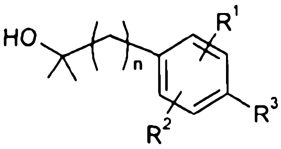
2b

wherein R^1, R^2, R^3 and n have the meanings given in any one of claims 1 to 5 and

R^5 denotes Me,

with a strong base in a suitable solvent.

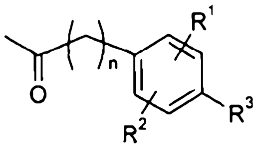
14. A process according to claim 13 wherein the compound of formula **2b** is prepared by reacting a compound of formula **3b**,



3b

wherein R^1, R^2, R^3 and n have the meanings given in any one of claims 1 to 5, in a suitable solvent with acetonitrile in the presence of an acid.

15. A process according to claim 14 wherein the compound of formula **3b** is prepared by subjecting a compound of formula **4b**,



4b

wherein R^1, R^2, R^3 and n have the meanings given in any one of claims 1 to 5, to a Grignard reaction in a suitable solvent with methylmagnesium bromide.

16. A process as defined in any one of claims 1 to 15, substantially as hereinbefore described and with reference to the Examples