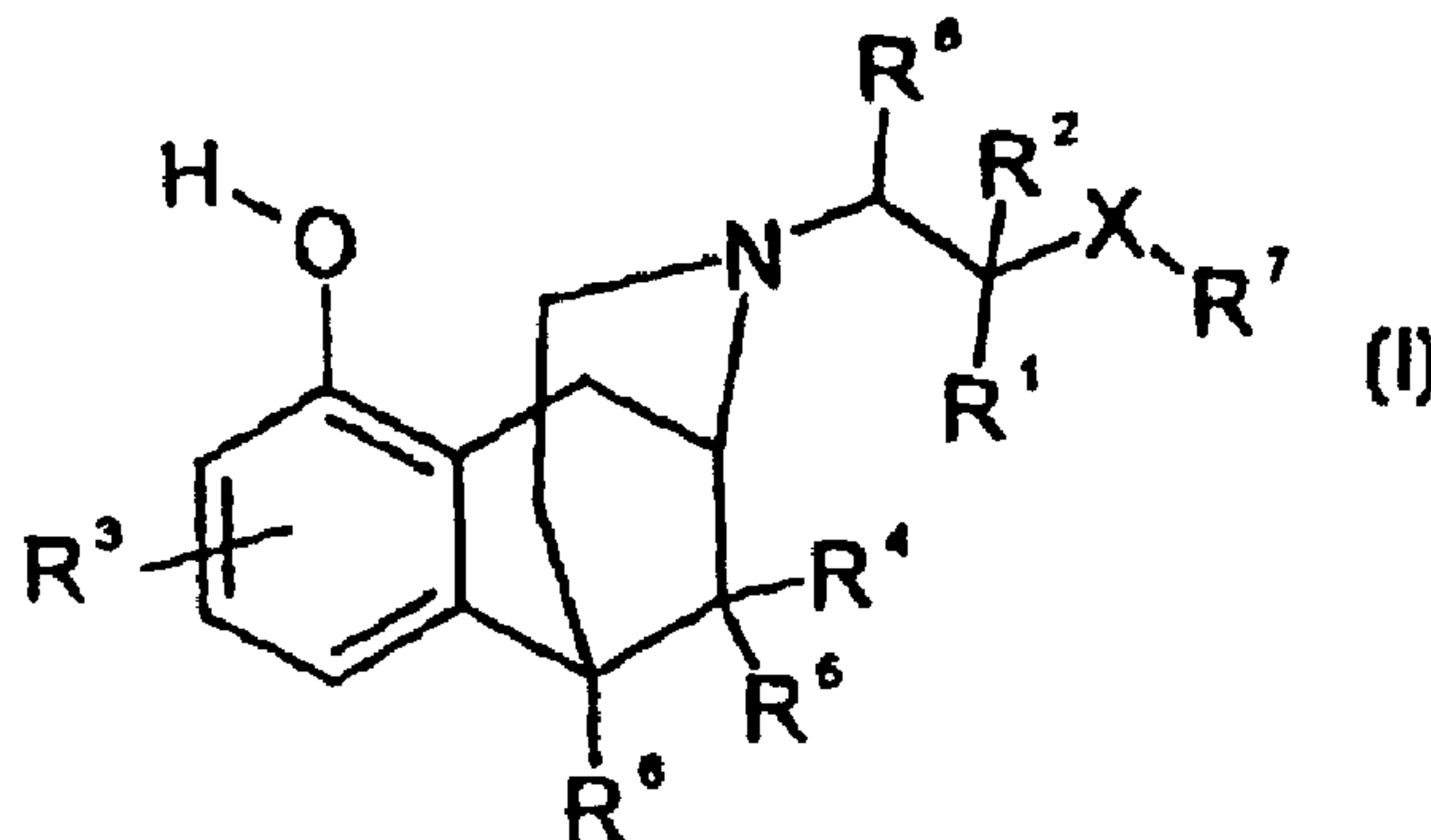




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(51) Int.Cl.⁷ C07D 221/26, A61K 31/485, A61K 31/435
(30) 1997/09/12 (197 40 110.4) DE
(54) **1,2,3,4,5,6-HEXAHYDRO-2,6-METHANO-3-BENZAZOCINE-10-
OLES SUBSTITUES, PROCEDES PERMETTANT DE LES
PREPARER ET LEUR UTILISATION COMME
MEDICAMENTS**
(54) **SUBSTITUTED 1,2,3,4,5,6-HEXAHYDRO-2,6-METHANO-3-
BENZAZOCINE-10-OLES, METHOD FOR THE PRODUCTION
AND USE THEREOF AS MEDICAMENTS**

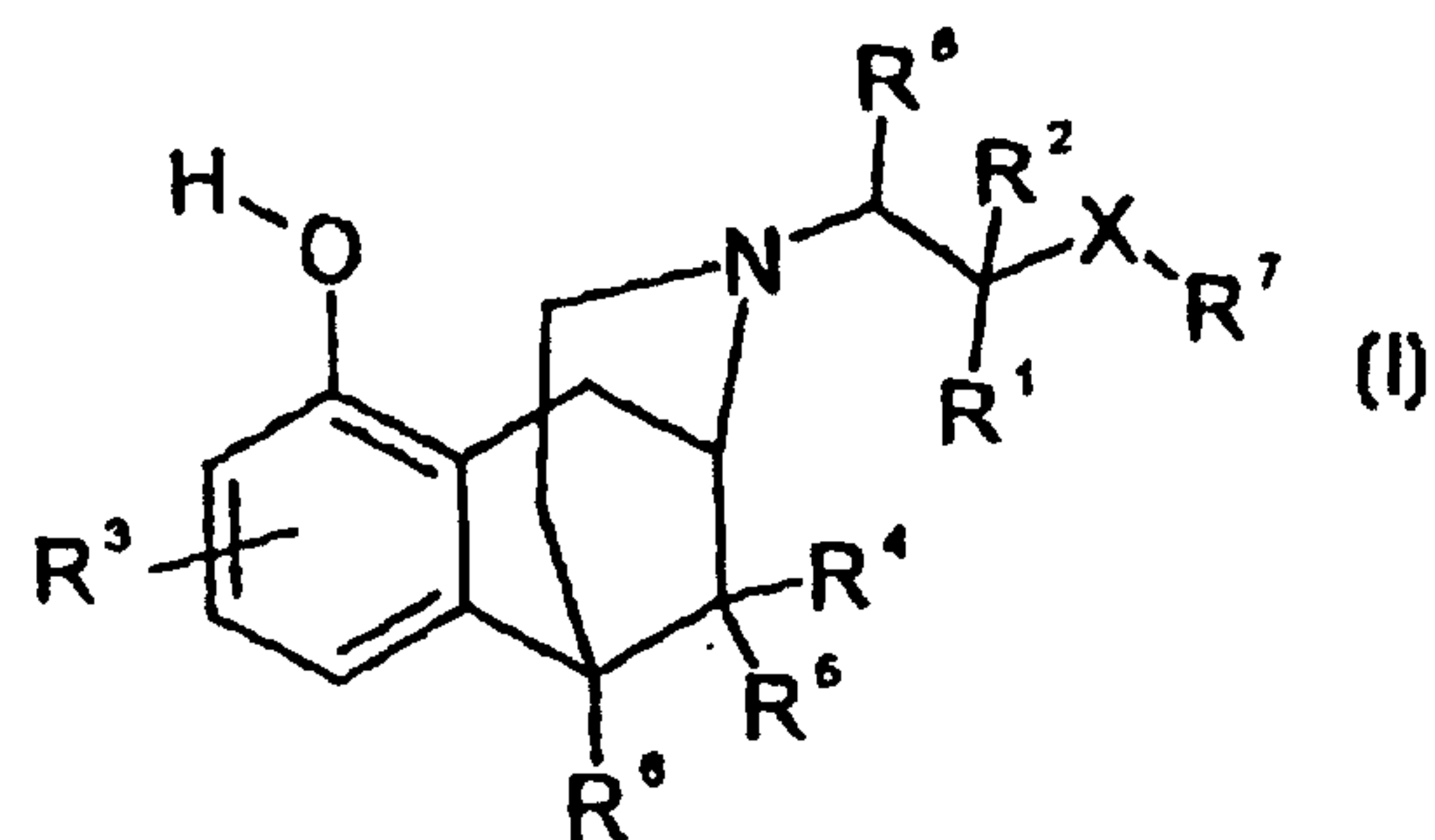


(57) L'invention concerne de nouveaux 1,2,3,4,5,6-hexahydro-2,6-méthano-3-benzazocine-10-oles de la formule générale (I), des procédés permettant des les préparer et leur utilisation comme médicaments.

(57) The invention relates to novel substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-10-oles of general formula (I), and to a method for the production and the use thereof as medicaments.

(57) Abstract

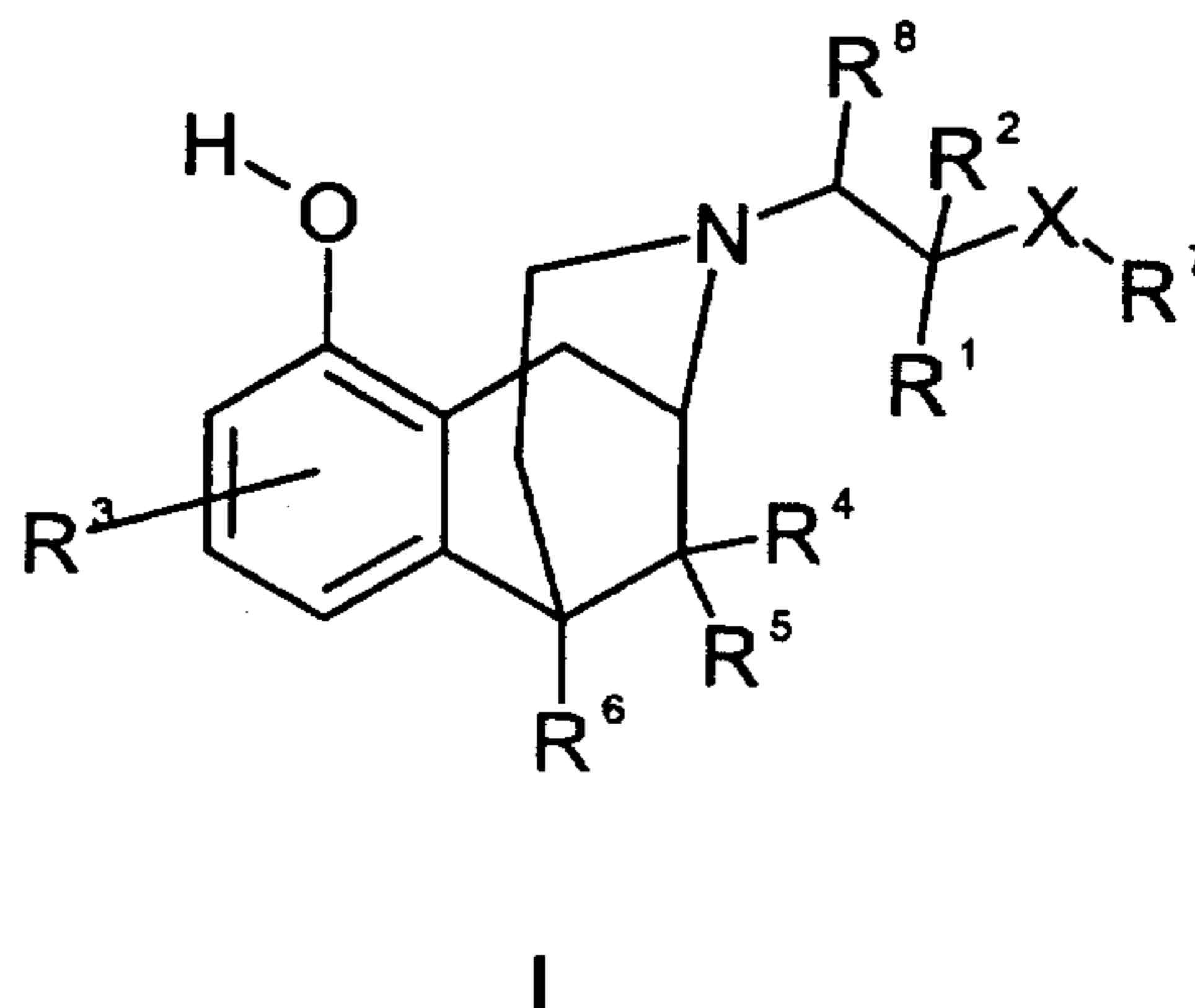
The invention relates to novel substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine-10-oles of general formula (I), and to a method for the production and the use thereof as medicaments.



S018-528pct.202

5 **Substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ols, processes for preparing them and their use as pharmaceutical compositions**

10 The present application relates to new substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ols of general formula I:



15 wherein

20 X denotes a single bond, -O-, C₁-C₄-alkylene, an alkylene bridge having 1 to 8 carbon atoms which may be branched or unbranched and may have one or two oxygen atom(s) anywhere in the bridge, preferably C₁-C₃-alkylene-O- or -O-CH₂-CH₂-O-, -O-CH₂-CH₂-NH-;

 R¹ denotes hydrogen, methyl, ethyl, phenyl;

25 R² denotes hydrogen, methyl;

 R³ denotes hydrogen, fluorine, chlorine, bromine, hydroxy, methyl, methoxy;

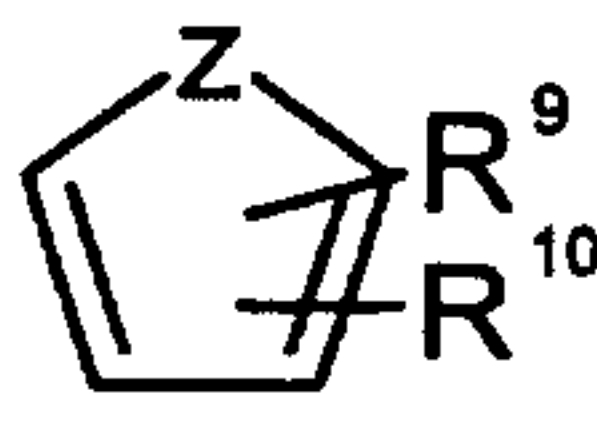
- 2 -

R⁴ denotes hydrogen, methyl, ethyl;

R⁵ denotes hydrogen, methyl, ethyl;

5 R⁶ denotes hydrogen, methyl, ethyl;

R⁷ denotes tert.-butyl, cyclohexyl, phenyl
optionally substituted by R⁹ and R¹⁰, which may be

identical or different,  ;

10

R⁸ denotes hydrogen, C₁-C₄-alkyl;

Z denotes oxygen, NH, sulphur;

15 R⁹ denotes hydrogen, methyl, fluorine, chlorine,
bromine, methoxy;

R¹⁰ denotes hydrogen, methyl, fluorine, chlorine,
bromine, methoxy;

20

optionally in the form of the individual optical
isomers, mixtures of the individual enantiomers or
racemates as well as in the form of the free bases or
the corresponding acid addition salts with
25 pharmacologically acceptable acids such as e.g. acid
addition salts with hydrohalic acids - for example
hydrochloric or hydrobromic acids - or corresponding
organic acids - for example fumaric or diglycolic
acid.

30

Preferred compounds of general formula I are those
wherein, in the above definition R⁴ and R⁵ either
both simultaneously denote methyl or independently of
one another may denote hydrogen or methyl, with at

least one of the substituents denoting a methyl group;

5 Compounds of general formula 1 are preferred wherein

X denotes oxygen;

10 R^1 denotes hydrogen, methyl or ethyl;

R^2 denotes hydrogen,

R^3 denotes hydrogen;

15 R^4 denotes hydrogen or methyl;

R^5 denotes hydrogen or methyl;

20 R^6 denotes methyl;

R^7 denotes phenyl;

R^8 denotes hydrogen

25 R^9 and R^{10} independently of one another denote hydrogen, methyl, fluorine or methoxy

particularly compounds of general formula I wherein, in the above definition, R^4 and R^5 either both
30 simultaneously denote methyl or independently of one another denote hydrogen or methyl, with at least one of the substituents denoting a methyl group;

The following compounds are most particularly
35 preferred:

(-) - (1R,2"S) -2- (2"-benzyloxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan

and

5 (-) - (1R,2"S) -2- [2"- (2' ",6' "-difluorobenzyl)oxy]propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan

in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids.

10

Unless otherwise stated, the general definitions are used in the following sense:

15 C₁-C₄-alkyl or C₁-C₈-alkyl generally denotes a branched or unbranched hydrocarbon group having 1 to 4 or 1 to 8 carbon atom(s), which may optionally be substituted with one or more halogen atom(s) - preferably fluorine - which may be identical to or different from one another. The following hydrocarbon
20 groups are mentioned by way of example:

25 methyl, ethyl, propyl, 1-methylethyl (isopropyl), n-butyl, 1-methylpropyl, 2-methylpropyl, 1,1-dimethylethyl, pentyl, 1-methylbutyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, hexyl, 1-methylpentyl, 2-methylpentyl, 3-methylpentyl, 4-methylpentyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,2,-dimethylbutyl,
30 2,3-dimethylbutyl, 3,3-dimethylbutyl, 1-ethylbutyl, 2-ethylbutyl, 1,1,2-trimethylpropyl, 1,2,2-trimethylpropyl, 1-ethyl-1-methylpropyl and 1-ethyl-2-methylpropyl. Unless otherwise stated, lower alkyl groups having 1 to 4 carbon atoms, such as methyl,
35 ethyl, propyl, iso-propyl, n-butyl, 1-methylpropyl, 2-methylpropyl or 1,1-dimethylethyl are preferred.

Accordingly alkylene denotes a branched or unbranched divalent hydrocarbon bridge having 1 to 8 carbon atoms which may optionally be substituted with one or more halogen atom(s) - preferably fluorine - which may be identical to or different from one another.

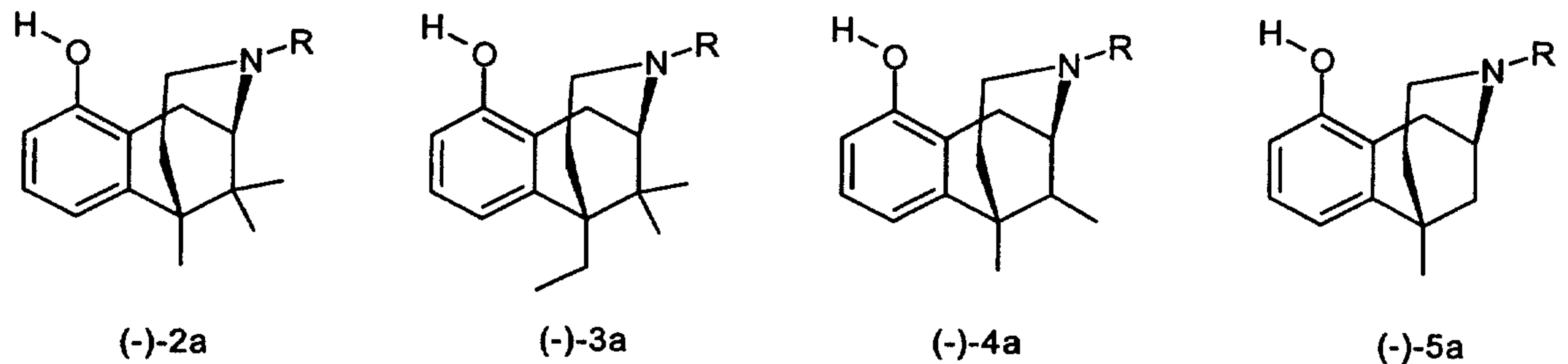
Alkoxy generally denotes a straight-chained or branched hydrocarbon group bound via an oxygen atom - a lower alkoxy group having 1 to 4 carbon atom(s) is preferred. The methoxy group is particularly preferred.

15 **Methods of preparation**

The compounds according to the invention may be prepared by methods known from the prior art [WO 97/06146]. The invention relates to the enantiomerically pure compounds as well as the associated racemates.

The key compounds are the nor-benzomorphans 2a to 5a, which are shown in the diagram as the corresponding (-)-enantiomers:

Diagram 1:



R = H

5

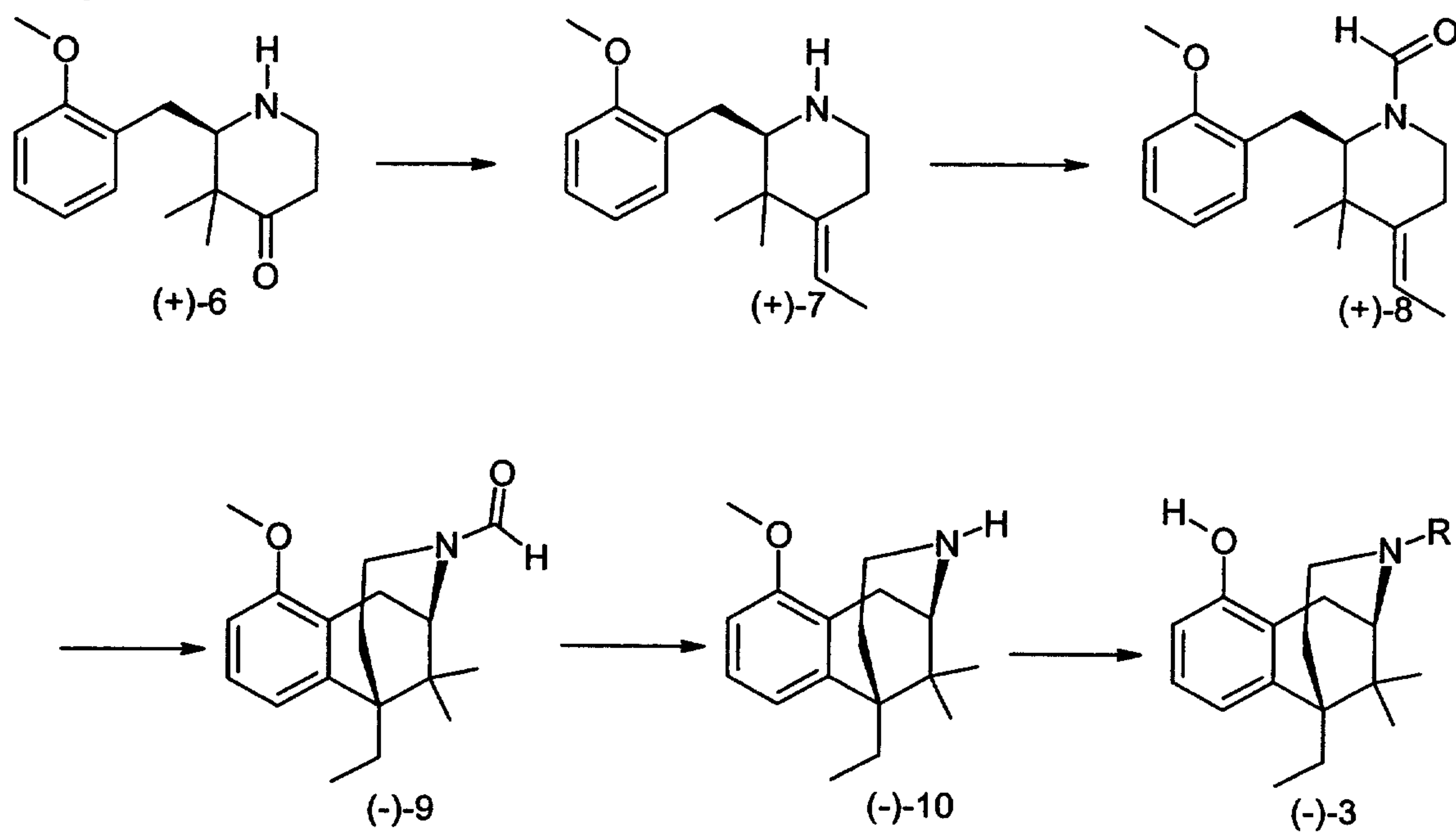
The synthesis of 2 where R=H is described in published German Application No.: 195 28 472.

10

Compound 3 can be prepared analogously to compound 2. The starting compound is the piperidone 6 which occurs as an intermediate in the synthesis of 2, and which is reacted for example with an ethyltriphenylphosphonium salt instead of with the corresponding ethyl derivative - as is already known from the prior art (cf. Diagram 2!).

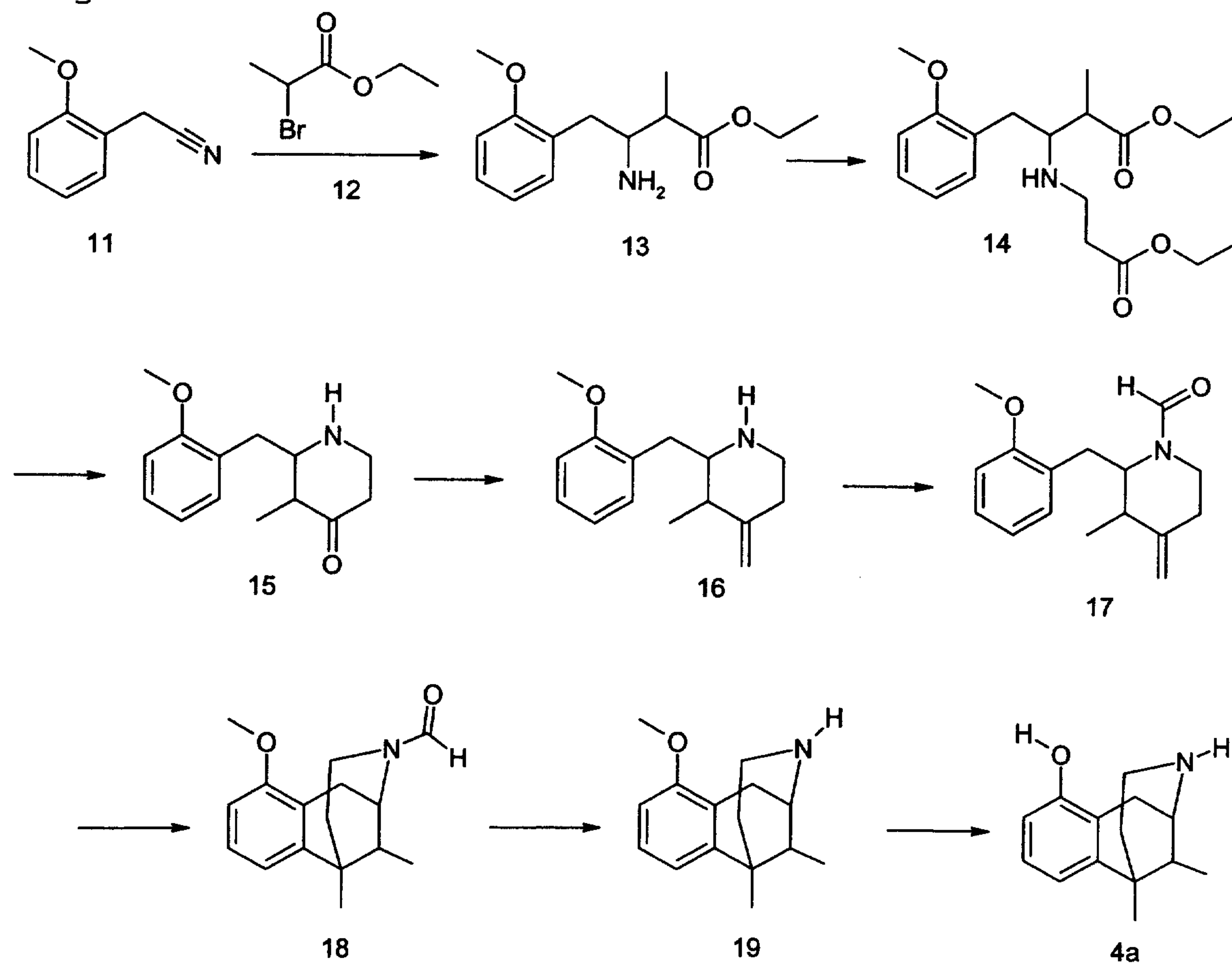
15

Diagram 2:

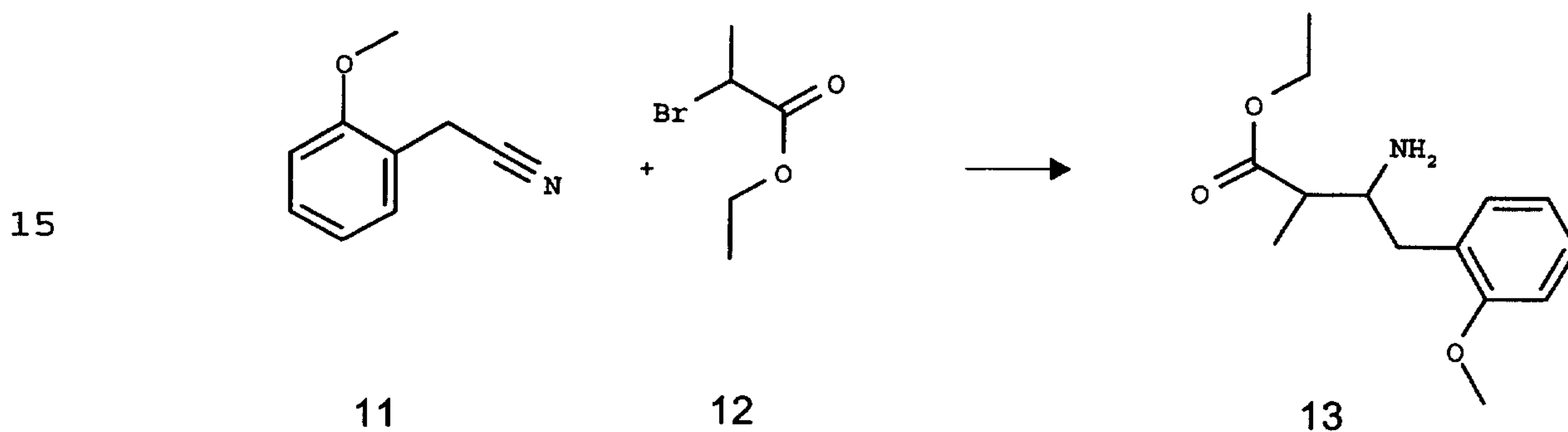


- 5 Compound 4 is prepared analogously to the process described in WO 97/06146 from 2-methoxybenzylcyanide (11) and 2-bromopropionic acid (12).

Diagram 3:



In the first step, for example, 2-methoxybenzyl
 5 cyanide (11) is reacted with ethyl 2-bromopropionate
 (12) to obtain the correspondingly substituted 3-
 amino-2-methylbutanoic acid ester derivative (13)
 (since in view of the desired end product the alcohol
 10 component of the partial ester structure is not
 important, any other C₁-C₈-alkyl ester or a benzyl
 ester may be used):

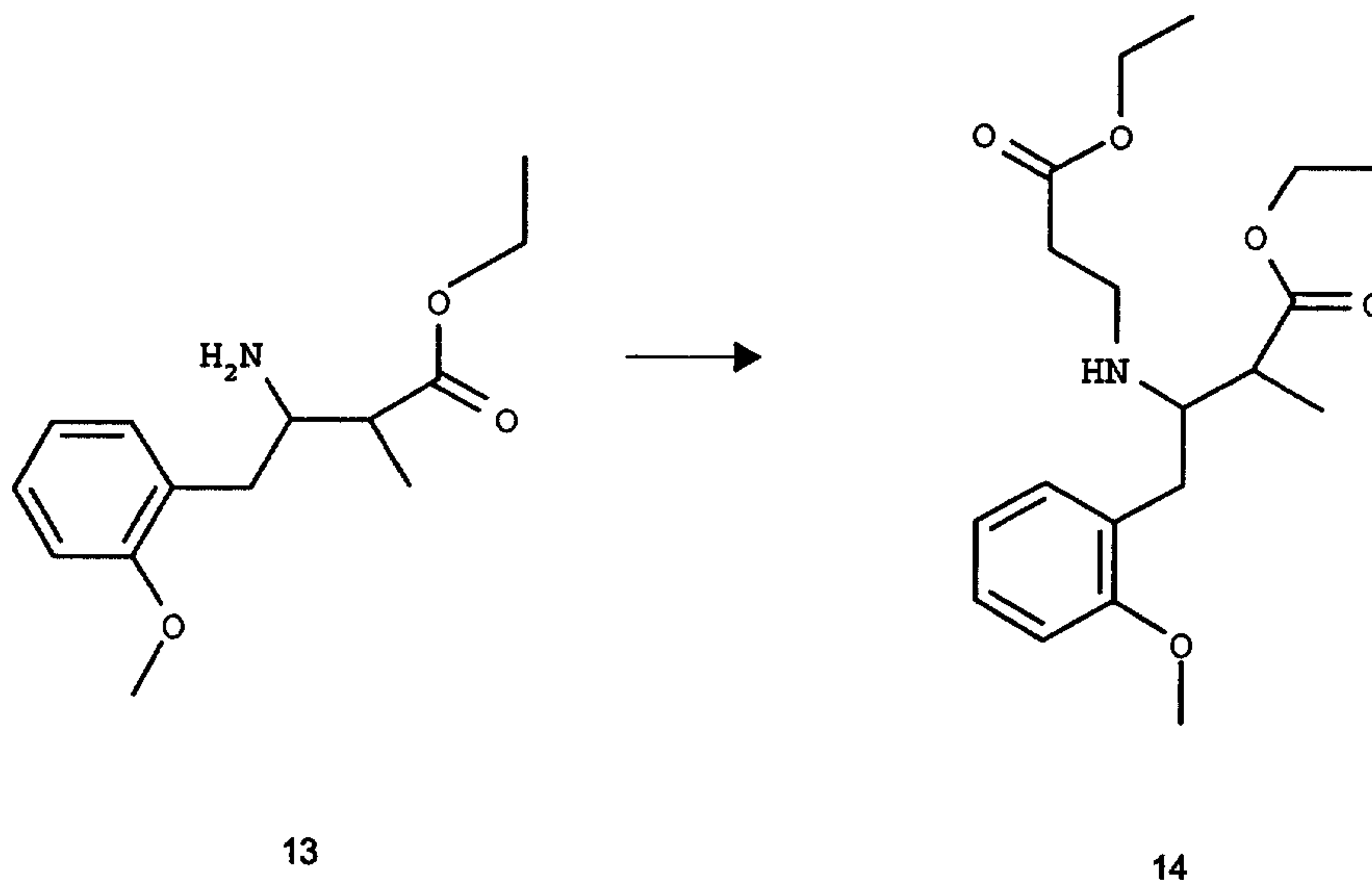


In order to carry out this conversion, of the Reformatsky reaction type, an alkylhalosilane, preferably a trialkylchlorosilane, most preferably trimethylchlorosilane - and zinc powder are placed in a solvent which is inert under the reaction conditions used, preferably an ether, or in a halohydrocarbon, most preferably dichloromethane. After this mixture has been diluted with a polar - inert - solvent, preferably a cyclic ether, most preferably tetrahydrofuran - the reaction mixture is heated - preferably to reflux temperature - and combined with a mixture of the ethyl 2-bromopropionate of general formula 3 with the o-methoxybenzylcyanide and heated further, preferably to reflux temperature. After cooling and filtering off the zinc powder, the reaction mixture is mixed with a reducing agent which is selective regarding the reduction of imino functions - preferably a complex alkali metal borohydride derivative, most preferably sodium cyanoborohydride - and then mixed with an alkanol - preferably a straight-chained or branched C₁-C₄-alcohol, most preferably ethanol. Then an aqueous solution of a basically reacting compound - preferably ammonia solution, most preferably with concentrated ammonia solution - is added and the organic phase of the reaction mixture is isolated. After drying and evaporation *in vacuo*, the residue remaining is taken up in an inert solvent - preferably in an aliphatic or aromatic hydrocarbon, most preferably in toluene - and extracted with the aqueous solution of an acid - preferably a mineral acid, most preferably 2N hydrochloric acid. Finally the aqueous phase is made alkaline with the aqueous solution of a basically reacting compound - preferably ammonia solution, most preferably with

- 10 -

concentrated ammonia solution - and then extracted with an organic, water-immiscible extraction agent - preferably with a halohydrocarbon, most preferably with dichloromethane. The extract thus obtained is dried and then concentrated and the 3-amino-2-methylbutanoate derivative of general formula 4 is isolated.

In the second reaction step the ethyl 3-amino-2-methylbutanoate derivative 13 thus obtained is reacted with ethyl acrylate (as, in the light of the desired end product, the alcohol component of the ester structure is not critical, any other C₁-C₈-alkyl ester or even a benzyl ester may be used here) to obtain the corresponding ethyl 3-(2-ethoxycarbonyl-ethyl)-amino-2-methylbutanoate derivative 14:



In order to carry out this Michael addition reaction the ethyl 3-amino-2-methylbutanoate derivative 13 is dissolved with the ethyl acrylate in a reaction medium which is inert under the reaction conditions - preferably in a straight-chained or branched C₁-C₄-alkanol, most preferably ethanol - and heated - preferably to reflux temperature. After the reaction

- 11 -

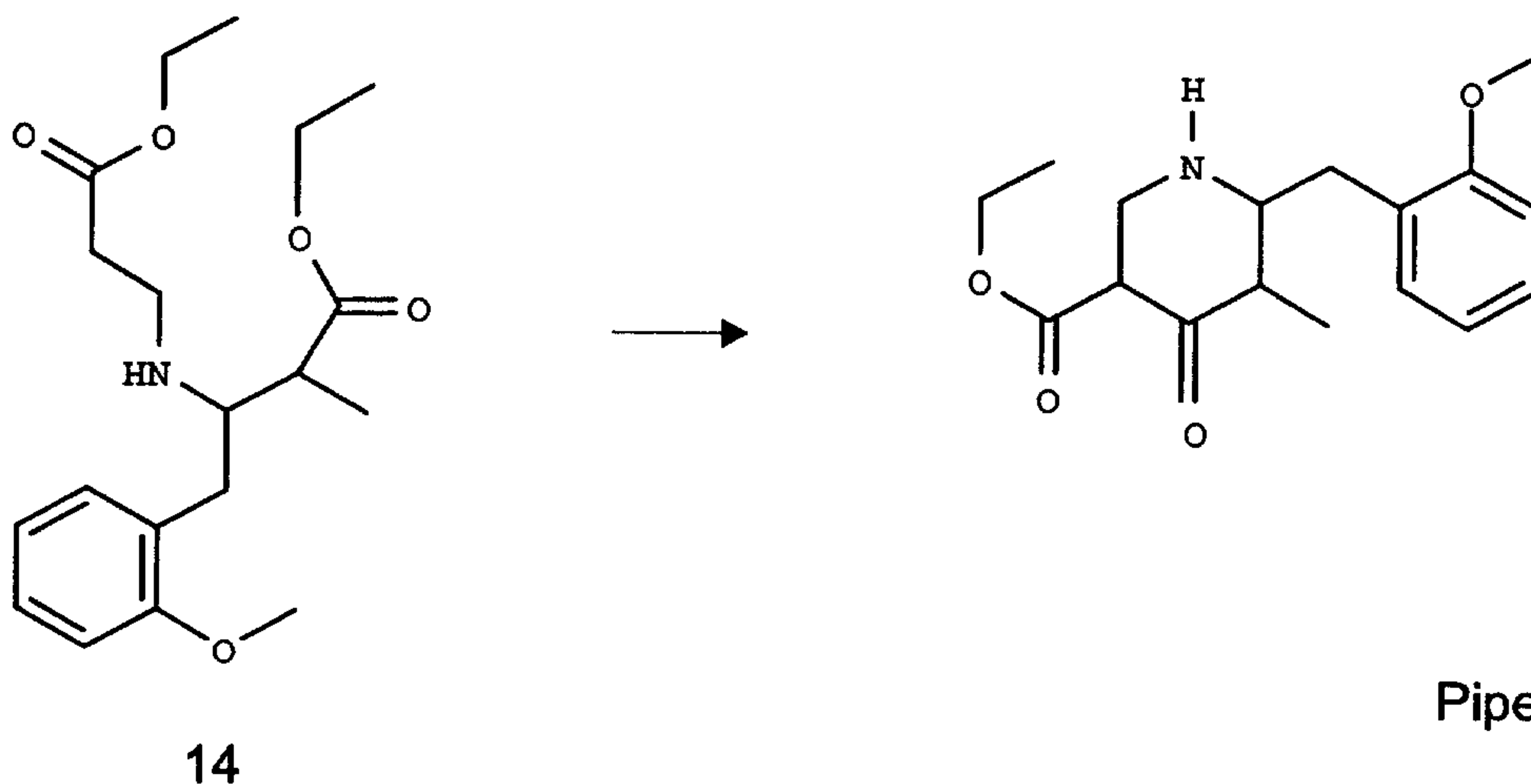
has ended the solvent is eliminated *in vacuo* and the resulting ethyl 3-(2-ethoxycarbonylethyl)amino-2-methylbutanoate derivative 14 is isolated.

5 In the subsequent third step of the reaction the 3-(2-ethoxycarbonylethyl)amino-2-methylbutanoate derivative 14 resulting from the preceding step of the reaction is cyclised to form the corresponding piperidone derivative 15:

10

15

20



In order to carry out the Dieckmann's ester condensation type cyclisation step, the 3-(2-ethoxycarbonylethyl)amino-2-methylbutanoate derivative 14 is dissolved in a solvent which is inert under the cyclisation conditions - preferably in an aliphatic or aromatic hydrocarbon, most preferably in toluene - and heated to reflux temperature in the presence of a basically reacting compound, preferably an alkali metal alkoxide of a branched or unbranched C₁-C₄-alcohol, most preferably potassium-*tert.*-butoxide, and the components of the reaction mixture which are volatile at these temperatures are eliminated by distillation - for example by azeotropic reaction. After the reaction

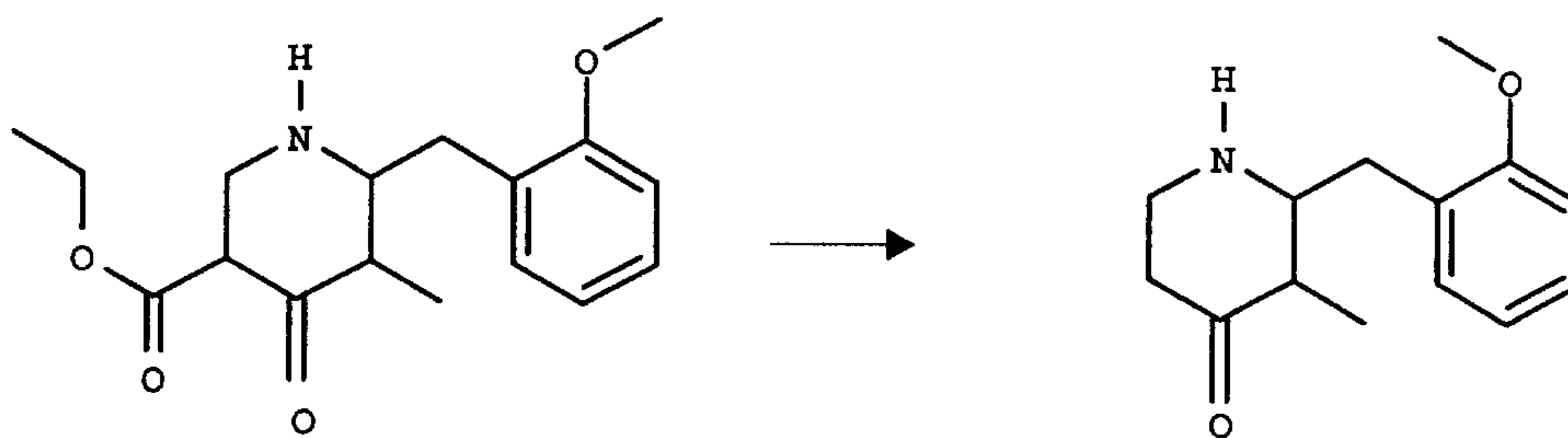
has ended, the reaction mixture is hydrolysed and mixed with the aqueous solution of an acidically reacting compound - preferably with aqueous inorganic acids, most preferably with concentrated hydrochloric acid. Then a water-immiscible extraction agent which is inert under these conditions, - preferably a dialkylether, most preferably diethylether - is added and mixed with the aqueous solution of a basically reacting compound, preferably with aqueous ammonia solution, most preferably with concentrated ammonia solution. After separation of the organic phase as well as exhaustive extraction of the aqueous phase the combined organic extracts are washed with water, dried and evaporated down *in vacuo* and the resulting piperidone ester is isolated.

Alternatively the Dieckmann condensation described above can also be carried out by means of titanium tetrachloride in a halogenated hydrocarbon - preferably dichloromethane [M.N. Deshmukh et al., Synth. Commun. 25 (1995) 177].

In the fourth step of the reaction the piperidone derivative (piperidone ester) thus obtained is saponified and decarboxylated under alkaline or acid conditions to form the corresponding 3-methyl-4-piperidone derivative.

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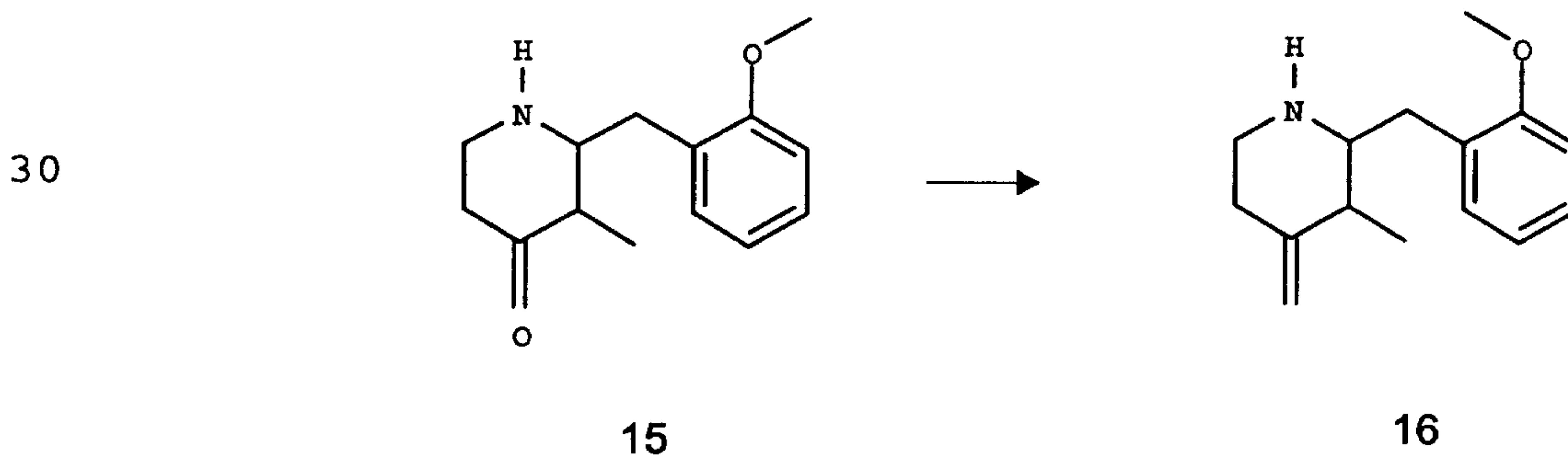
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Piperidone-Ester

For this the piperidone ester is heated, preferably to reflux temperature, in a polar, aqueous solvent or solvent mixture - preferably in a mixture of a
5 straight-chained or branched C₁-C₄-alkanol and water, most preferably in an ethanol/water mixture - with a basically or acidically reacting compound - preferably with an alkali metal hydroxide or an inorganic acid, most preferably with sodium hydroxide
10 or if an acid is used, for example, in the presence of hydrochloric acid or sulphuric acid. After saponification has been completed the reaction medium is eliminated *in vacuo* and the residue is taken up in a solvent suitable for the subsequent salt formation
15 - preferably a polar organic solvent, most preferably in acetone - and the corresponding acid addition salt is precipitated.

The subsequent Wittig reaction with
20 methyltriphenylphosphonium bromide leads in the next step to the corresponding 4-methylene-piperidine derivative 16, which can be isolated in the form of its acid addition salt - preferably in the form of a hydrohalide, most preferably in the form of its
25 hydrochloride.



In order to carry out the Wittig reaction the 3-methylpiperidone derivative 15 in the form of its acid addition salt - for example as the hydrochloride - is dissolved in water and combined with a basically reacting compound or - preferably - the aqueous solution thereof; most preferably, concentrated aqueous ammonia solution is used.

The aqueous phase is extracted with an organic, water-immiscible solvent - preferably with a haloalkane, most preferably with dichloromethane. After drying and evaporation *in vacuo* the residue is taken up in a reaction medium which is inert under the conditions used for the Wittig reaction - preferably in a cyclic ether, most preferably in tetrahydrofuran - and combined with a Wittig reagent which generates a methylene group - preferably a methyltriphenylphosphonium halide, most preferably with methyltriphenylphosphonium bromide - in the presence of a basically reacting compound, preferably an alkali metal alkoxide, most preferably potassium *tert.*-butoxide and - depending on the reactivity of the particular educts used - reacted at a temperature in the range from 0 to 80 °C - preferably in a range from 20 to 60 °C and most preferably at about 40 °C. After the reaction has ended the reaction mixture is combined with water and a water-immiscible organic solvent - preferably with a haloalkane, most preferably dichloromethane - and the organic phase is separated off. After exhaustive extraction of the aqueous phase and drying of the combined extracts, the extraction agent is eliminated, the residue is dissolved in a solvent suitable for the formation of an acid addition salt, preferably in a branched or unbranched C₁-C₄-alkanol, most preferably in isopropanol, and combined with a suitable acid,

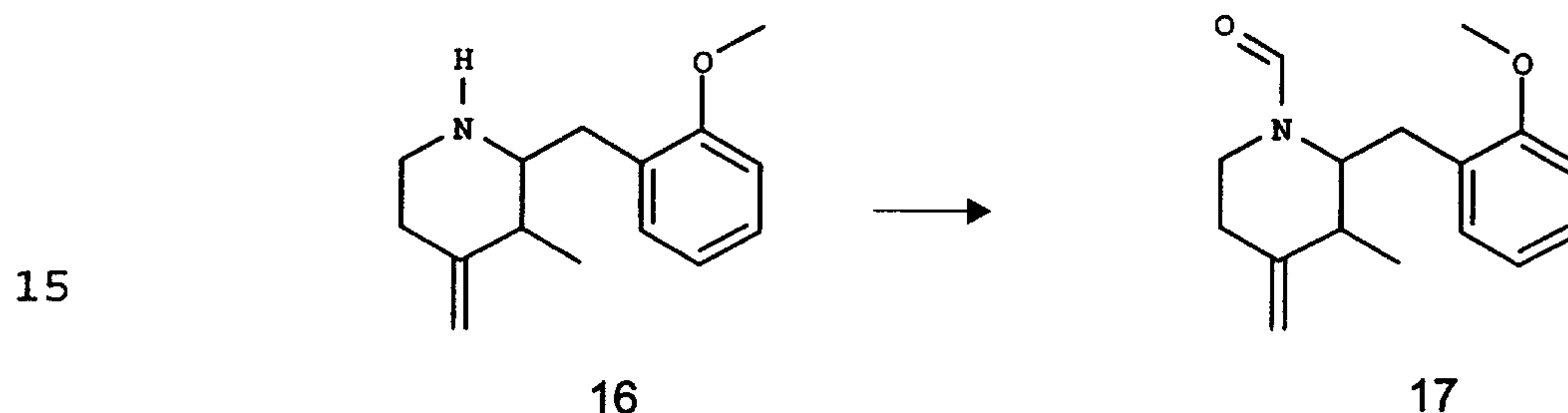
- 15 -

preferably an inorganic acid - such as, for example, a hydrohalic acid, most preferably with concentrated hydrochloric acid - and the acid addition salt of the Wittig product 16 which crystallises out is isolated.

5

In the subsequent reaction step the piperidine nitrogen is formylated - for example with n-butylformate - yielding the corresponding N-formyl-3-methyl-4-methylene-piperidine derivative:

10



20 To do this the piperidine derivative of type 16, which can be isolated in the preceding step as for example, a hydrohalide, is first converted into the corresponding free base, for example by dissolving the piperidine derivative in water and combining it with a basically reacting compound - preferably with the aqueous solution of a basically reacting compound and most preferably with concentrated ammonia solution, and extracting the free piperidine with a organic solvent, preferably with a halogenated hydrocarbon and most preferably with dichloromethane.

30 After the extract has been dried and the extraction agent has been distilled off the free base is taken up in an organic solvent - such as, for example, a hydrocarbon, preferably in an alkyl-aromatic compound, most preferably in toluene - and reacted

35 with a formylating agent - preferably with an

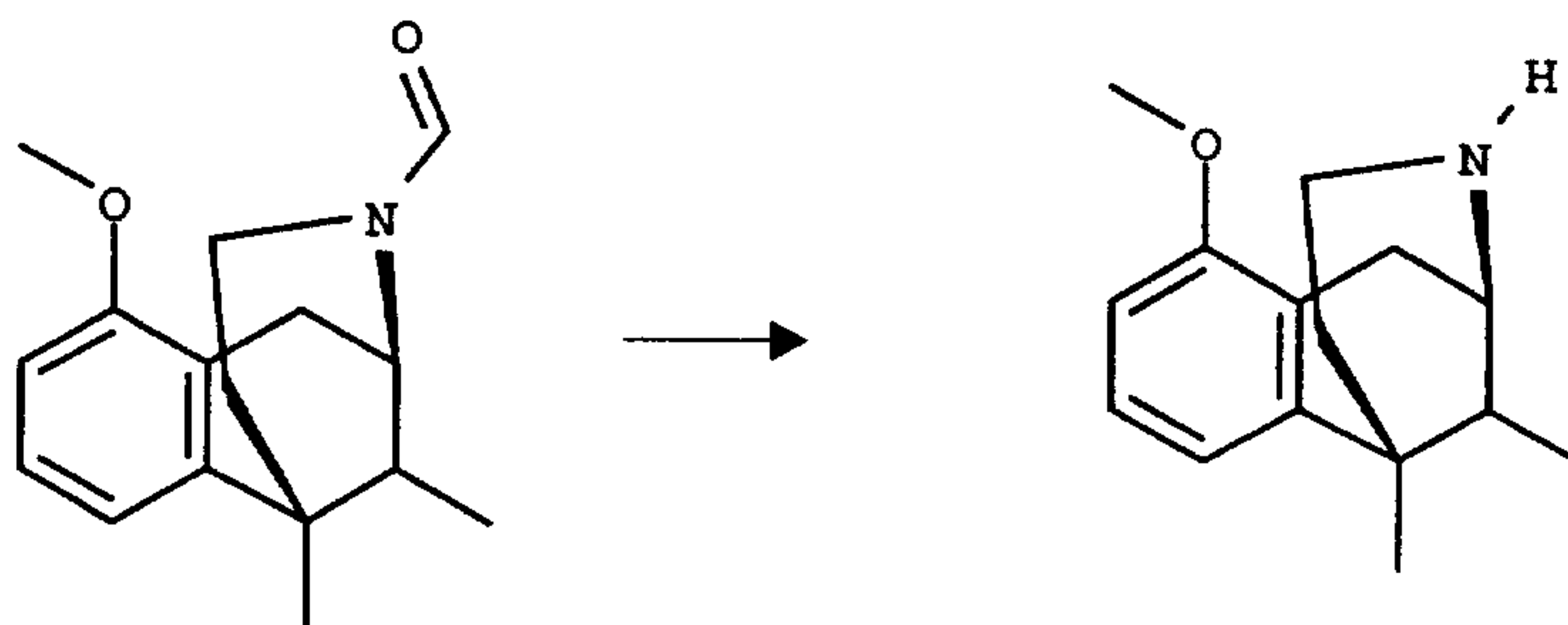
- 16 -

alkylformate, most preferably with n-butylformate -
and the reaction product 17 is isolated.

5 In the subsequent cyclisation reaction, in the eighth
step of the process, the benzomorphan structure of
type 18 is finally synthesised in the presence of
correspondingly reactive Lewis acids - such as, for
example, inorganic salt acids, particularly
10 hydrobromic acid and preferably with sulphonic acids
or with aluminium(III) halides, such as e.g.
aluminium trichloride.

The following reaction step results in the cleaving
of the formyl group and thus produces the
15 corresponding 4'-methoxy-5,9-dimethyl-6,7-
benzomorphan (19).

20



25

18

19

30 To do this the formylbenzomorphan 18 is dissolved in
a polar solvent - preferably in an alkanol, most
preferably in n-propanol - and combined with an
acidically reacting compound - preferably with the
aqueous solution of an inorganic acid, most
35 preferably with concentrated hydrochloric acid - and
then heated. After cleaving the formyl group, the

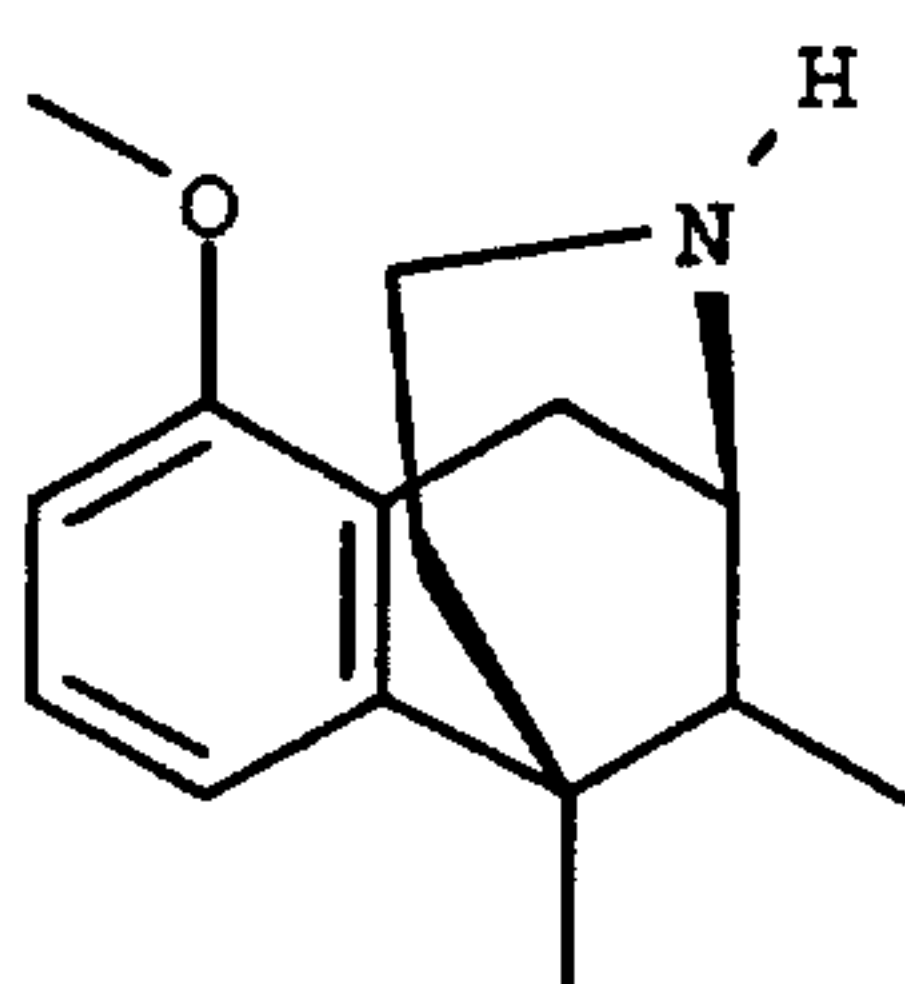
- 17 -

reaction mixture is evaporated down, combined with water and extracted with a water-immiscible solvent - preferably with an ester of a carboxylic acid, most preferably ethyl acetate. The aqueous phase thus
5 purified is made basic, preferably with concentrated ammonia solution, and extracted with an organic solvent - preferably with a halohydrocarbon, most preferably with dichloromethane. After drying and concentration by evaporation of the combined organic
10 extracts, the corresponding (-)-4'-methoxy-5,9-dimethyl-6,7-benzomorphan (19) may be isolated, for example.

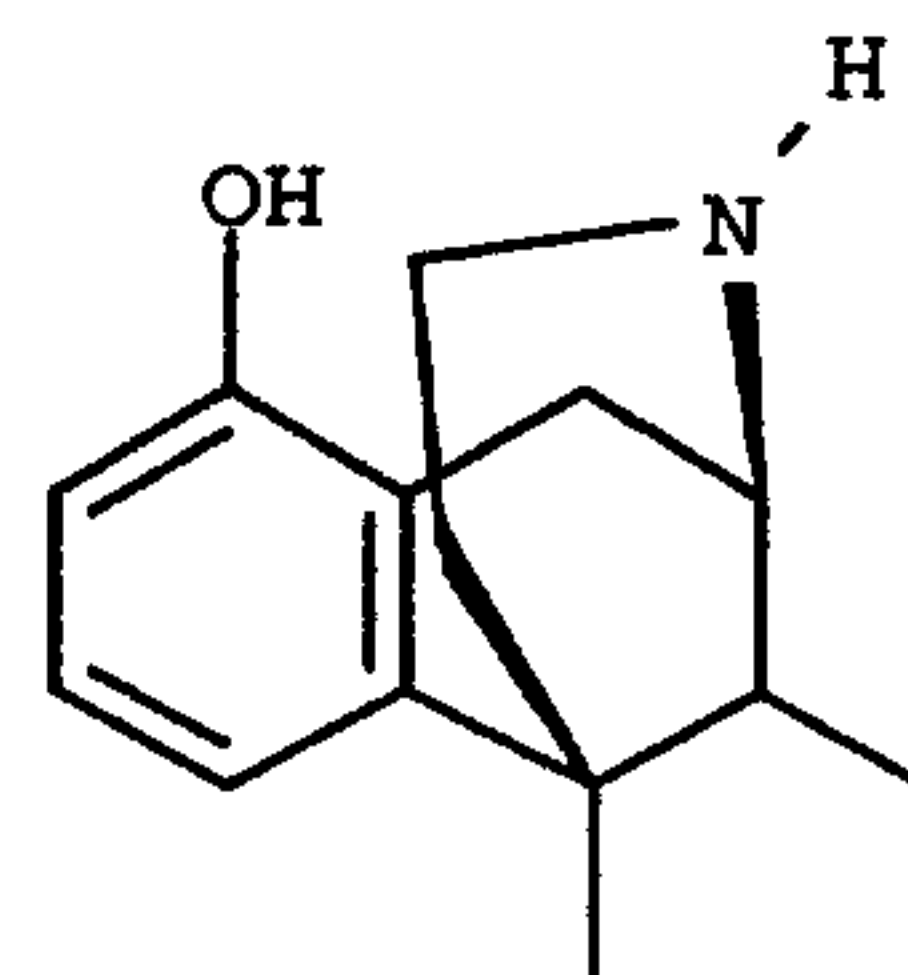
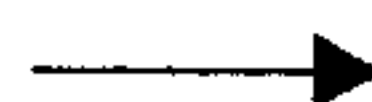
15 In this step, if this has not already been done, the stereoisomers which are still present as a mixture can be separated. The isolation may be effected using the methods described above or by methods known in the art for separating optical isomers.

20 In the following step the (-)-4'-methoxy-5,9-dimethyl-6,7-benzomorphan (19) thus obtained may be subjected to ether splitting under acidic conditions - preferably with an inorganic acid, e.g. with hydrohalic acid and most preferably with hydrobromic
25 acid - resulting in the corresponding free partial phenol structure.

30



19



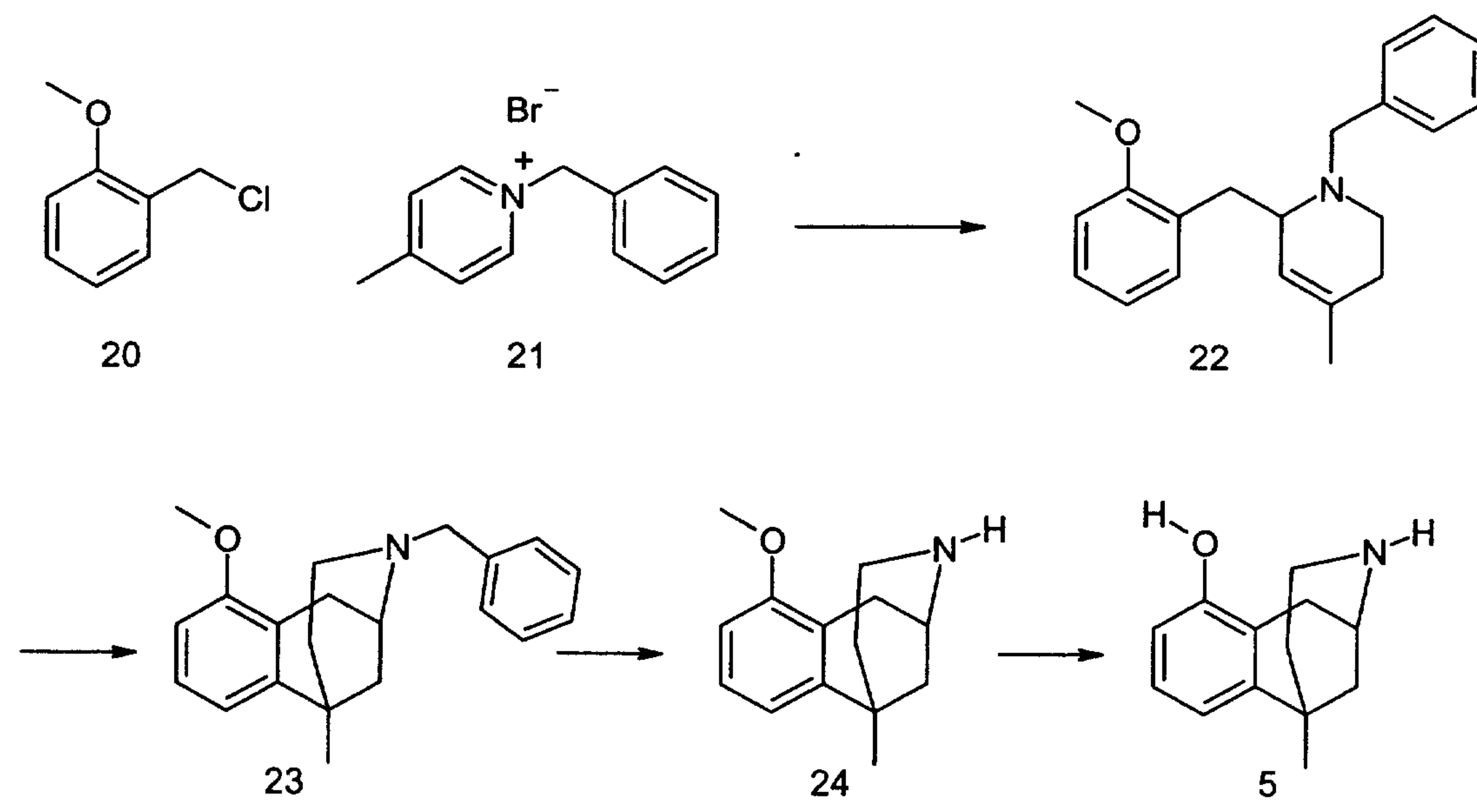
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35

The ether cleavage is carried out under acidic conditions; it has proved beneficial to use inorganic acids. The use of hydrobromic acid has proved particularly advantageous. The saponification product resulting from this saponification can be obtained in this way - for example - in the form of its hydrobromide.

Compound 5 is prepared by the reaction sequence shown in Diagram 4.

Diagram 4:

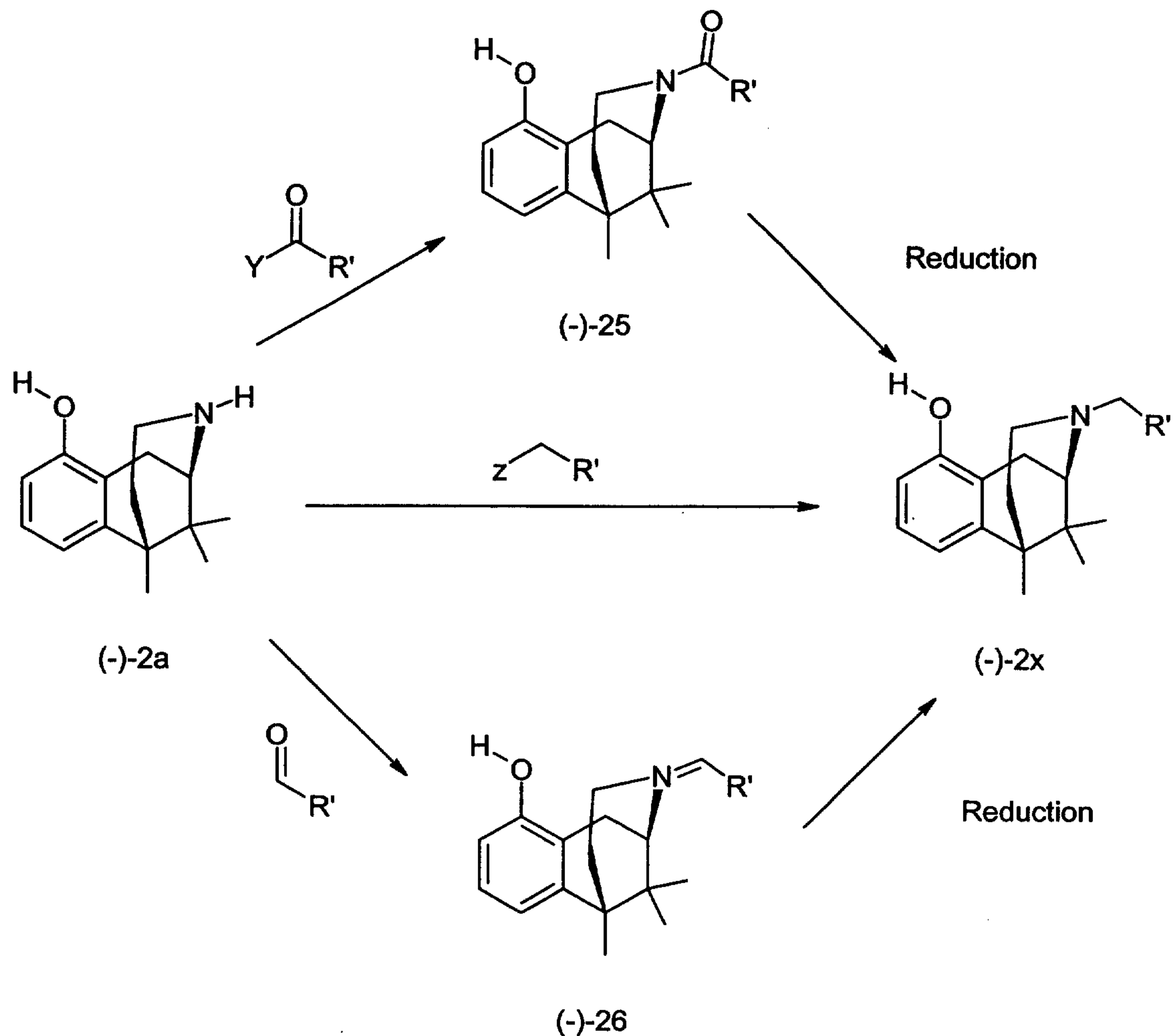


15

The N-substituent is introduced by reacting the key compounds 2a to 5a with acylating agents to obtain the intermediate compounds 25 and subsequently reducing them or by directly alkylating the key compounds 2a to 5a with alkylating agents or by reacting with aldehydes to obtain 26 and subsequent reduction. Diagram 5 shows these methods for the key compound (-)-2a by way of example.

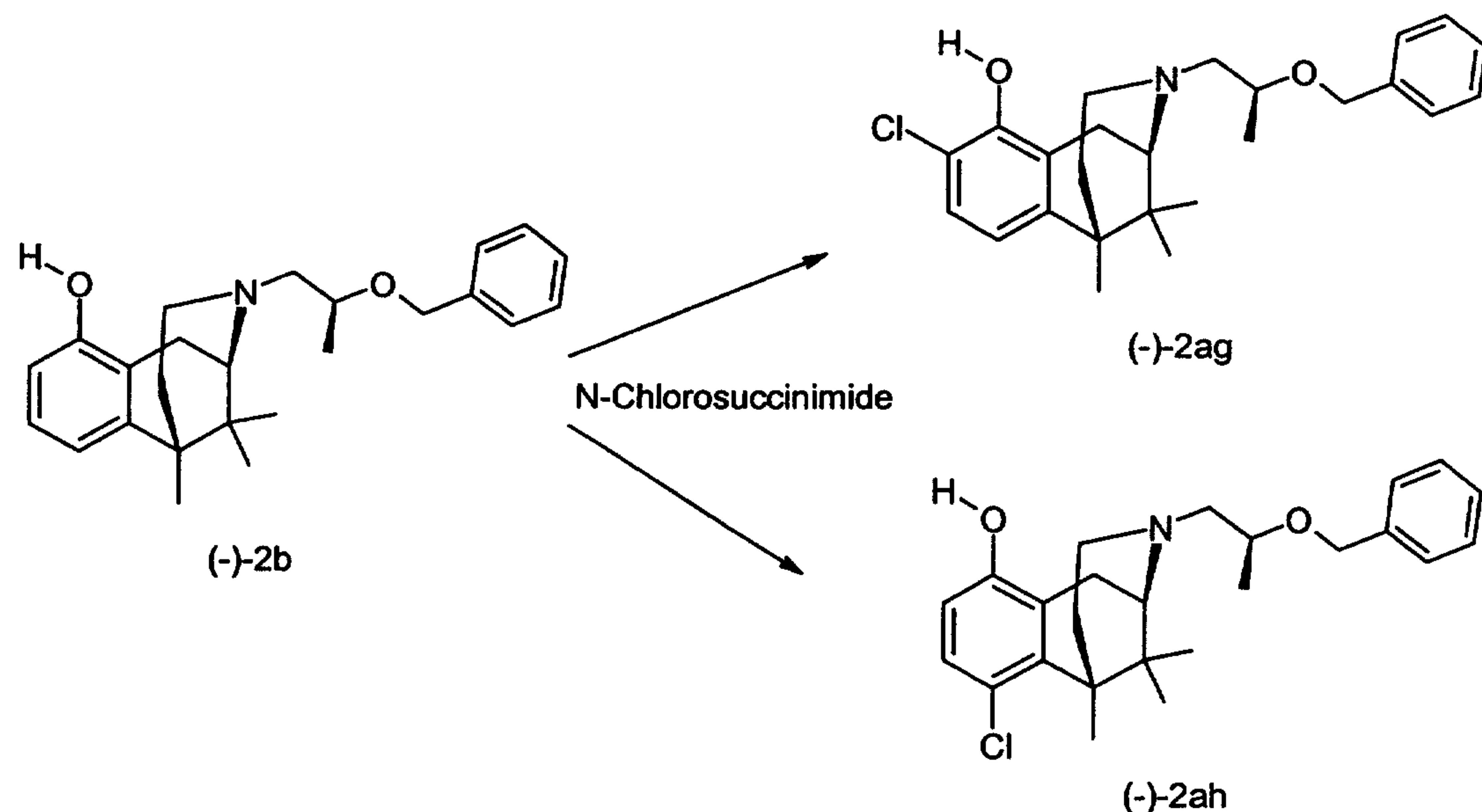
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Diagram 5:



- 5 The compounds according to the invention can be synthesised by regioselectively substituting the aromatic benzomorphan species - using the methods known *per se* from the prior art. An example of the introduction of a substituent R^3 according to general
- 10 formula I is given for compound (-)-2b in Diagram 6.

Diagram 6:



5

Biological Properties

It has been found that cell damage and loss of function occurring as a result of hypoglycaemia, hypoxia, anoxia and ischaemia are due to increased synaptic activity to some extent. A series of experiments have demonstrated that hypoglycaemic and hypoxic conditions of this kind lead to massive depolarisation of the affected cells. This depolarisation in turn causes a pathogenic rise in intracellular calcium and additionally causes an increased release of excitatory amino acids in the neuronal tissue. The voltage-dependent sodium channel has a key role in this cascade. Thus, blocking it can prevent the depolarisation of the cells, thereby reducing the calcium influx through voltage-dependent calcium channels and in the neuronal tissue through NMDA-receptor channels. Furthermore, the reduced influx of sodium ions into the cell prevents the

calcium/sodium exchanger from operating in the other direction and carrying calcium into the cell. In neuronal tissue the reduced influx of sodium ions into the cell also prevents the glutamate transporter
5 from operating in the other direction and releasing glutamates [C.P. Taylor and B.S. Meldrum, TIPS 16 (1995) 309; J. Urenjak and T.P. Obrenovitch Am. Soc. Phar. Exp. Ther. 48 (1996) 21].

10 Surprisingly, it has now been found that the compounds according to the invention of general formula I, unlike the compounds known from the prior art [EP-B-0 521422], have no appreciable affinities for the NMDA-receptor (K_i [^3H] MK801: > 10000 nM). On
15 the contrary, it was found rather that the compounds according to the invention are blockers of the voltage-dependent sodium channel. These are compounds which competitively or non-competitively displace batrachotoxin (BTX) with a high affinity from the
20 binding site on the sodium channel. Such substances exhibit "use-dependency" when the sodium channels are blocked, i.e. for binding the substances at the sodium channel, first of all the sodium channels have to be activated. Maximum blockage of the sodium
25 channels is only achieved after repeated stimulation of the sodium channels. Consequently, the substances preferably bind to sodium channels which are multiply activated. As a result the substances are capable of activity preferentially in those regions of the body
30 which are pathologically overstimulated.

BTX-binding to the sodium channel serves as a test system for detecting the sodium channel-blocking effect [S.W. Postma & W.A. Catterall, Mol. Pharmacol.
35 25, 219-224 (1984)], as do patch-clamp experiments which show that the compounds according to the

invention block the electrically stimulated sodium channel in a "use-dependent" manner [W.A. Catterall, Trends Pharmacol. Sci., 8, 57-65 (1987)].

5 Moreover, the compounds according to the invention
are shown to have a neuroprotective effect by the
blockade of veratridin-induced glutamate release [S.
Villauneva, P. Frenz, Y. Dragnic, F. Orrego, Brain
Res. 461, 377-380 (1988)]. Veratridine is a toxin
10 which permanently opens up the sodium channel. This
leads to an increased influx of sodium ions into the
cell. By means of the cascade described above, this
increased influx of sodium leads to an increased
release of glutamate in the neuronal tissue. This
15 increased release of glutamate can be antagonised
with the compounds according to the invention.

Anticonvulsant properties of the substances according
to the invention were demonstrated by their
20 protective effect against spasms caused by the
maximum electric shock in mice [M.A. Rogawski & R.J.
Porter, Pharmacol Rev. 42, 223-286 (1990)] -
neuroprotective properties were demonstrated by a
protective effect in a rat-MCAO model [U. Pschorn &
25 A.J. Carter, J Stroke, Cerebrovascular diseases, 6,
93-99 (1996)].

There are also descriptions of sodium channel
blockers being used to treat cyclophrenia (manic
30 depressive disorder) [J.A. Calabrese, C. Bowden, M.J.
Woyshville in : Psychopharmacology: The fourth
generation of progress (Eds.: D.E. Bloom & J. Kupfer)
1099-1111, Raven Press Ltd. New York]. These results
demonstrate that the 1,2,3,4,5,6-hexahydro-2,6-
35 methano-3-benzazocin-10-ols of general formula I

can be used for treating diseases caused by dysfunction due to overstimulation. These include diseases such as arrhythmia, spasms, cardiac and cerebral ischaemia as well as neurodegenerative disorders of various origins. 5 For example, the following may be mentioned: epilepsy, hypoglycaemia, hypoxia, anoxia, brain trauma, cerebral oedema, cerebral stroke, perinatal asphyxia, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, cyclophrenia, hypotonia, 10 cardiac infarct, cardiac rhythm disorders, angina pectoris, pain, anaesthesia and local anaesthesia.

The following compounds have proved particularly effective in this context:

15

(-)-(1R,2"S)-2-(2"-benzyloxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan and

20

(-)-(1R,2"S)-2-[2"-(2'",6'"-difluorobenzyl)oxy]-propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan.

25

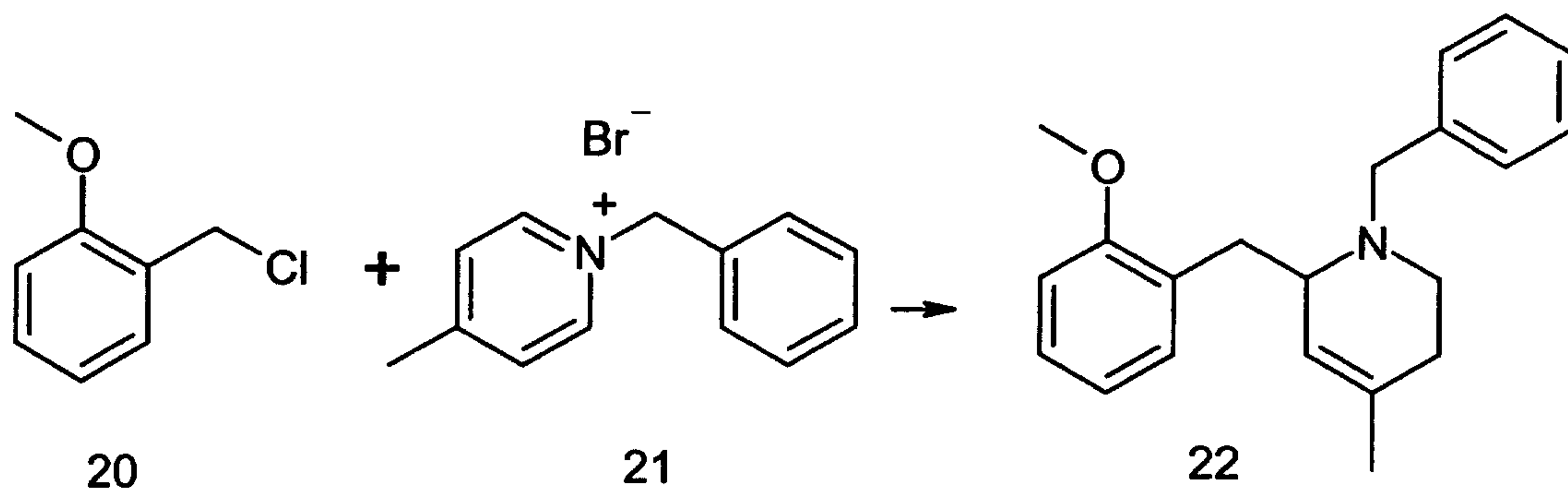
The compounds according to the invention can be prepared from compounds known in the art, using the processes described in the following Examples, *inter alia*.

30

In particular the present invention relates *inter alia* to the following method of preparing norbenzomorphans of general formula 5, characterised in that

a) o-methoxychlorbenzylchloride (20) is reacted with the benzylpyridinium bromide 21 to obtain tetrahydropyridine 22

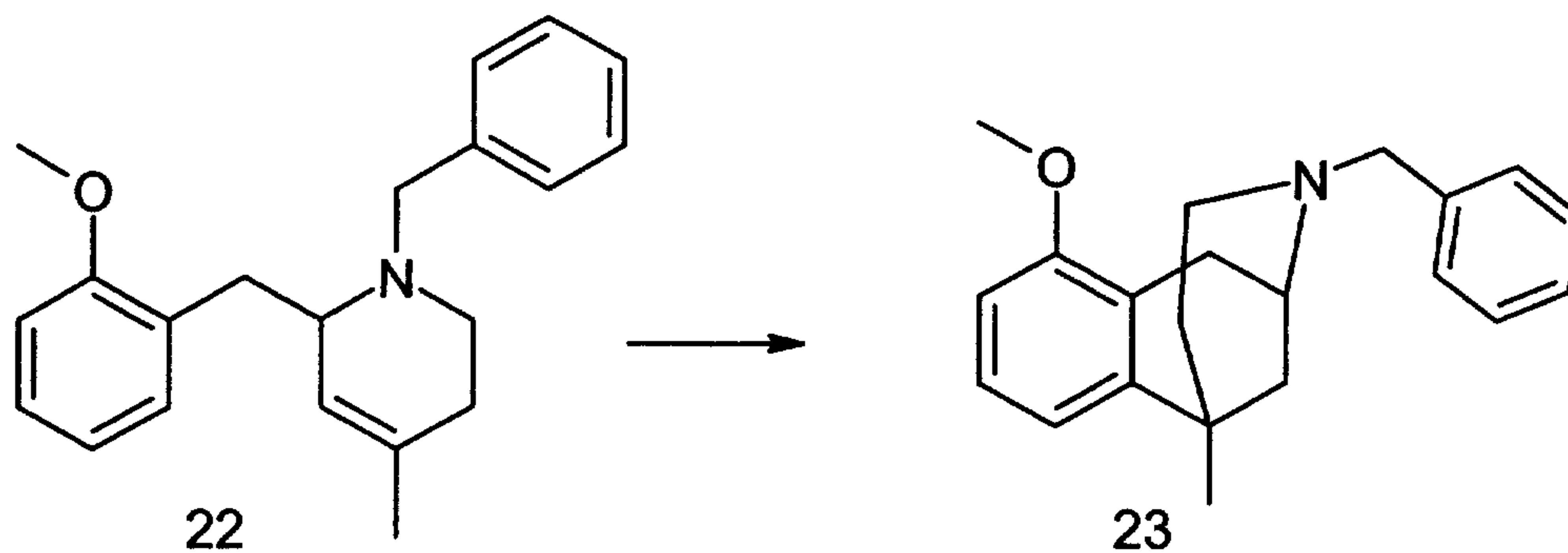
- 24 -



and

5

b) the tetrahydropyridine derivative 22 is rearranged to obtain the N-benzylbenzomorphan derivative 23



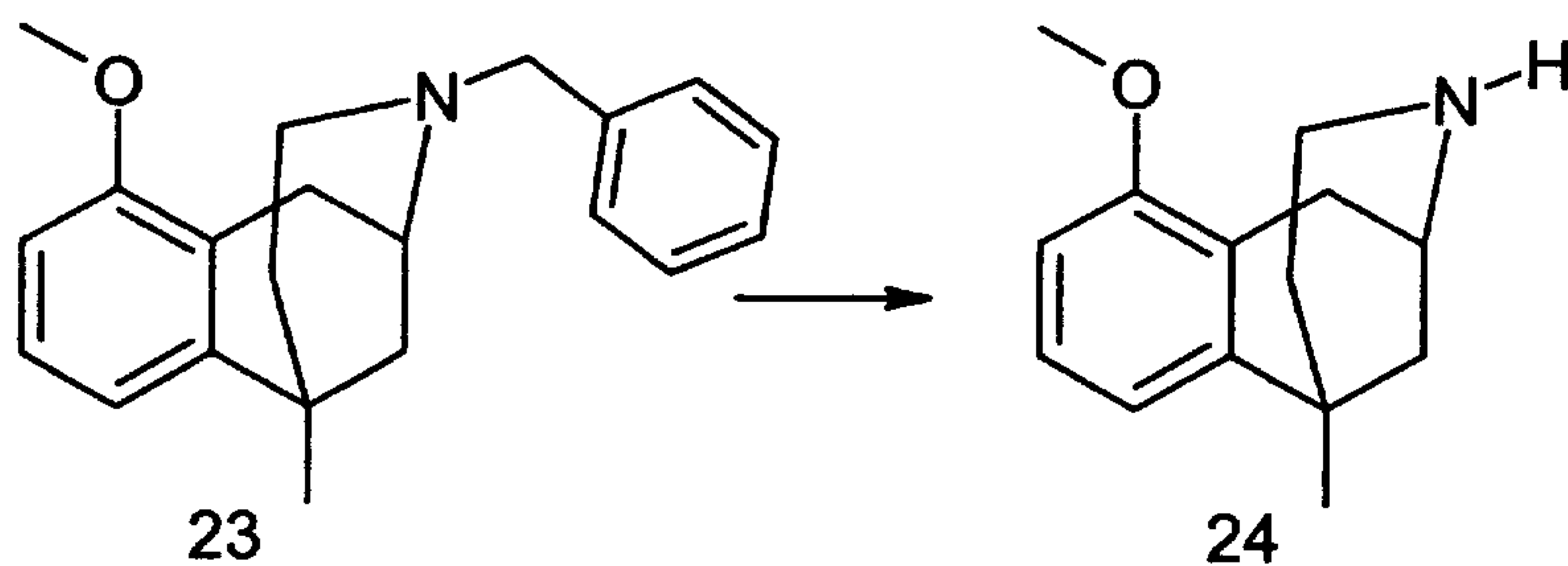
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and

15

c) the amino nitrogen is debenzylated to obtain the methoxybenzomorphan derivative 24

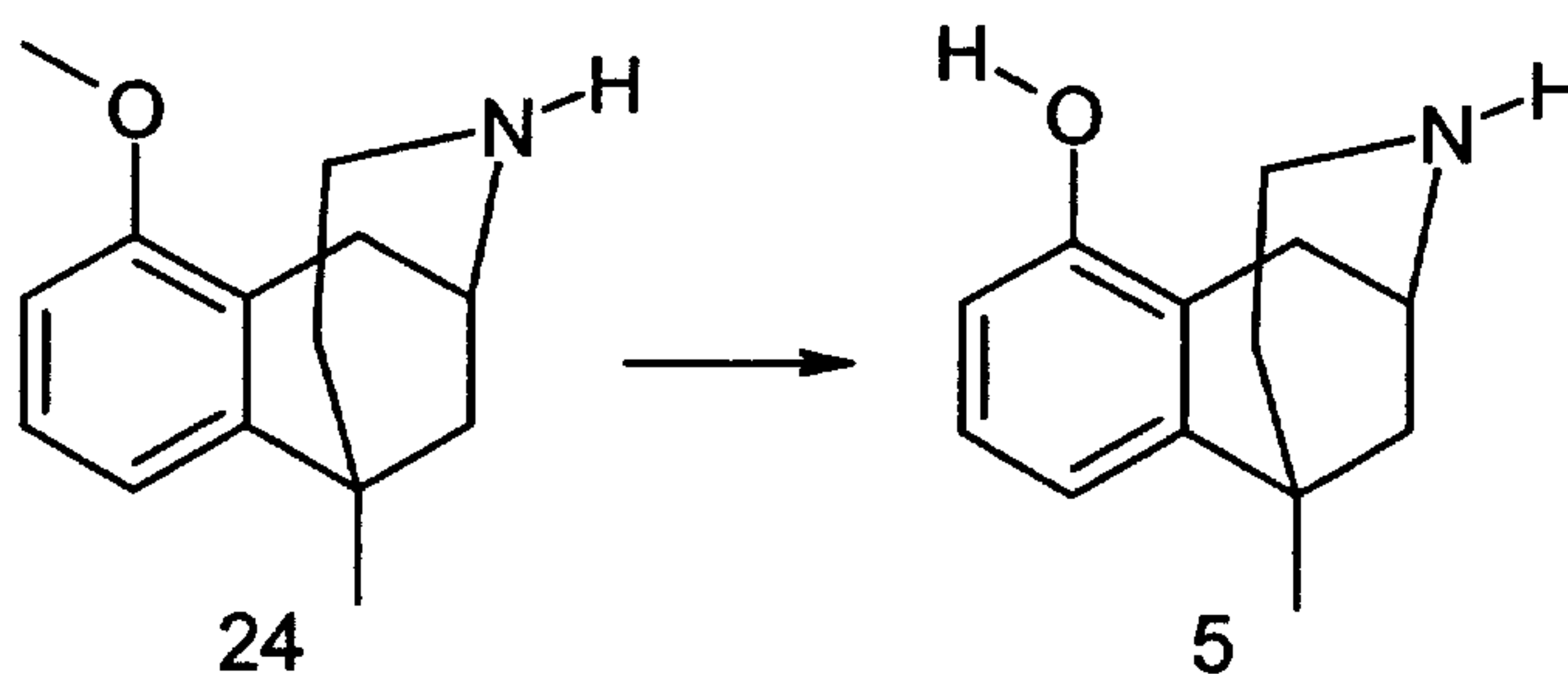
- 25 -



and

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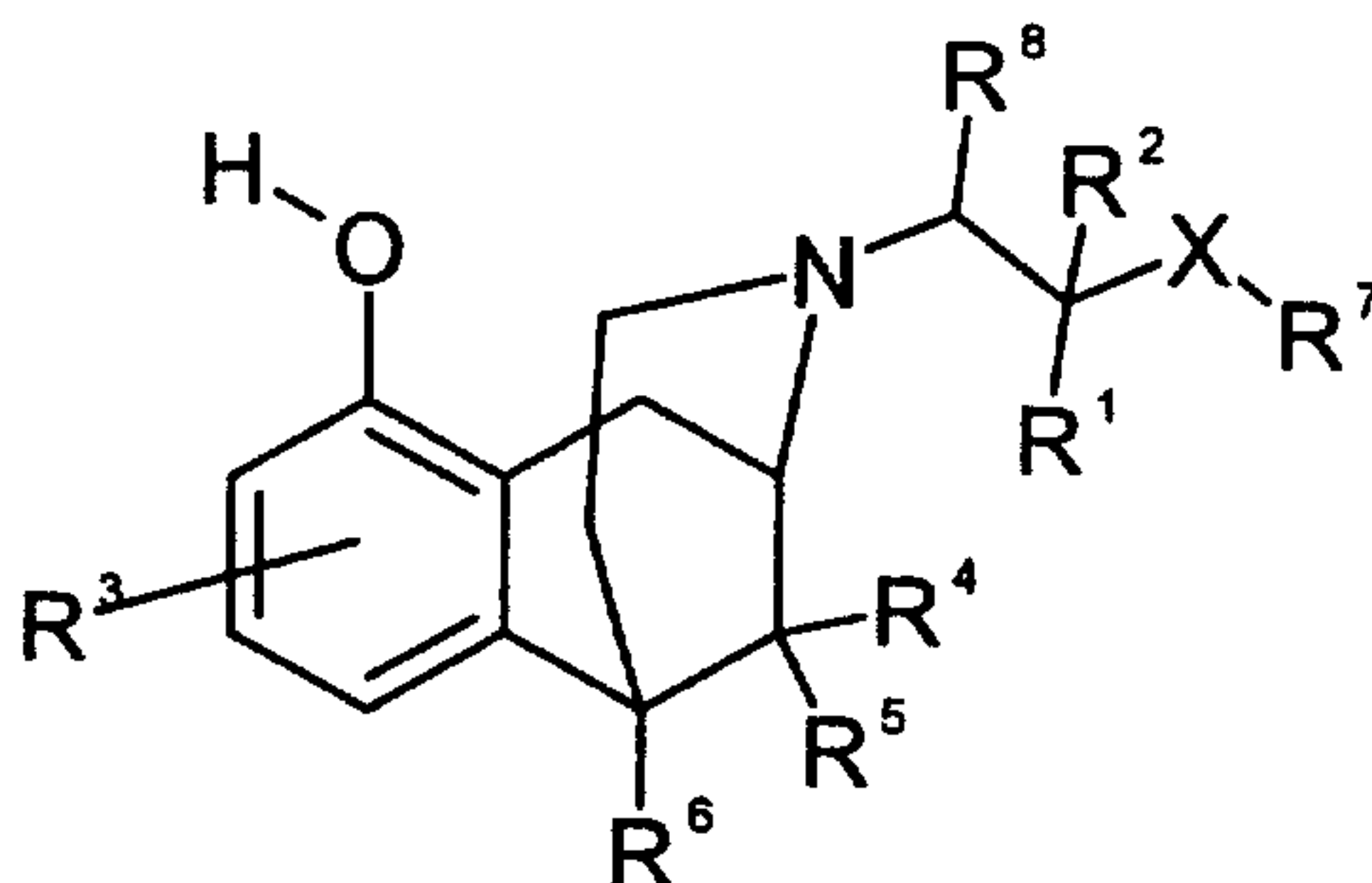
d) the phenolether 24 and the benzomorphan derivative 5 are isolated



10

In addition, the present invention relates to a process for preparing norbenzomorphans of general formula 1

15

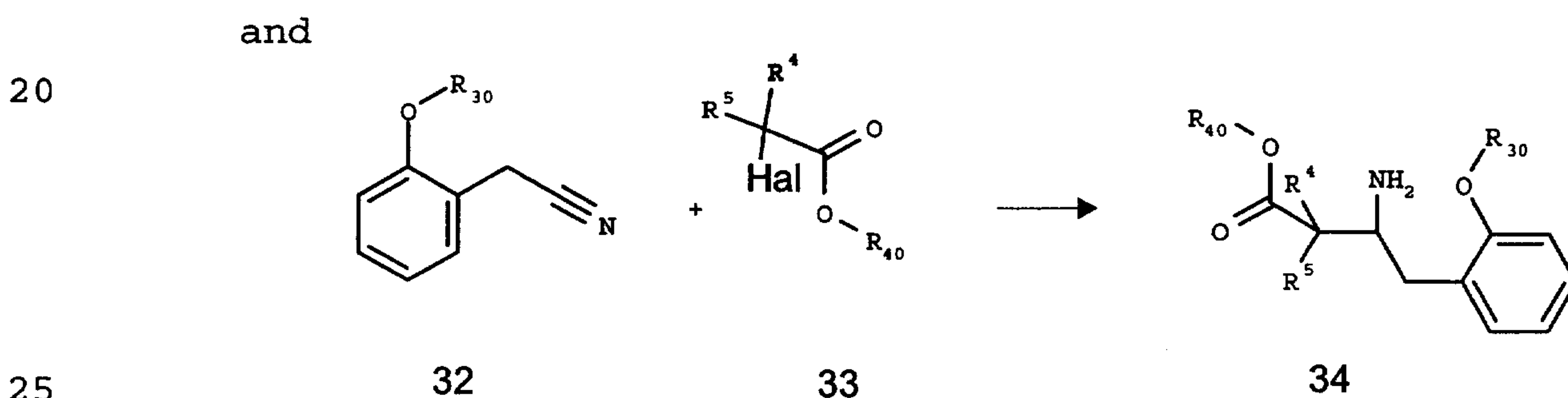


I

wherein

- 26 -

a) a benzylcyanide of general formula 32 wherein R_{30} denotes a C_1 - C_4 -alkyl group, is subjected to the conditions of a Reformatsky reaction with a
 5 halocarboxylate of general formula 33, wherein R_{40} denotes C_1 - C_8 -alkyl or benzyl, in the presence of an alkylhalosilane - preferably a trialkylchlorosilane and most preferably trimethylchlorosilane - and zinc powder in an inert solvent - preferably in an ether or in a
 10 halohydrocarbon and most preferably with dichloromethane and in the presence of a reducing agent which is selective with regard to the reduction of imino functions - preferably in the presence of an alkali metal borohydride derivative and most preferably in the presence of sodium cyanoborohydride - and the resulting carboxylic acid ester derivative of general formula 34 is isolated



b) the carboxylic acid ester derivative of general formula 34 is subjected to the conditions of a
 30 Michael addition reaction with an acrylic acid ester, wherein the alcohol component R_{50} denotes a C_1 - C_8 -alkyl group or a benzyl group, in a solvent which is inert under the reaction conditions selected - preferably in an alkanol and most preferably in ethanol - and the resulting Michael addition product of general formula 35 is isolated

35



30



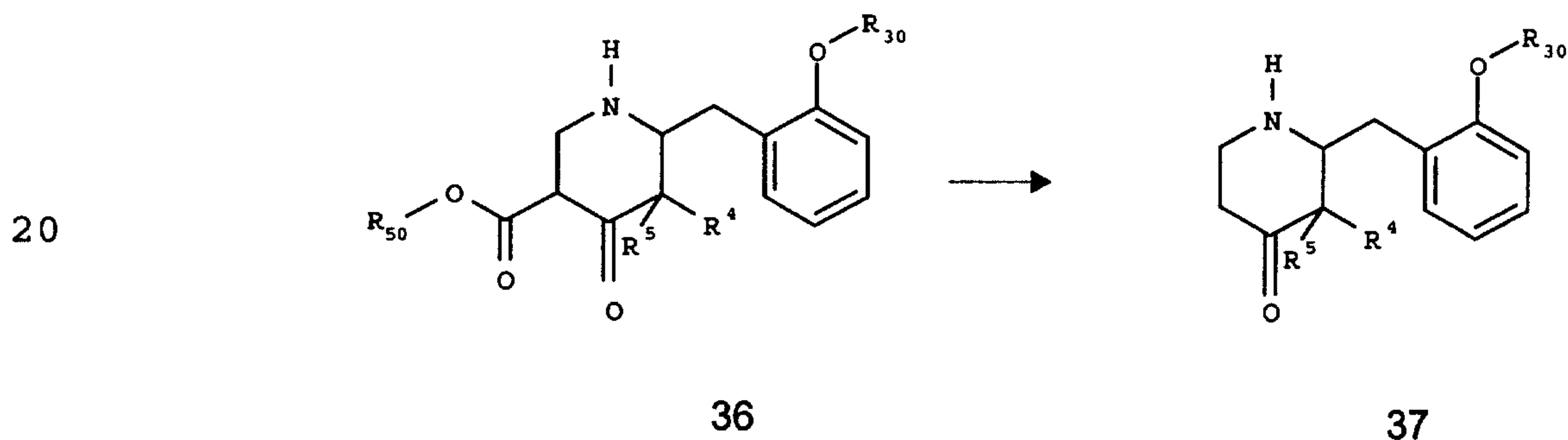
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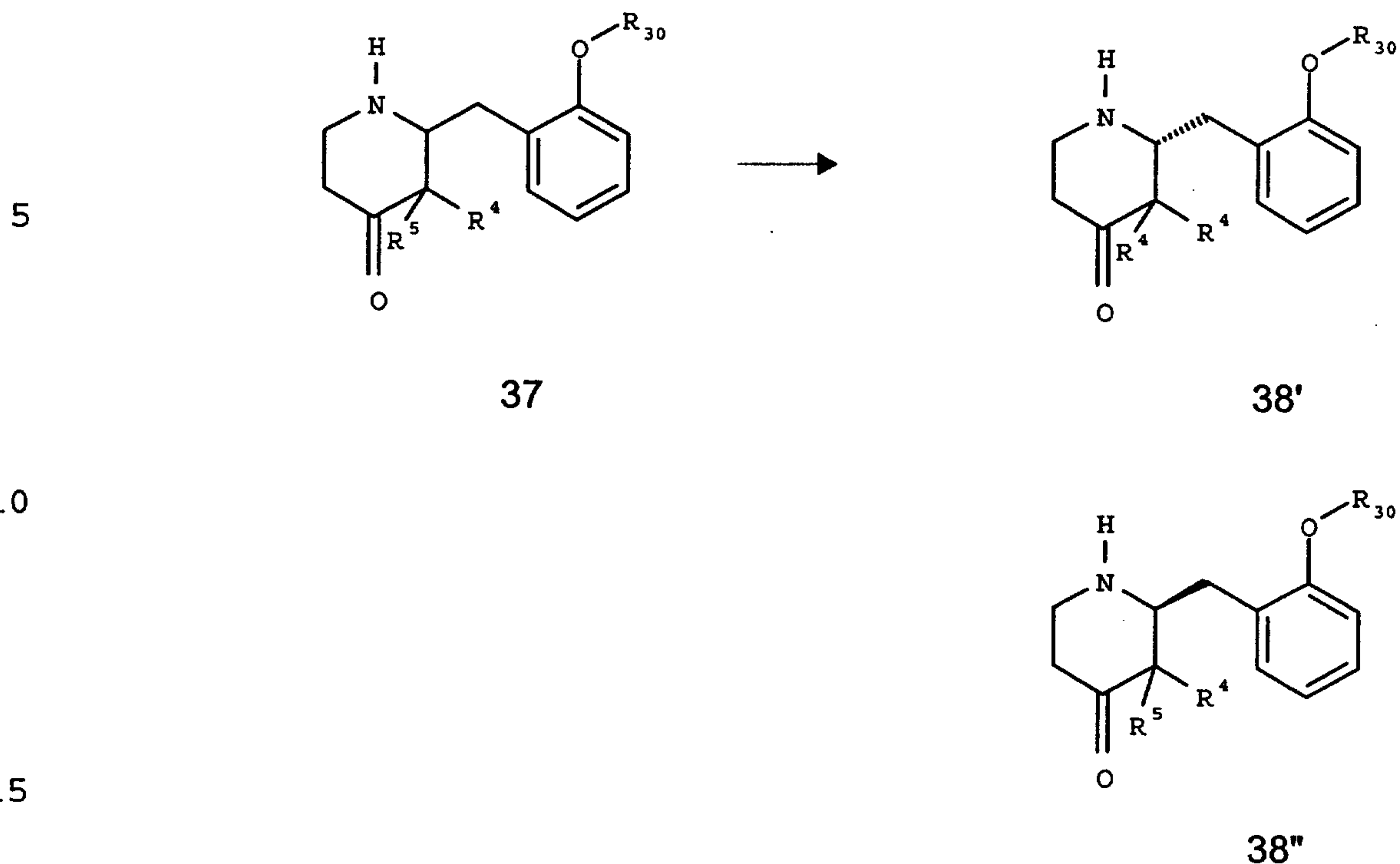
and

d) the piperidone derivative 36 is saponified and
5 decarboxylated under acid or alkaline conditions -
preferably in the presence of an alkali metal
hydroxide or an inorganic acid and most preferably in
the presence of sodium hydroxide - in a polar solvent
or solvent mixture - preferably in a mixture of a
10 straight-chained or branched C₁-C₄-alkanol and water
and most preferably in an ethanol/water mixture -
with heating, to obtain the corresponding piperidone
ester derivative of general formula 37, which is
isolated, and optionally the corresponding acid
15 addition salt is prepared with an acid and isolated



25 and

e) if desired, the mixture of stereoisomers thus
obtained is dissolved in a reaction medium which is
inert with regard to the enantiomer separation,
30 optionally after the release of the enantiomeric free
bases, combined with a suitable stereoisomer of an
organic acid suitable for salt formation with a
stereoisomer of the enantiomer mixture, the desired
stereoisomer is isolated in the form of its addition
35 salt with the optically active acid



and

20 f) the pure stereoisomer 38' or 38'' or the isomer mixture 38 thus obtained is subjected to a Wittig reaction after liberation from the enantiomerically pure acid addition salt in an inert solvent with a Wittig reagent generating a CH₂= or CH₃-CH=

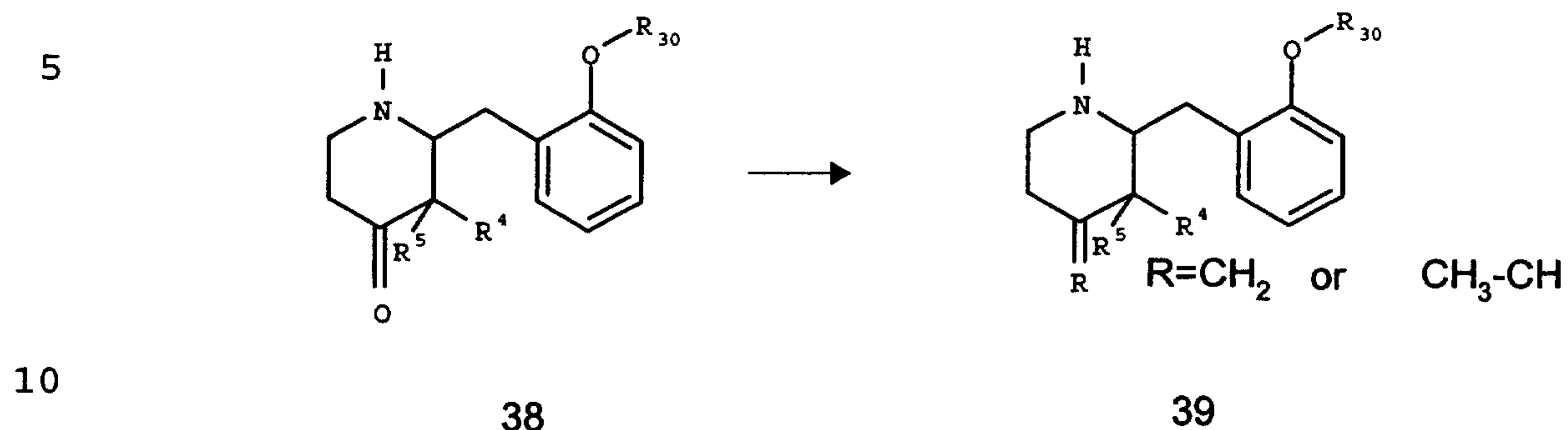
25 grouping, preferably with an ethyltriphenylphosphonium halide or with a methyltriphenylphosphonium halide, most preferably with methyltriphenylphosphonium bromide or ethyltriphenylphosphonium bromide in the presence

30 of a basically reacting compound - preferably in the presence of an alkali metal alkoxide, most preferably potassium tert.-butoxide - in an inert reaction medium - preferably in a cyclic ether, most preferably in tetrahydrofuran - and the

35 reaction product of type 39 or the corresponding

- 30 -

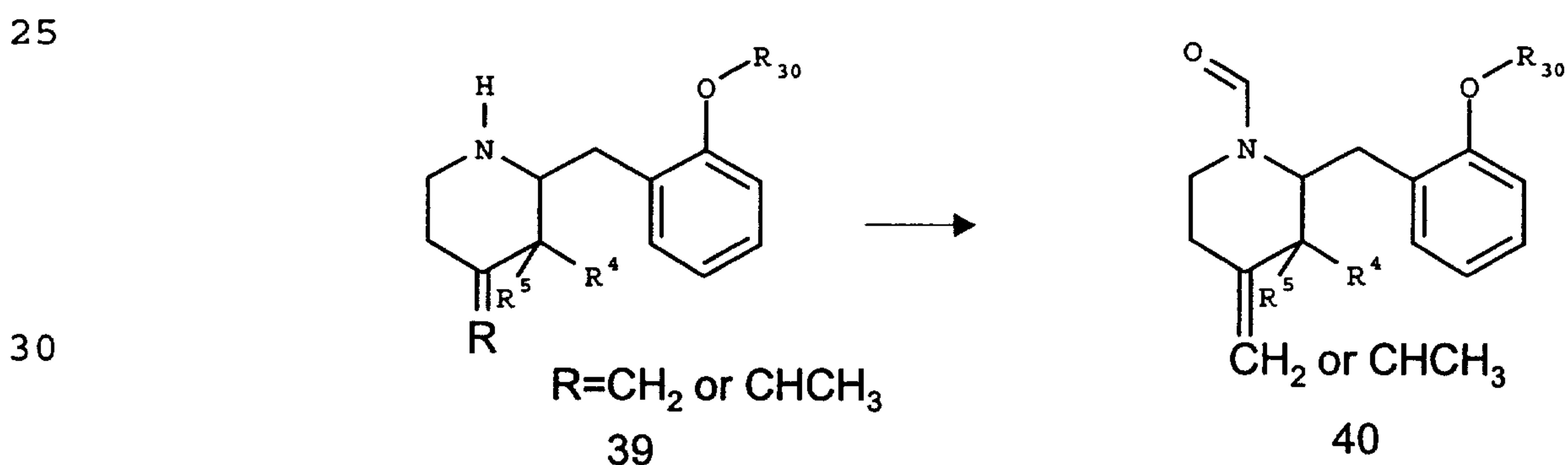
stereoisomer is optionally isolated in the form of its acid addition salt



and

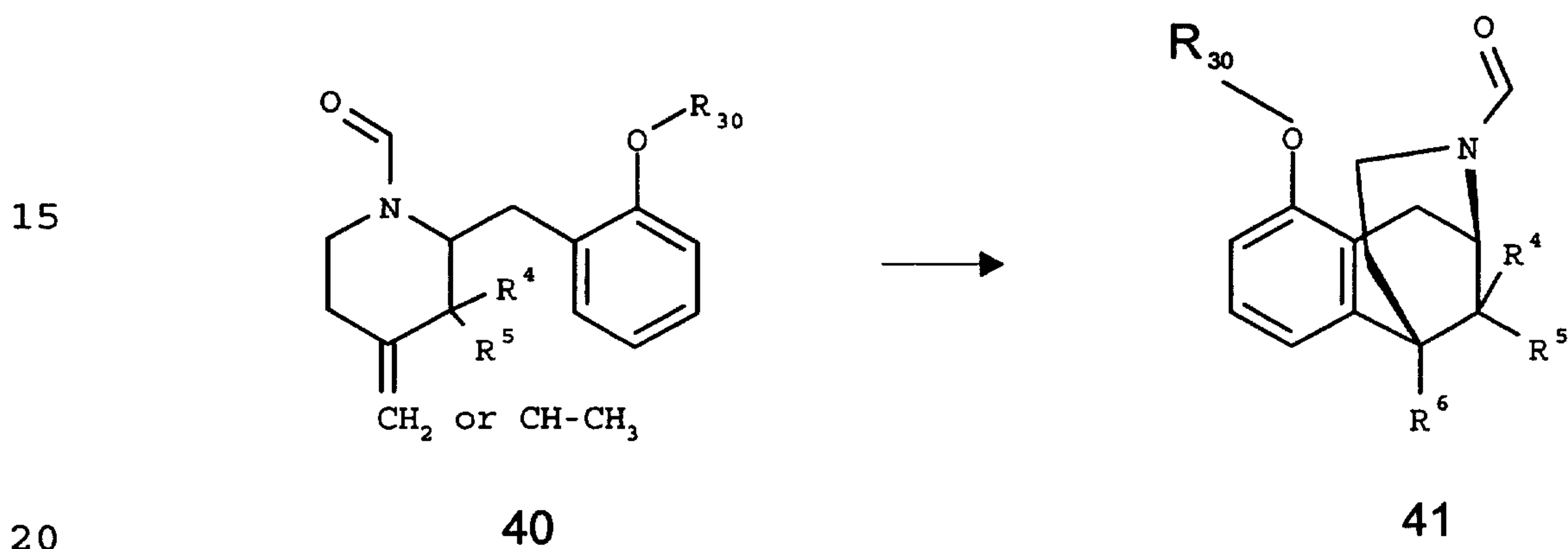
15 g) the alkene 39 obtained from the Wittig reaction is optionally first liberated from the acid addition salt thereof and the free base of type 39 is dissolved in an organic solvent - preferably in a halogenated hydrocarbon and most preferably in dichloromethane - and subjected to a formylation

20 reaction at the piperidine nitrogen with a formylating agent - preferably n-butylformate - and the reaction product of type 40 or the corresponding stereoisomer is isolated



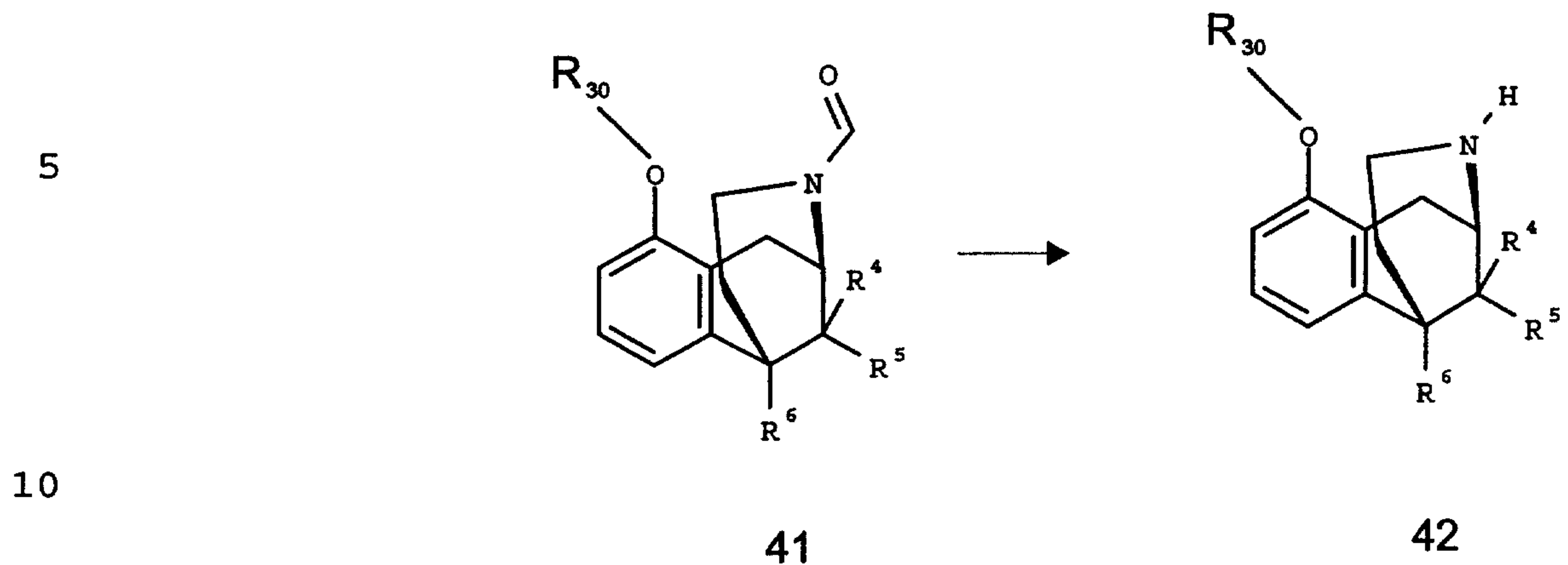
and

h) the formyl compound 40 thus obtained - or the corresponding stereoisomer - is reacted with an inorganic acid or with a Lewis acid - preferably aluminium(III)chloride - dissolved in an inert solvent - preferably in a halogenated hydrocarbon and most preferably in dichloromethane - and the cyclisation product of type 41 resulting from this reaction is isolated



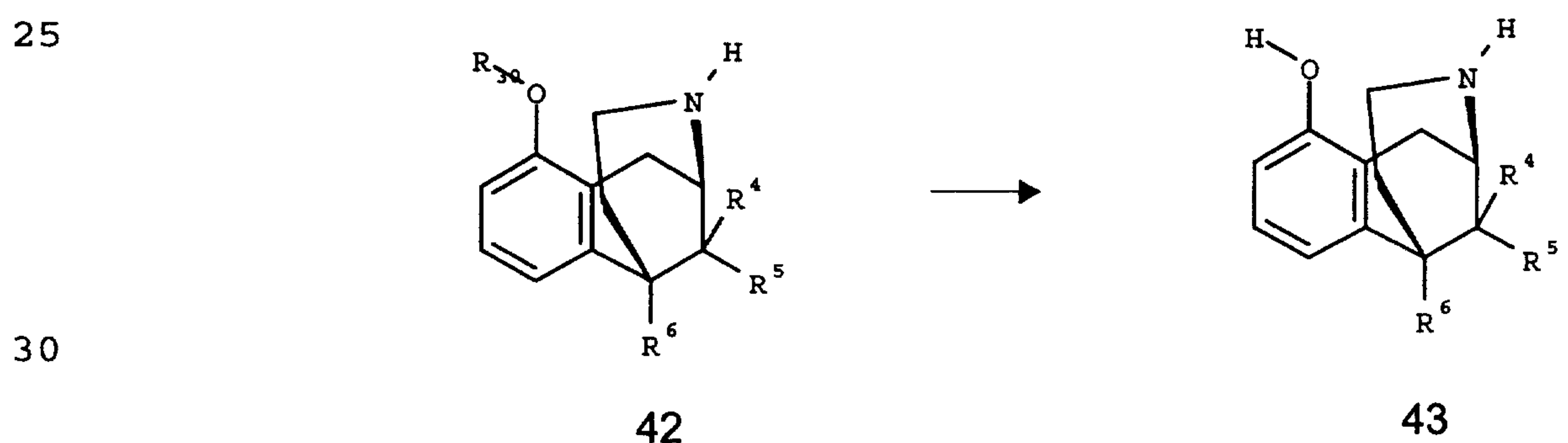
and

i) the benzomorphan derivative resulting from the cyclisation reaction is dissolved in a polar solvent - preferably in a C₁-C₄-alkanol, most preferably in n-propanol - and reacted with an acidically reacting compound - preferably with the aqueous solution of an inorganic acid and most preferably with concentrated hydrochloric acid - and the deformylated norbenzomorphan of type 42 resulting from this reaction is optionally isolated in the form of its acid addition salt



and

15 j) if the stereoisomers have not yet been separated,
 at this stage the stereoisomers are separated in a
 manner known *per se* and after the release of the free
 benzomorphan base the phenoylether is cleaved with an
 20 acidically reacting compound - preferably with an
 inorganic acid and most preferably with hydrobromic
 acid - and the cleavage product of type 43 is
 isolated

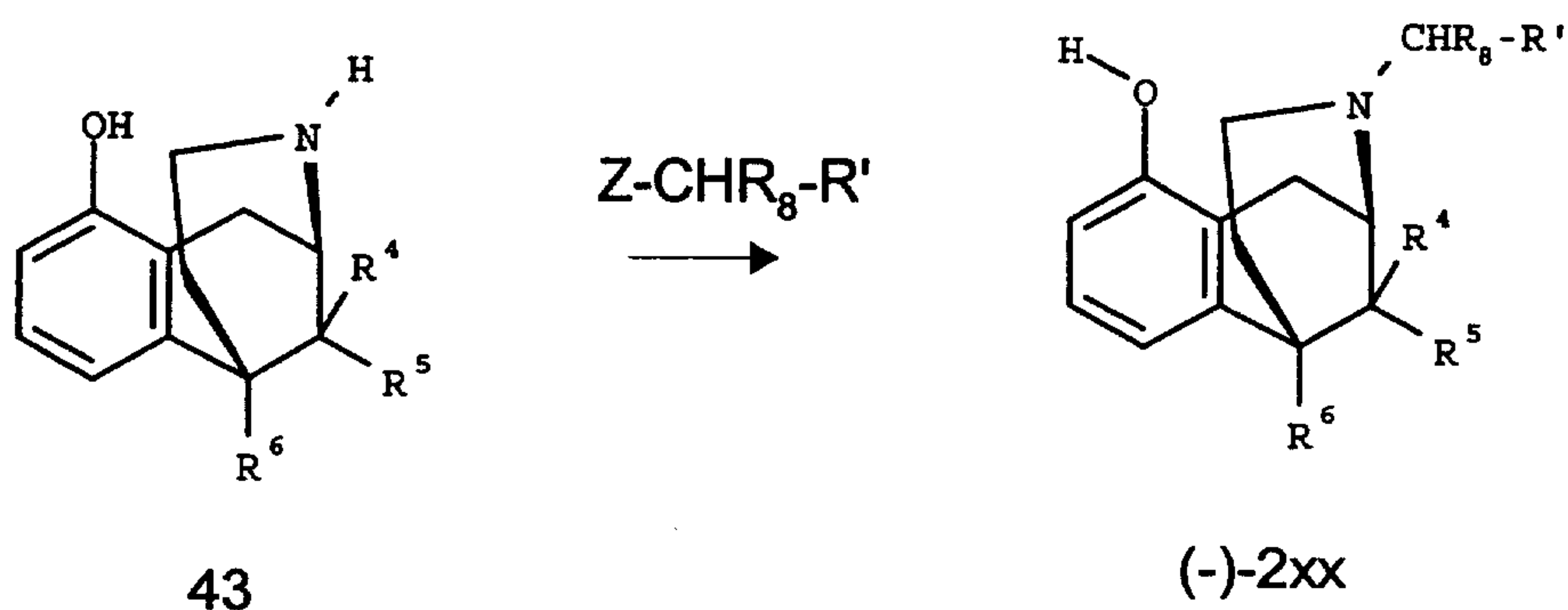


35 k) the cleavage product 43 is reacted with a
 compound of type $Z-CHR_g-R'$ wherein Z denotes a
 secondary amino substituted leaving group

preferably a halogen such as chlorine, bromine, iodine or an organic sulphonate, preferably trifluoromethanesulphonate - and R' denotes -CR¹R²XR⁷,

5

10



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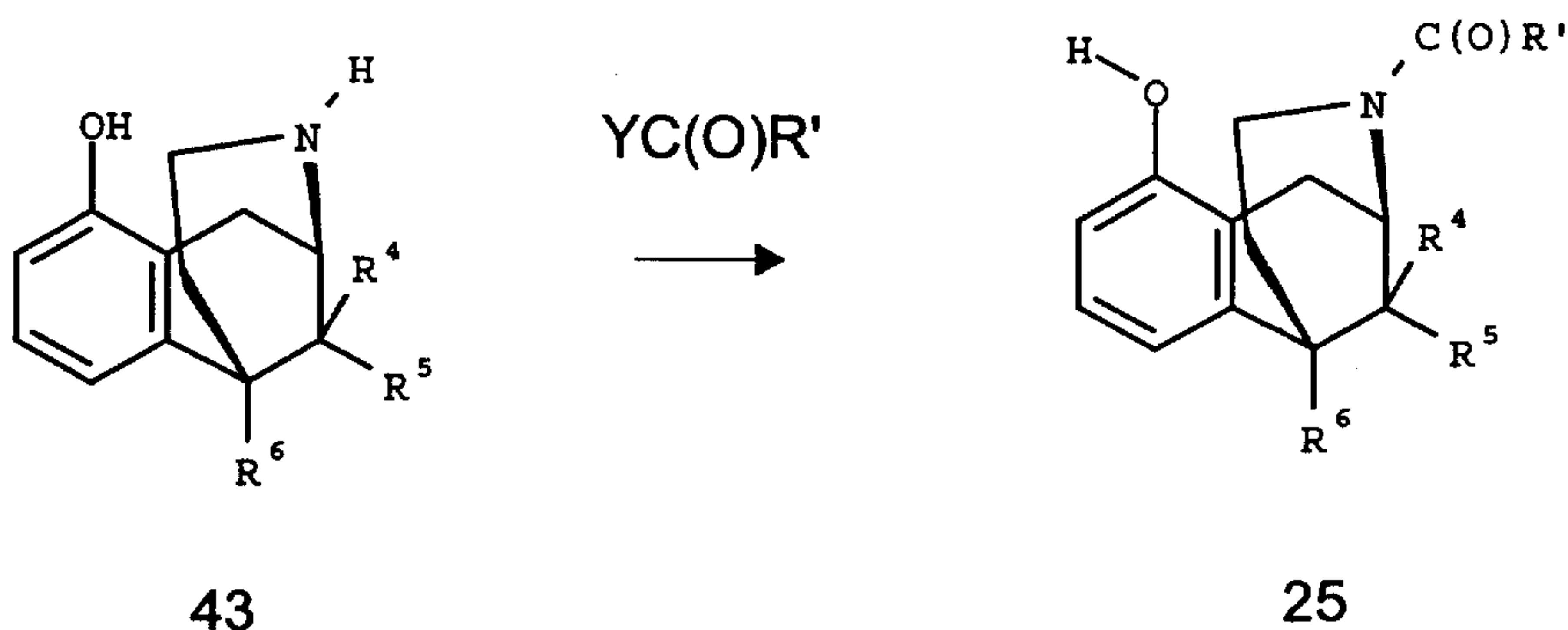
or

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25

is reacted with a compound of type YC(O)R' wherein Y denotes a secondary amino nitrogen substituted leaving group, preferably a halogen such as chlorine, bromine, iodine or an organic sulphonate, preferably trifluoromethanesulphonate - and R' denotes -CR¹R²XR⁷, and subsequently the carbonyl compound is reduced to the compound (-)-2xx as shown above

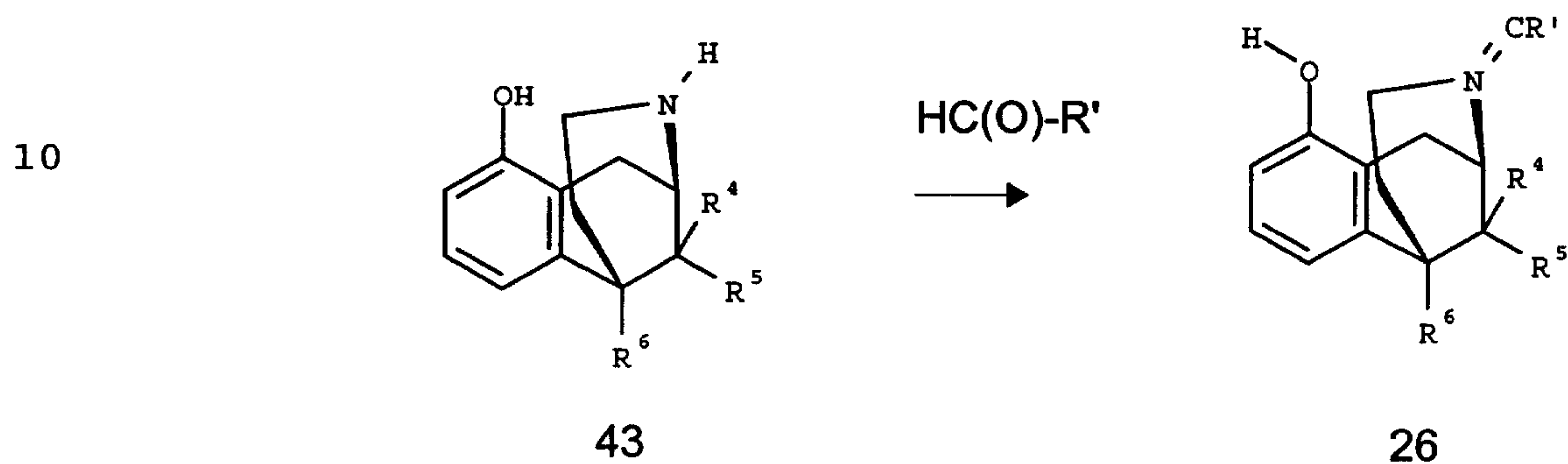
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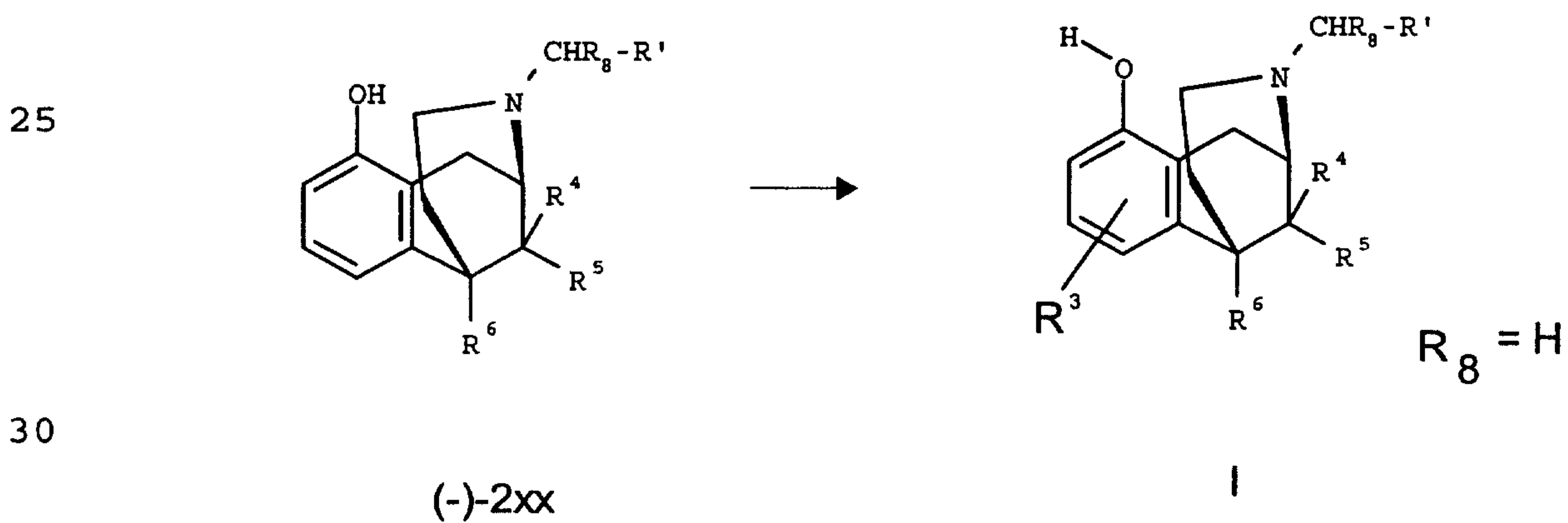
or

reacted with an aldehyde of general formula $\text{HC(O)-R}'$, wherein R' denotes $-\text{CR}^1\text{R}^2\text{XR}^7$, and the resulting Schiff base 26 is reduced to the compound $(-)-2\text{xx}$ as shown above



and

20 1) optionally within the framework of an electrophilic substitution the substituent R^3 is introduced



35

5 Various other embodiments of the processes will be
apparent to the skilled person from the present
description. However, it is expressly pointed out
that these Examples and the associated description
are provided solely for the purpose of illustration
and are not to be regarded as restricting the
invention.

10 In addition, reference is expressly made to the
contents of German Patent Application No. 197 40
110.4, from which the present application claims
priority.

Examples

Example 1: Ethyl 3-amino-4-(2-methoxyphenyl)-2-methylbutanoate (**13**)

5
150 g of zinc in 1.5 L of absolute dichloromethane are combined with 15 ml of trimethylchlorosilane under nitrogen and stirred for 30 min. at ambient temperature. Then 900 ml of absolute tetrahydrofuran (THF) are added and heated to 42 °C. To this is added dropwise a mixture of 147 g (1.0 mol) of 2-methoxybenzylcyanide (**11**) and 362 g (2.0 mol) of ethyl 2-bromopropionate in 100 ml of THF and the resulting mixture is then refluxed for a further 2 h.
15 It is left to cool, decanted off from the excess zinc and after cooling to about 5 °C combined with 70 g (1.8 mol) of sodium borohydride. Then 250 ml of ethanol are added dropwise (development of gas). The mixture is left to react for 3 h at 5 °C, 1 litre of 2N hydrochloric acid is slowly added, the phases are separated and the aqueous phase is extracted twice with 200 ml of dichloromethane. The solvent of the combined organic phase is eliminated *in vacuo*, the residue is combined with ice and toluene and made
20 alkaline with conc. ammonia. The phases are separated and the aqueous phase is extracted twice more with 800 ml of toluene. The combined organic phases are dried over magnesium sulphate, and the solvent is eliminated *in vacuo*. Yield 149 g (61%) oil.

30

Example 2: Ethyl 3-(2-ethoxycarbonyl)ethylamino-4-(2-methoxyphenyl)-2-methylbutanoate (**14**)

35 148 g (0.6 mol) of ethyl 3-amino-4-(2-methoxyphenyl)-2-methylbutanoate (**13**) and 119 g (1.2 mol) of ethyl

acrylate are dissolved in 250 ml of abs. ethanol and refluxed for 6 h. Then the mixture is concentrated by evaporation *in vacuo*. The residue is again taken up in 300 ml of toluene and once more concentrated by evaporation *in vacuo*. 210 g (100%) of the desired product are isolated as an oil.

Example 3: 2-(2-methoxyphenyl)methyl-3-methyl-4-piperidone (15)

210 g (0.6 mol) of ethyl 3-(2-ethoxycarbonyl)ethyl-amino-4-(2-methoxyphenyl)-2-methylbutanoate (14) are dissolved in 3 l toluene and first about 100 ml of a solvent/water mixture are entrained. The mixture is cooled to about 70 °C, combined with 80 g (0.7 mol) of potassium *tert.*-butoxide and heated for 30 min. to 105 °C, while the ethanol formed is distilled off. Then the mixture is left to cool and the solvent is eliminated *in vacuo*. The residue is combined with 400 ml of ethanol and 200 ml of 40% sodium hydroxide solution and refluxed for 3 h. The alcohol is eliminated *in vacuo* and the aqueous phase is extracted three times with 400 ml of diethylether (ether). The combined organic phases are dried over magnesium sulphate, and the solvent is eliminated *in vacuo*. Yield 109 g (78%) oil.

Example 4: (+)-4-ethylen-2-(2-methoxyphenyl)methyl-3,3-dimethyl-piperidine ((+)-7)

74.2 g (200 mmol) of ethyl-triphenylphosphonium bromide are suspended in 200 ml of absolute tetrahydrofuran and combined under nitrogen with 80 ml of a 2.5 N solution of n-butyl-lithium in hexane.

The mixture is stirred for 30 min at 30°C, and then combined with a solution of 23 g (93 mmol) of the piperidone (+)-6 in 100 ml of THF. This is then left to react for 12 h at ambient temperature, 100 ml of water are added and the THF is eliminated *in vacuo*. The residue is extracted three times with 200 ml of ethyl acetate and the combined organic extracts are washed again with 50 ml of water, dried over magnesium sulphate and the solvent is eliminated *in vacuo*. The residue is purified over a flash column (300 ml of silica gel; 4 l cyclohexane/ethyl acetate 3:1). The desired product is isolated as an oil in a yield of 17.4 g (72%).

The following was prepared analogously to Example 4:

2-(2-methoxyphenyl)methyl-3-methyl-4-methylene-piperidine (16)

20.1 g (56 mmol) of methyl-triphenylphosphonium bromide, 6.3 g (56 mmol) of potassium tert.-butoxide and 11 g (47 mmol) of 2-(2-methoxyphenyl)methyl-3-methyl-4-piperidone (15) in 200 ml of abs. THF are used. The product is crystallised from acetone as the oxalate. Yield: 13.1 g (87%); melting point: 145°C.

Example 5: (+)-4-ethylene-N-formyl-2-(2-methoxyphenyl)methyl-3,3-dimethyl-piperidine ((+)-8)

3.5 g (12.6 mmol) of (+)-4-ethylene-2-(2-methoxyphenyl)methyl-3,3-dimethyl-piperidine (7) are stirred with 20 ml of n-butylformate for 4 h at 80°C. The mixture is then evaporated down *in vacuo*. 3.6 g (100%) of the desired product are left in the form of an oil.

The following was prepared analogously to Example 5:
N-formyl-2-(2-methoxyphenyl)methyl-3-methyl-4-methylene-piperidine (17)

- 5 8 g (34 mmol) of 2-(2-methoxyphenyl)methyl-3-methyl-4-methylene-piperidine (16) as base and 30 ml of n-butylformate were used. Yield: 9.1 g (100%) as an oil.
- 10 Example 6: N-benzyl-2-(2-methoxyphenyl)methyl-4-methyl-piperi-3-dene (22)
- 15 6.0 g (250 mmol) of magnesium chips and some iodine are placed in 150 ml of ether. To this are added dropwise 31.32 g (200 mmol) of 2-methoxybenzyl chloride in 50 ml of ether so that the mixture boils gently. It is left to react for 1 h. The Grignard reagent thus obtained is then rapidly added dropwise
- 20 to a suspension of 52.8 g (200 mmol) of N-benzyl-4-methyl-pyridiniumbromide in 100 ml of ether cooled to -10 °C under nitrogen. The mixture is left to react for 2.5 h. Then the entire reaction mixture is added to 200 ml of a 10% ammonium chloride solution. The
- 25 organic phase is separated off and the aqueous phase is extracted twice more with 100 ml of ether. The combined organic phases are dried over magnesium sulphate and the solvent is eliminated *in vacuo*. To avoid oxidation, the rotary evaporator is ventilated
- 30 with nitrogen. The residue is immediately dissolved in 250 ml of methanol and 9.5 g (250 mmol) of sodium borohydride and 20 ml of 2 N sodium hydroxide solution are added. The mixture is stirred overnight at RT and evaporated down *in vacuo*. The aqueous
- 35 residue is extracted twice with 150 ml of ether and the combined organic phase is concentrated by

evaporation *in vacuo*. The residue is taken up in ethyl acetate and extracted five times with 150 ml of 2 N hydrochloric acid. The combined aqueous phase is then made alkaline again with sodium hydroxide solution and extracted twice with 200 ml of ethyl acetate. The combined organic phases are dried over magnesium sulphate (MgSO₄) and the solvent is eliminated *in vacuo*. The residue is purified by filtration over 200 ml of silica gel (eluant: ether). 31 g (51%) of the desired product are obtained as an oil.

Example 7: (-)-5-Ethyl-2-formyl-4'-methoxy-9,9-dimethyl-6,7-benzomorphan ((-)-9)

3.6 g (12.6 mmol) of (+)-4-ethylene-N-formyl-2-(2-methoxyphenyl)methyl-3,3-dimethyl-piperidine (8) are combined with 35 ml of methanesulphonic acid and stirred for 3 h at 80 °C. The reaction mixture is cooled and poured onto 50 g ice, neutralised with ammonia and extracted twice with 100 ml of ethyl acetate. The combined organic extracts are washed again with 50 ml of water, dried over MgSO₄ and the solvent is eliminated *in vacuo*. The residue is purified over a flash column (50 ml of silica gel; 750 ml of cyclohexane/ ethyl acetate 3:1). The desired product is isolated as an oil in a yield of 2.1 g (58%).

The following are prepared analogously to Example 7: N-formyl-4'-methoxy-5,9-dimethyl-6,7-benzomorphan (18)

5.0 g (19 mmol) of N-formyl-2-(2-methoxyphenyl)-methyl-3-methyl-4-methylene-piperidine (17) and 30 ml

of methanesulphonic acid are used. 4.8 g (96%) of the desired product (oil) are obtained as a mixture of 90% α -epimer and 10 % β -epimer.

5

N-benzyl-4'-methoxy-9-methyl-6,7-benzomorphan-oxalate (23OX)

31 g (100 mmol) of N-benzyl-2-(2-methoxyphenyl)methyl-4-methyl-piperi-3-dene (22) and 100 ml of methanesulphonic acid are used. The residue is dissolved in 100 ml of methanol and briefly boiled with 60 g activated charcoal and suction filtered while hot over silica gel. The solvent is eliminated *in vacuo*, the residue is dissolved in ether and the oxalate is precipitated with oxalic acid. 30 g (75%) are obtained; melting point: 152 °C (**MK 1-11**).

20

Example 8: 4'-methoxy-9-methyl-6,7-benzomorphan-oxalate (24OX)

30 g (75 mmol) of N-benzyl-4'-methoxy-9-methyl-6,7-benzomorphan-oxalate (23OX) are dissolved in 600 ml of methanol and hydrogenated at 60 °C and 5 bar on 3 g Pd/charcoal (10%). The mixture is cooled to 5 °C and the precipitated product is suction filtered. 17 g (56%) are obtained, melting point: 250 °C (**MK 1-15**).

30

Example 9: (-)-5-ethyl-4'-methoxy-9,9-dimethyl-6,7-benzomorphan ((-)-10)

35

2.0 g (6.9 mmol) of (-)-5-ethyl-2-formyl-4'-methoxy-9,9-dimethyl-6,7-benzomorphan (9) are dissolved in 30

ml of n-propanol and heated with 10 ml of conc. hydrochloric acid in the microwave at 300 Watt for 2h. Then the solvent is eliminated *in vacuo*, the residue is combined with 15 ml of ice water and
5 extracted twice with 20 ml of ethyl acetate (which is discarded). The aqueous phase is neutralised with conc. ammonia and extracted three times with 20 ml of ethyl acetate. The combined organic extracts are dried over MgSO_4 and the solvent is eliminated *in vacuo*. The residue is dissolved in acetone and the
10 hydrochloride is precipitated with ethereal hydrochloric acid. Yield: 1.7 g (82%), melting point: $>250\text{ }^\circ\text{C}$, $[\alpha]_{\text{D}}^{25} = (-) 43.0^\circ$ ($c=1$ in methanol).

15

The following is prepared analogously to Example 9:
4'-methoxy-5,9-dimethyl-6,7-benzomorphan (19)

4.8 g (18 mmol) of N-formyl-4'-methoxy-5,9-dimethyl-
20 6,7-benzomorphan (18), 50 ml of n-propanol and 50 ml of conc. hydrochloric acid are used. The mixture is refluxed for 8 h. Yield: 2.9 g (57%). A sample is converted with oxalic acid into the corresponding oxalate (HB), which has a melting point of $229\text{ }^\circ\text{C}$.

25

Example 10: $(-)-(1R,9\alpha)$ -4'-methoxy-5,9-dimethyl-6,7-benzomorphan ($(-)-$ 19)

9.5 g (41 mmol) of 4'-methoxy-5,9-dimethyl-6,7-
30 benzomorphan (19) are dissolved in 80 ml of ethanol and combined with 6.2 g (41 mmol) of R-(+)-tartaric acid. The crystals precipitated are suction filtered and recrystallised from methanol twice. Yield 2.6 g (17%), melting point: $236\text{ }^\circ\text{C}$, ee $> 98\%$ (determined
35 by NMR-spectroscopy using the free base by the addition of shift reagent). The tartrate is dissolved

in water, the base is liberated with potassium carbonate and extracted twice with 50 ml of ethyl acetate. The combined organic extracts are dried over MgSO₄ and the solvent is eliminated *in vacuo*.
5 1.6 g of the free base are obtained.

Example 11: (-)-(1R,9 α)-4'-hydroxy-5,9-dimethyl-6,7-benzomorphan-hydrobromide ((-)-4aBr)

10

1.5 g (6.5 mmol) of (-)-4'-methoxy-5,9-dimethyl-6,7-benzomorphan ((-)-19) are refluxed with 15 ml of 48% hydrobromic acid for 2 h. Then the mixture is concentrated by evaporation *in vacuo* and the residue
15 is digested with THF. 1.5 g (78%) of the desired product are obtained as the hydrobromide (amorphous precipitate).

20 The following is prepared analogously to Example 11: 4'-hydroxy-9-methyl-6,7-benzomorphan-oxalate-hydrobromide (5aBr)

9.5 g (31 mmol) of 4'-methoxy-9-methyl-6,7-benzomorphan-oxalate (24OX) are first dissolved in a little water and converted into the free base with 7 g potassium carbonate. The mixture is extracted three times with 200 ml of ethyl acetate and the solvent is eliminated from the combined organic phase. Then 30
25 ml of 48% hydrobromic acid are added. 6.1 g (70%) of the desired hydrobromide is obtained; melting point:
30 227°C

Example 12: (-)-(1R,9 α ,2''S)-2-(2''-benzyloxy)propyl-4'-hydroxy-5,9-dimethyl-6,7-benzomorphan-hydrochloride ((-)-4bCl)

5 0.75 g (2.5 mmol) of (-)-4'-hydroxy-5,9-dimethyl-6,7-benzomorphan-hydrobromide ((-)-4aBr) are suspended in 15 ml of dichloromethane and combined with 3 ml of N-methylmorpholine. After 30 min. the mixture is cooled to -5 °C and a solution of 1.1 g (5.5 mmol) of (-)-S-10 2-benzyloxypropionic acid chloride in 10 ml of dichloromethane is slowly added dropwise. The mixture is stirred for a further 30 min. at -5 °C, combined with 20 ml of 2 N hydrochloric acid and the organic phase is separated off. The organic phase is dried 15 over MgSO₄, the solvent is eliminated in vacuo and the residue is taken up in 40 ml of THF. To this solution are added 0.5 g (13 mmol) of LiAlH₄ whereupon the temperature rises to 35 °C. The mixture is left to react for 30 min, then 0.4 ml of water and 20 0.2 ml of 5 N sodium hydroxide solution are added and the inorganic precipitate is separated off. The precipitate is washed with 100 ml of THF and the combined organic phases are concentrated by evaporation in vacuo. The residue is taken up in 100 25 ml of ether, dried over MgSO₄ and the hydrochloride is precipitated with ethereal hydrochloric acid. The crystals are separated off and washed with acetone. Yield: 0.6 g (55%), melting point: 227 °C, $[\alpha]_D^{25} =$ (-) 13.3° (c=1 in methanol).

30

The following are prepared analogously to Example 12:

(-)-(1R,9 α ,2''R)-2-(2''-benzyloxy)propyl-4'-hydroxy-5,9-dimethyl-6,7-benzomorphan-hydrochloride ((-)-4cCl)

35

0.75 g (2.5 mmol) of (-)-4'-hydroxy-5,9-dimethyl-6,7-benzomorphan-hydrobromide ((-)-4aBr) and 1.1 g (5.5 mmol) of (+)-R-2-benzyloxypropionic acid chloride are used.

5 Yield: 0.7 g (65%), melting point: 217 °C, $[\alpha]_D^{25} =$
(-) 76.1° (c=1 in methanol).

(-)-(1R,9α)-4'-hydroxy-5,9-dimethyl-2-[2-(2-
phenoxy)ethoxy]ethyl-6,7-benzomorphan-hydrochloride
10 ((-)-4cCl)

0.75 g (2.5 mmol) of (-)-4'-hydroxy-5,9-dimethyl-6,7-benzomorphan-hydrobromide ((-)-4aBr) and 1.1 g (5.5 mmol) of phenoxyethoxyacetylchloride are used. Yield:
15 0.2 g (20%) amorphous powder.

(-)-(1R,2"S)-2-(2"-benzyloxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2bCl)
20

1.6 g (6.9 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 2.3 g (11.6 mmol) of (-)-S-2-benzyloxypropionic acid chloride are used. Yield: 2.1 g (73%), melting point: 254 °C, $[\alpha]_D^{25} =$
25 (-) 20.7° (c=1 in methanol).

(+)-(1S,2"R)-2-(2"-benzyloxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((+)-2bCl)
30

1.5 g (6.5 mmol) of (+)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((+)-2a) and 1.5 g (7.6 mmol) of (+)-R-2-benzyloxypropionic acid chloride are used. Yield: 1.4 g (52%), melting point: 256 °C, $[\alpha]_D^{25} =$
35 (+) 20.3° (c=1 in methanol).

(-) - (1R,2''R) - 2 - (2''-benzyloxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2cCl)

5 1.6 g (6.9 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.5 g (7.6 mmol) of (+)-R-2-benzyloxypropionic acid chloride are used. Yield: 1.7 g (59%), melting point: 245 °C, $[\alpha]_D^{25} = (-) 96.5^\circ$ (c=1 in methanol).

10 (+) - (1S,2''S) - 2 - (2''-benzyloxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((+)-2cCl)

15 1.6 g (6.9 mmol) of (+)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((+)-2a) and 2,3 g (11.6 mmol) of (-)-S-2-benzyloxypropionic acid chloride are used. Yield: 2.0 g (70%), melting point: 245 °C, $[\alpha]_D^{25} = (+) 97.8^\circ$ (c=1 in methanol).

20 (-) - (1R,2''S) - 2 - (2''-(2'''-fluorobenzyl)oxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2dCl)

25 0.8 g (3.4 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.4 g (6.5 mmol) of (-)-S-2-(2'-fluorobenzyl)oxypropionic acid chloride are used. Yield: 0.9 g (61%), melting point: 212 °C, $[\alpha]_D^{25} = (-) 24.7^\circ$ (c=1 in methanol).

30 (-) - (1R,2''R) - 2 - (2''-(2'''-fluorobenzyl)oxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2eCl)

35 0.5 g (2,3 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 0.6 g (3.0 mmol) of (+)-R-2-(2'-fluorobenzyl)oxypropionic acid chloride

are used. Yield: 0.7 g (70%), melting point: 145 °C, $[\alpha]_D^{25} = (-) 88.4^\circ$ (c=1 in methanol).

- 5 (-) - (1R,2"S) - 2 - (2" - (4'" - fluorobenzyl)oxy)propyl - 4' - hydroxy - 5,9,9-trimethyl - 6,7-benzomorphan - hydrochloride ((-) - 2fCl)
- 10 0.8 g (3.4 mmol) of (-) - 4' - hydroxy - 5,9,9-trimethyl - 6,7-benzomorphan ((-) - 2a) and 1.4 g (6.5 mmol) of (-) - S - 2 - (2' - fluorobenzyl)oxypropionic acid chloride are used. Yield: 1.0 g (68%), melting point: 250 °C, $[\alpha]_D^{25} = (-) 21.9^\circ$ (c=1 in methanol).
- 15 (-) - (1R,2"R) - 2 - (2" - (4'" - fluorobenzyl)oxy)propyl - 4' - hydroxy - 5,9,9-trimethyl - 6,7-benzomorphan - hydrochloride ((-) - 2gCl)
- 20 0.5 g (2,3 mmol) of (-) - 4' - hydroxy - 5,9,9-trimethyl - 6,7-benzomorphan ((-) - 2a) and 0.6 g (3.0 mmol) of (+) - R - 2 - (2' - fluorobenzyl)oxypropionic acid chloride are used. Yield: 0.6 g (58%), melting point: 128 °C, $[\alpha]_D^{25} = (-) 95.4^\circ$ (c=1 in methanol).
- 25 (-) - (1R,2"S) - 2 - (2" - (2'" , 6'" - difluorobenzyl)oxy) - propyl - 4' - hydroxy - 5,9,9-trimethyl - 6,7-benzomorphan - hydrochloride ((-) - 2hCl)
- 30 1.5 g (6.5 mmol) of (-) - 4' - hydroxy - 5,9,9-trimethyl - 6,7-benzomorphan ((-) - 2a) and 2.4 g (10.2 mmol) of (-) - S - 2 - (2' , 6' - difluorobenzyl)oxypropionic acid chloride are used. Yield: 2.0 g (68%), melting point:
- 35 245 °C, $[\alpha]_D^{25} = (-) 272.3^\circ$ (c=1 in methanol).

- (-)-(1R,2"S)-2-(2"-(2'"',6'"'-dichlorobenzyl)oxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2iCl)
- 5 2.3 g (10 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 3.2 g (12 mmol) of (-)-S-2-(2',6'-dichlorobenzyl)oxypropionic acid chloride are used. Yield: 2.8 g (58%), melting point: 260 °C, $[\alpha]_D^{25} = (-) 14.1^\circ$ (c=1 in methanol).
- 10
- (-)-(1R,2"S)-2-(2"-(2'"'-methyl-benzyl)oxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2jCl)
- 15 0.8 g (3.4 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.4 g (6.5 mmol) of (-)-S-2-(2'-methyl-benzyl)oxypropionic acid chloride are used. Yield: 0.8 g (55%), melting point: 249 °C, $[\alpha]_D^{25} = (-) 10.9^\circ$ (c=1 in methanol).
- 20
- (-)-(1R,2"S)-2-(2"-cyclohexylmethoxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2kCl)
- 25 1.9 g (8.2 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 2.0 g (10 mmol) of (-)-S-2-(2'-cyclohexylmethoxy)propionic acid chloride are used. Yield: 1.8 g (52%), melting point: 249 °C, $[\alpha]_D^{25} = (-) 24.6^\circ$ (c=1 in methanol).
- 30
- (-)-(1R,2"R)-2-(2"-cyclohexylmethoxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2lCl)
- 35

1.9 g (8.2 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 2.0 g (10 mmol) of (+)-R-2-(2'-cyclohexylmethoxy)propionic acid chloride are used. Yield: 1.7 g (49%), melting point: 140 °C,
5 $[\alpha]_D^{25} = (-) 92.2^\circ$ (c=1 in methanol).

((-)-(1R)-4'-hydroxy-2-(5"-phenoxy)pentyl-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2mCl)

10

3.0 g (13 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 3.2 g (15 mmol) of 5-phenoxy-pentanoic acid chloride are used. Yield: 2.4 g (44%), melting point: 149 °C, $[\alpha]_D^{25} = (-) 74.6^\circ$ (c=1
15 in methanol).

((-)-(1R)-4'-hydroxy-2-(2"-(2'"-phenyl)ethoxy)ethyl-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2nCl)

20

2.0 g (8.7 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 2.2 g (11 mmol) of 2-phenylethoxyacetic acid chloride are used. Yield: 1.7 g (48%), melting point: 204 °C, $[\alpha]_D^{25} = (-) 72.4^\circ$ (c=1 in methanol).

25

((-)-(1R)-4'-hydroxy-2-(4"-phenoxy)butyl-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2oCl)

30

1.0 g (4.3 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.2 g (6 mmol) of 4-phenoxybutyric acid chloride are used. Yield: 0.7 g (39%), melting point: 250 °C, $[\alpha]_D^{25} = (-) 82.8^\circ$ (c=1
35 in methanol).

(-) - (1R) - 2 - (2''-benzyloxy)ethyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2pCl)

2.3 g (10 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 4.3 g (22 mmol) of 2-benzyloxyacetyl chloride are used. Yield: 2.5 g (62%), melting point: 253 °C, $[\alpha]_D^{25} = (-) 78.1^\circ$ (c=1 in methanol).

10

(-) - (1R) - 2 - (2''-(2'',6''-difluorobenzyloxy)ethyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2qCl)

15

1.2 g (5 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.1 g (5 mmol) of 2-(2',6'-difluorobenzyloxyacetyl chloride are used. Yield: 1.5 g (68%), melting point: 246 °C, $[\alpha]_D^{25} = (-) 71.0^\circ$ (c=1 in methanol).

20

(-) - (1R) - 2 - (3''-(2'',6''-difluorophenyl)propyl)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2rCl)

25

1.9 g (8.2 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.7 g (8.3 mmol) of 3-(2',6'-difluorophenylpropionic acid chloride are used. Yield: 1.6 g (46%), melting point: >250 °C, $[\alpha]_D^{25} = (-) 68.6^\circ$ (c=1 in methanol).

30

Example 13: (+) - (1R,2''S) - 2 - (2''-benzyloxy)propyl-4'-hydroxy-5-methyl-6,7-benzomorphan-hydrochloride ((+)-5bCl) and (+) - (1S,2''S) - 2 - (2''-benzyloxy)propyl-4' -

35

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hydroxy-5-methyl-6,7-benzomorphan-hydrochloride ((+)-
5cCl)

5.1 g (17 mmol) of 4'-hydroxy-9-methyl-6,7-
5 benzomorphan-oxalate-hydrobromide (5aBr) and 1.7 g
(17 mmol) of N-methylmorpholine are dissolved in 20
ml of DMF and cooled to -5 °C. A solution of 3.5 g
(19 mmol) of (-)-S-2-benzyloxypropionic acid, 1.8 g
(19 mmol) of methyl chloroformate and 2.0 g (19 mmol)
10 of N-methylmorpholine in 20 ml of dichloromethane
prepared at -5 °C is slowly added dropwise thereto.
The mixture is left to react for 1 h at ambient
temperature, the solvent is largely eliminated *in*
vacuo, the residue is taken up in 60 ml of
15 dichloromethane, extracted twice with 20 ml of 2 N
hydrochloric acid and once with 20 ml of water. The
organic phase is dried over MgSO₄ and the solvent is
eliminated *in vacuo*. After the addition of a little
ether the product crystallises out (melting point:
20 110 °C), is suction filtered and taken up in 80 ml of
THF. To this solution are added 0.8 g (21 mmol) of
LiAlH₄, whereupon the temperature rises to 35°C. The
mixture is left to react for 1 h, combined with 25 ml
of water and 25 ml of 40% sodium tartrate solution.
25 The organic phase is separated off, the aqueous phase
is extracted twice with 100 ml of ether and the
combined organic phases are concentrated by
evaporation *in vacuo*. The residue is taken up in 100
ml of ether, dried over magnesium sulphate and the
30 hydrochloride is precipitated with ethereal
hydrochloric acid. The crystals are separated off
and recrystallised from i-propanol. 1.1 g (17%) of
(+)-5bCl are obtained, melting point: 246 °C, $[\alpha]_D^{25} =$
(+) 11.8° (c=1 in methanol). The mother liquor was
35 concentrated by evaporation, the base was liberated
and chromatographed (300 g silica gel; ethyl

acetate/cyclohexane 1:3). The hydrochloride is again precipitated with ethereal hydrochloric acid. 0.3 g (5%) of (+)-5cCl are obtained, melting point: 241 °C, $[\alpha]_D^{25} = (+) 52.4^\circ$ (c=1 in methanol).

5

The following are prepared analogously to Example 13:

10 (+) - (1R,2"S) - 2 - [2" - (2'" , 6'" - difluorobenzyloxy)] - propyl-4'-hydroxy-5-methyl-6,7-benzomorphan-hydrochloride ((+)-5dCl) and (+) - (1S,2"S) - 2 - (2" - (2'" , 6'" - difluorobenzyloxy))propyl-4'-hydroxy-5-methyl-6,7-benzomorphan-hydrochloride ((+)-5eCl)

15 4.0 g (14 mmol) of 4'-hydroxy-5-methyl-6,7-benzomorphan-hydrobromide (5aBr) and 3.0 g (14 mmol) of (+)-R-2-(2',6'-difluorobenzyloxy)propionic acid are used. 0.3 g (5%) of (+)-5dCl are obtained, melting point: 122 °C, $[\alpha]_D^{25} = (+) 20.9^\circ$ (c=1 in
20 methanol) and 1.8 g (30%) of a mixture of (+)-5dCl and (+)-5eCl, melting point: 194 °C, $[\alpha]_D^{25} = (+) 42.2^\circ$ (c=1 in methanol).

25 Example 14: (-) - (1R) - 4' - hydroxy-5,9,9-trimethyl-2-[2" - (2'" - phenoxy)ethoxy]ethyl-6,7-benzomorphan-hydrochloride ((-)-2uCl):

30 1.5 g (6.5 mmol) of (-) - 4' - hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.5 g (7.5 mmol) of 2-(2-phenoxy)ethoxy-ethylchloride are dissolved in 20 ml of DMF, a catalytic quantity of KI and 1 g potassium carbonate are added. The mixture is stirred for 5 h at 130 °C, and then the solvent is
35 eliminated in vacuo. The residue is taken up in 100 ml of water, extracted three times with 100 ml of

ethyl acetate and the combined organic extracts are once again washed with 50 ml of water, dried over MgSO_4 and the solvent is eliminated *in vacuo*. The residue is dissolved in 40 ml of ether and the
 5 hydrochloride is precipitated with ethereal hydrochloric acid. Yield: 1.4 g (50%), melting point: 190 °C, $[\alpha]_D^{25} = (-) 81.1^\circ$ (c=1 in methanol).

10 The following are prepared analogously to Example 14:

(+) - (1S) - 4' -hydroxy-5,9,9-trimethyl-2-[2'' - (2''' - phenoxy)ethoxy]ethyl-6,7-benzomorphan-hydrochloride ((+) - 2vCl) :

15

1.5 g (6.5 mmol) of (+) - 4' -hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((+) - 2a) and 1.5 g (7.5 mmol) of 2-(2-phenoxy)ethoxy-ethylchloride are used. Yield: 1.8 g (64%), melting point: 190 °C, $[\alpha]_D^{25} = (+) 81.0^\circ$
 20 (c=1 in methanol).

(-) - (1R, 2''S) - 2 - [2'' - (2''' - cyanobenzyl)oxy]propyl-4' - hydroxy-5,9,9-trimethyl-6,7-benzomorphan-
 25 hydrochloride ((-) - 2wCl)

0.8 g (3.4 mmol) of (-) - 4' -hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-) - 2a) and 1.0 g (3.7 mmol) of 2-(2' - cyanobenzyl)oxypropyl S-methanesulphonate are
 30 used. Yield: 0.2 g (13%), melting point: 234 °C.

(-) - (1R) - 2 - [2'' - (2''' - cyclohexyloxy)ethoxy]ethyl-4' - hydroxy-5,9,9-trimethyl-6,7-benzomorphan-
 35 hydrochloride ((-) - 2xCl)

1.0 g (4.3 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.1 g (5.4 mmol) of 2-(2'-cyclohexyloxy)ethoxyethylchloride are used. Yield: 0.7 g (37%), melting point: 204 °C, $[\alpha]_D^{25} =$
5 (-) 71.1° (c=1 in methanol).

(-)-(1R)-2-{2''-[2'''-(2,6-difluorophenoxy)ethoxy]ethyl}-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-
10 hydrochloride ((-)-2yCl):

2.3 g (10 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 2.8 g (12 mmol) of 2-(2'-(2,6-difluorophenoxy)ethoxy)ethylchloride are
15 used. Yield: 2.3 g (49%), melting point: 183 °C, $[\alpha]_D^{25} =$ (-) 73.3° (c=1 in methanol).

(-)-(1R)-2-[2''-(2,6-difluorophenoxy)ethyl]-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-
20 hydrochloride ((-)-2zCl):

1.2 g (5 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.4 g (9.8 mmol) of 2-(2,6-difluorophenoxy)ethylchloride are used. Yield: 0.3 g
25 (14%), melting point: 241 °C.

(-)-(1R)-2-(2''-cyclohexyloxy)ethyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2aaCl):
30

1.2 g (5 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.1 g (6.8 mmol) of 2-cyclohexyloxy-ethyl chloride are used. Yield: 0.8 g
35 (41%), melting point: >250 °C, $[\alpha]_D^{25} =$ (-) 71.1° (c=1 in methanol).

(-)-(1R)-2-[2''-(2'''-tert.-butyloxy)ethoxy]ethyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2acCl)

1.5 g (6.4 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.4 g (7.7 mmol) of 2-(2'-tert.-butyloxy)ethoxyethyl chloride are used.
Yield: 0.8 g (30%), melting point: 209 °C, $[\alpha]_D^{25} = (-) 72.4^\circ$ (c=1 in methanol).

Example 15: (-)-(1R)-5-ethyl-4'-hydroxy-9,9-dimethyl-2-(2-(2-phenoxy)ethoxy)ethyl-6,7-benzomorphan-hydrochloride (3bCl):

1.0 g (3.4 mmol) of (-)-5-ethyl-4'-methoxy-9,9-dimethyl-6,7-benzomorphan (10) are refluxed with 20 ml of 48% hydrobromic acid for 2 h. Then the mixture is concentrated by evaporation *in vacuo* and the residue is dissolved twice with 20 ml of ethanol and evaporated down again. Then it is taken up in 20 ml of DMF and 800 mg (4.0 mmol) of 2-(2-phenoxy)ethoxyethyl chloride in 10 ml of DMF, a catalytic quantity of KI and 1 g of potassium carbonate are added. The mixture is stirred for 4 h at 80 °C, the solvent is eliminated *in vacuo*. The residue is taken up in 100 ml of water, extracted three times with 100 ml of ethyl acetate and the combined organic extracts are again washed with 50 ml of water, dried over MgSO_4 and the solvent is eliminated *in vacuo*. The residue is dissolved in 40 ml of ether and the hydrochloride is precipitated with ethereal hydrochloric acid.
Yield: 1.0 g (66%), melting point: 90 °C (decomposition).

Example 16: (-)-(1R)-4'-hydroxy-2-(2"-phenylethyl)-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2adCl)

5 1.0 g (4.3 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.0 g (8.3 mmol) of phenylacetaldehyde are dissolved in 20 ml of methanol, combined with a molecular sieve and stirred for 3 h at RT. Then the molecular sieve is filtered
10 off and the filtrate is combined with 0.6 g (9.5 mmol) of sodium cyanoborohydride and 1.2 ml of glacial acetic acid. The mixture is left to stand for about 12 hours, combined with 20 ml of 4 N hydrochloric acid and evaporated down in vacuo. The
15 residue is mixed with a little acetone and the crystals are suction filtered. Yield: 0.9 g (56%), melting point: 250 °C, $[\alpha]_D^{25} = (-) 80.04^\circ$ (c=1 in methanol).

20 The following is prepared analogously to Example 16:

((-)-(1R)-4'-hydroxy-2-(2"-phenylpropyl)-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2aeCl)

25 1.0 g (4.3 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a), 1.2 g (8.9 mmol) of 3-phenylpropionaldehyde and 0.6 g (9.5 mmol) of sodium cyanoborohydride are used. Yield: 0.8 g (48%),
melting point: >250 °C, $[\alpha]_D^{25} = (-) 75.1^\circ$ (c=1 in
30 methanol).

Example 17: (-)-(1R)-4'-hydroxy-2-[2"-(2'"-phenylamino)ethoxy]ethyl-5,9,9-trimethyl-6,7-benzomorphan-dihydrochloride ((-)-2aeCl2)

35

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1.3 g (5.6 mmol) of (-)-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan ((-)-2a) and 1.7 g (5.6 mmol) of 2-(N-phenyl-2"-tert.-butoxycarbonylamino)-ethoxyethyl chloride are dissolved in 50 ml of DMF, a catalytic quantity of KI and 1 g potassium carbonate are added. The mixture is stirred for 7 h at 110 °C, and then the solvent is eliminated *in vacuo*. The residue is taken up in 100 ml of water, extracted three times with 100 ml of ethyl acetate and the combined organic extracts are once again washed with 50 ml of water, dried over MgSO₄ and the solvent is eliminated *in vacuo*. The residue is purified over a flash column (120 ml of silica gel; ethyl acetate/ cyclohexane 1:1) and stirred with 50 ml of conc. hydrochloric acid for 30 min. at RT. Then the mixture is diluted with 150 ml of ice water, extracted once with 50 ml of ethyl acetate (discarding the organic phase), and made alkaline with conc. ammonia. It is extracted three times with 100 ml of ethyl acetate, the combined organic extracts are dried over MgSO₄ and the solvent is eliminated *in vacuo*. The residue is dissolved in 10 ml of ethanol and the hydrochloride is precipitated with ethereal hydrochloric acid. Yield: 0.7 g (27%), melting point: 112 °C, $[\alpha]_D^{25} = (-) 75.8^\circ$ (c=1 in methanol).

Example 19: (-)-(1R,2"S)-2-(2"-benzyloxy)propyl-3'-chloro-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2agCl) and (-)-(1R,2"S)-2-(2"-benzyloxy)propyl-1'-chloro-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2ahCl) 3 g (7.3 mmol) of (-)-(1R,2"S)-2-(2"-benzyloxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan-hydrochloride ((-)-2bCl) and 1.0 g (7.3 mmol) of N-chlorosuccinimide are suspended in 70 ml

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of glacial acetic acid and stirred for 24 h at ambient temperature during which time the suspension goes into solution. Then the mixture is concentrated by evaporation *in vacuo*, the residue is combined with
 5 100 ml of ice-cold 2 N sodium hydroxide solution and extracted three times with 100 ml of ethyl acetate. The combined organic phases are dried over MgSO_4 and the solvent is eliminated *in vacuo*. Then the residue is chromatographed on silica gel (180 g silica gel;
 10 cyclohexane/ ethyl acetate 5: 1). The suitable fractions are concentrated by evaporation and the residue is dissolved in 15 ml of acetone and the hydrochloride is precipitated with ethereal hydrochloric acid.
 15 0.4 g (12%) of (-)-2agCl is obtained, melting point: 204 °C, $[\alpha]_D^{25} = (-) 21.5^\circ$ (c=1 in methanol) and 0.6 g (18%) of (-)-2ahCl is obtained, melting point: 258 °C, $[\alpha]_D^{25} = (-) 4.6^\circ$ (c=1 in methanol).

20

The following are some Examples of pharmaceutical preparations using the active substance:

Tablets:

25	active substance of general formula I	20 mg
	magnesium stearate	1 mg
	lactose	190 mg

Solution for injection

30	active substance of general formula I	0.3 mg
	sodium chloride	0.8 g
	benzalkonium chloride	0.01 mg
	water for injections	ad 100 ml

35 A similar solution to that described above is suitable for nasal administration in a spray, or in

conjunction with a device which produces an aerosol with a particle size preferably between 2 and 6 μM , for administration through the lungs.

5 Solution for infusion

A 5 % by weight xylitol solution which contains the active substance in a concentration of 2 mg/ml, for example, is adjusted to a pH of about 4 with a sodium acetate buffer.

10

Infusion solutions of this kind may contain the active substance of general formula 1 in an amount of from 0.001 to 20% by weight, from 0.001 to 10 % by weight and most preferably from 0.01 to 5 % by weight, based on the total mass of the pharmaceutical preparation.

15

Capsules for inhalation

The active substance according to general formula I is packed into hard gelatine capsules in micronised form (particle size essentially between 2 and 6 μM), optionally with the addition of micronised carriers such as lactose. The preparation is inhaled using conventional devices for powder inhalation. Each capsule contains e.g. between 0.2 and 20 mg of active substance and 0 to 40 mg of lactose.

25

Aerosol for inhalation

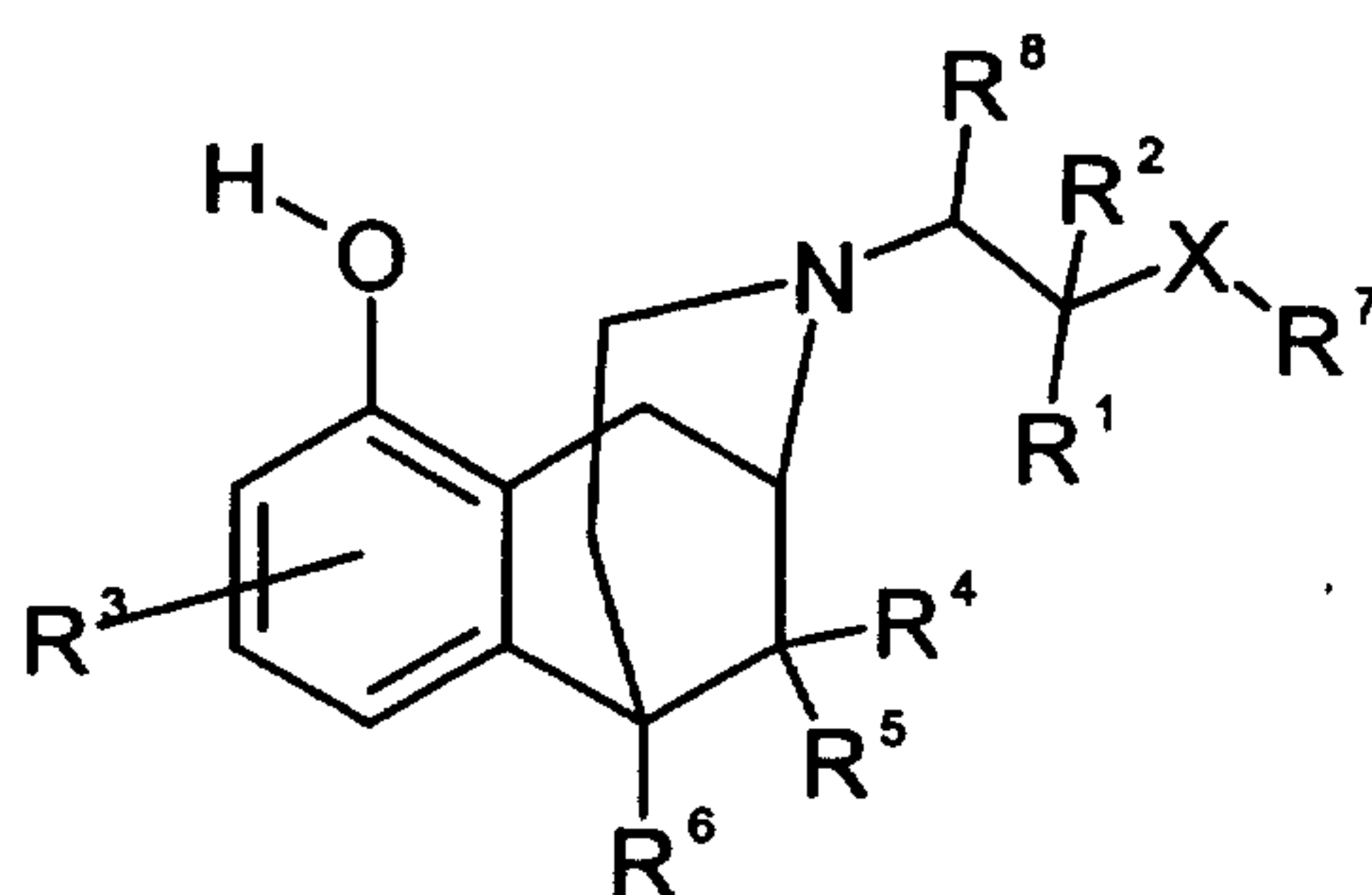
active substance of general formula I	1 part
soya lecithin	0.2 parts
propellent gas mixture ad	100 parts

30

S018-528cls.202

New Patent Claims

- 5 1. Compounds of general formula (I)



I

wherein

10

X denotes a single bond, -O-, C₁-C₄-alkylene, an alkylene bridge having 1 to 8 carbon atoms which may be branched or unbranched and may have one or two oxygen atom(s) anywhere in the bridge;

15

R¹ denotes hydrogen, methyl, ethyl, phenyl;

R² denotes hydrogen, methyl;

20

R³ denotes hydrogen, fluorine, chlorine, bromine, hydroxy, methyl, methoxy;

R⁴ denotes hydrogen, methyl, ethyl;

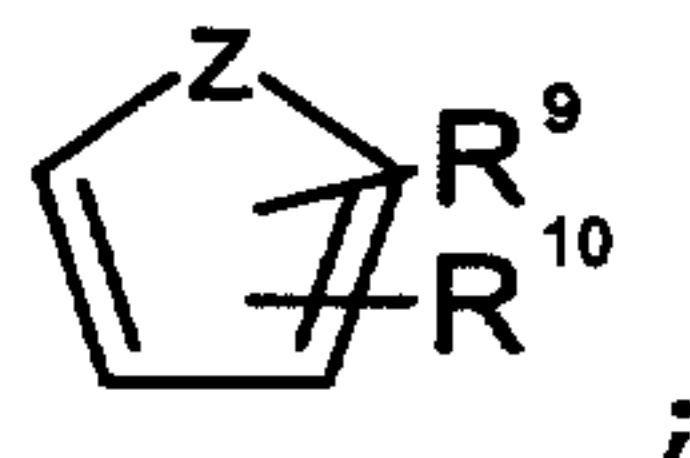
25

R⁵ denotes hydrogen, methyl, ethyl;

R⁶ denotes hydrogen, methyl, ethyl;

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R⁷ denotes tert.-butyl, cyclohexyl, phenyl optionally substituted by R⁹ and R¹⁰, which may



be identical or different,

5

R⁸ denotes hydrogen, C₁-C₄-alkyl;

Z denotes oxygen, NH, sulphur;

10

R⁹ denotes hydrogen, methyl, fluorine, chlorine, bromine, methoxy;

R¹⁰ denotes hydrogen, methyl, fluorine, chlorine, bromine, methoxy;

15

with the proviso that if

X denotes O-C₁-C₃-alkylene;

20

R¹ denotes methyl, ethyl or phenyl;

R² denotes hydrogen or methyl;

25

R³ denotes hydrogen, fluorine, chlorine, bromine, hydroxy, methyl or methoxy;

R⁴ denotes methyl or ethyl;

R⁵ denotes methyl or ethyl;

30

R⁶ denotes methyl or ethyl,

R⁷ cannot denote phenyl,

and with the proviso that if

X denotes oxygen;

R¹ denotes methyl, ethyl or phenyl;

5

R² denotes hydrogen or methyl;

R³ denotes hydrogen, fluorine, chlorine,
bromine, hydroxy, methyl or methoxy;

10

R⁴ denotes methyl or ethyl;

R⁵ denotes methyl or ethyl;

15

R⁶ denotes methyl or ethyl,

R⁷ cannot denote tert.butyl,

20

optionally in the form of the individual optical
isomers, mixtures of the individual enantiomers
or racemates as well as in the form of the free
bases or the corresponding acid addition salts
with pharmaceutically acceptable acids.

25

2. Compounds of general formula I according to claim
1, wherein

30

X denotes O-C₁-C₃-alkylene or -O-CH₂-CH₂-O- or
-O-CH₂-CH₂-NH-;

R¹ denotes hydrogen, methyl, ethyl or phenyl;

35

R² denotes hydrogen or methyl,

R^3 denotes hydrogen, fluorine, chlorine, bromine, hydroxy, methyl, methoxy;

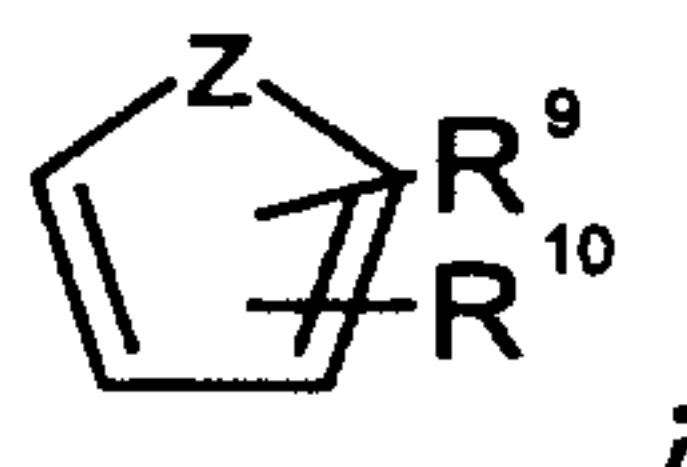
R^4 denotes hydrogen, methyl, ethyl;

5

R^5 denotes hydrogen, methyl, ethyl;

R^6 denotes hydrogen, methyl, ethyl;

10 R^7 denotes tert.-butyl, cyclohexyl, phenyl optionally substituted by R^9 and R^{10} , which may



be identical or different,

15 R^8 denotes hydrogen, C_1 - C_4 -alkyl;

Z denotes oxygen, NH, sulphur;

20 R^9 denotes hydrogen, methyl, fluorine, chlorine, bromine, methoxy;

R^{10} denotes hydrogen, methyl, fluorine, chlorine, bromine, methoxy;

25 optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates and also in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids.

30

3. Compounds of general formula I according to claim 1, characterised in that

5 X denotes a single bond, -O-, C₁-C₄-alkylene, an alkylene bridge having 1 to 8 carbon atoms which may be branched or unbranched and may have one or two oxygen atom(s) anywhere in the bridge, preferably O-C₁-C₃-alkylene or -O-CH₂-CH₂-O- or -O-CH₂-CH₂-NH-;

R¹ denotes hydrogen, methyl, ethyl, phenyl;

10 R² denotes hydrogen, methyl;

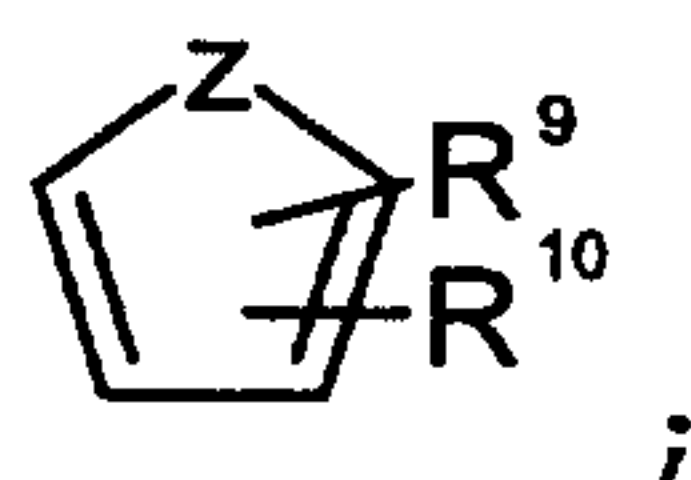
R³ denotes hydrogen, fluorine, chlorine, bromine, hydroxy, methyl, methoxy;

15 R⁴ and R⁵ independently of one another denote hydrogen or methyl, but at least one methyl;

R⁶ denotes hydrogen, methyl or ethyl;

20

R⁷ denotes tert.-butyl, cyclohexyl, phenyl optionally substituted by R⁹ and R¹⁰, which may



be identical or different,

25

R⁸ denotes hydrogen, C₁-C₄-alkyl;

Z denotes oxygen, NH, sulphur;

30 R⁹ denotes hydrogen, methyl, fluorine, chlorine, bromine, methoxy;

R¹⁰ denotes hydrogen, methyl, fluorine, chlorine, bromine, methoxy;

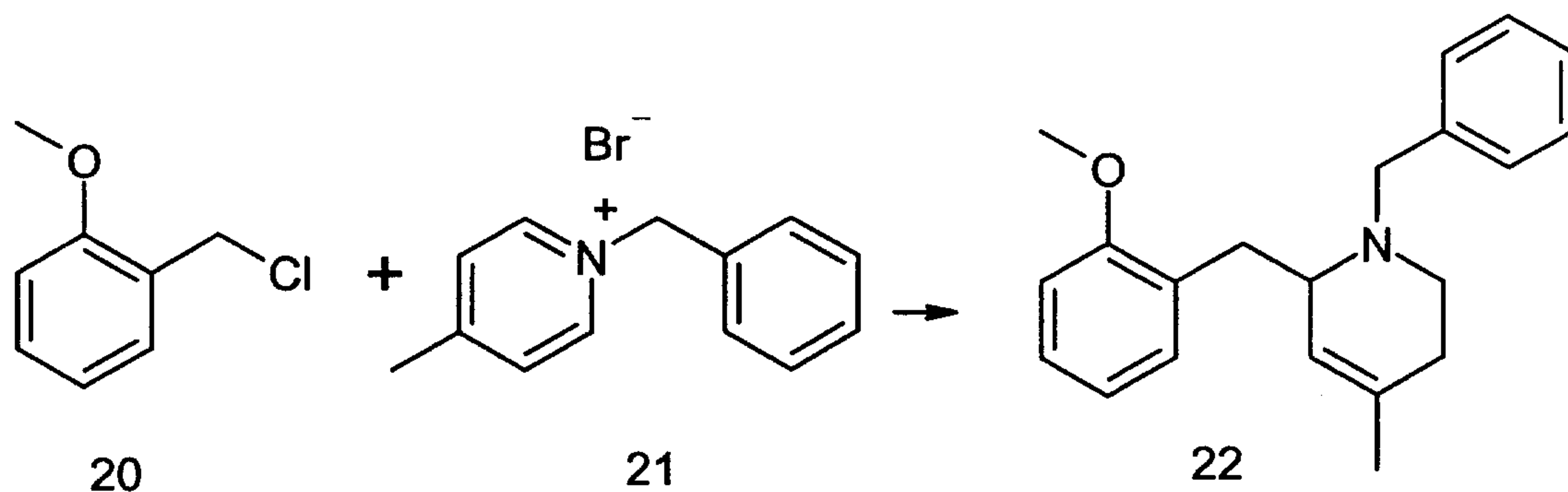
optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates and also in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids.

4. (-) - (1R,2"S) - 2 - (2"-Benzyloxy)propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan according to general formula I in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids.

5. (-) - (1R,2"S) - 2 - [2" - (2'",6'" - Difluorobenzyl) - oxy]propyl-4'-hydroxy-5,9,9-trimethyl-6,7-benzomorphan according to general formula I, in the form of the free bases or the corresponding acid addition salts with pharmacologically acceptable acids.

6. Process for preparing norbenzomorphans of general formula 5 according to claim 1, characterised in that

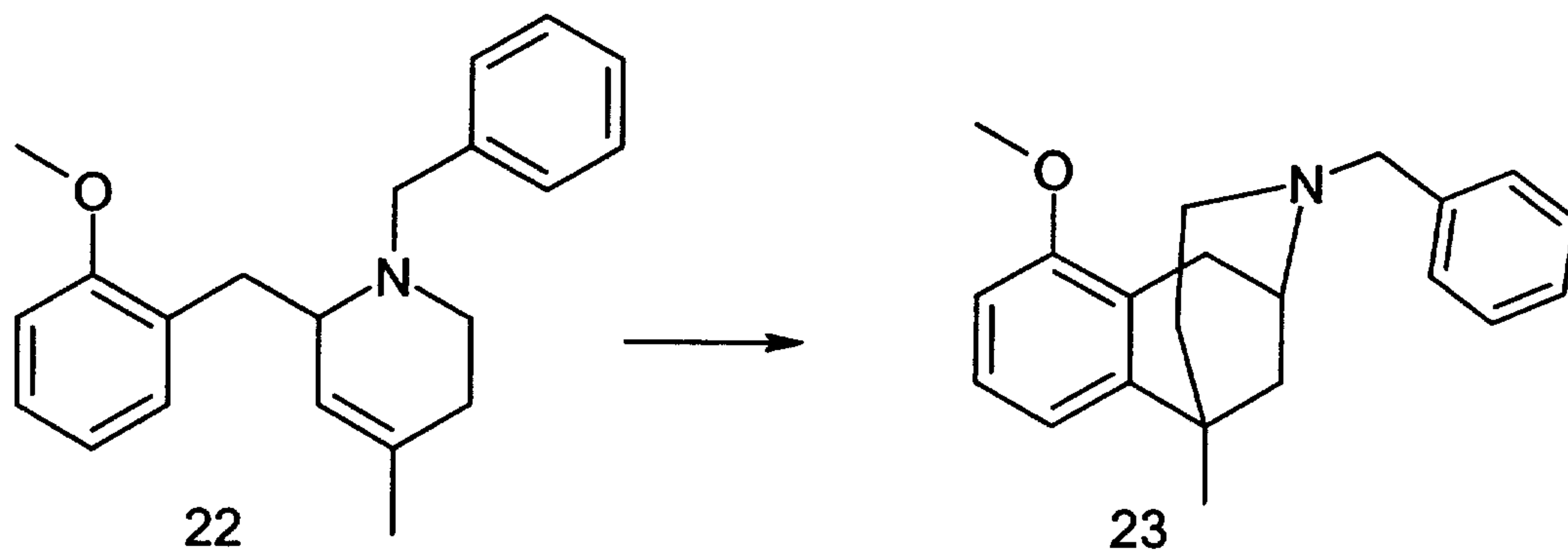
a) o-methoxychlorobenzylchloride (20) is reacted with the benzylpyridinium bromide 21 to obtain tetrahydropyridine 22



and

b) the tetrahydropyridine derivative 22 is rearranged to obtain the N-benzylbenzomorphan derivative 23

5

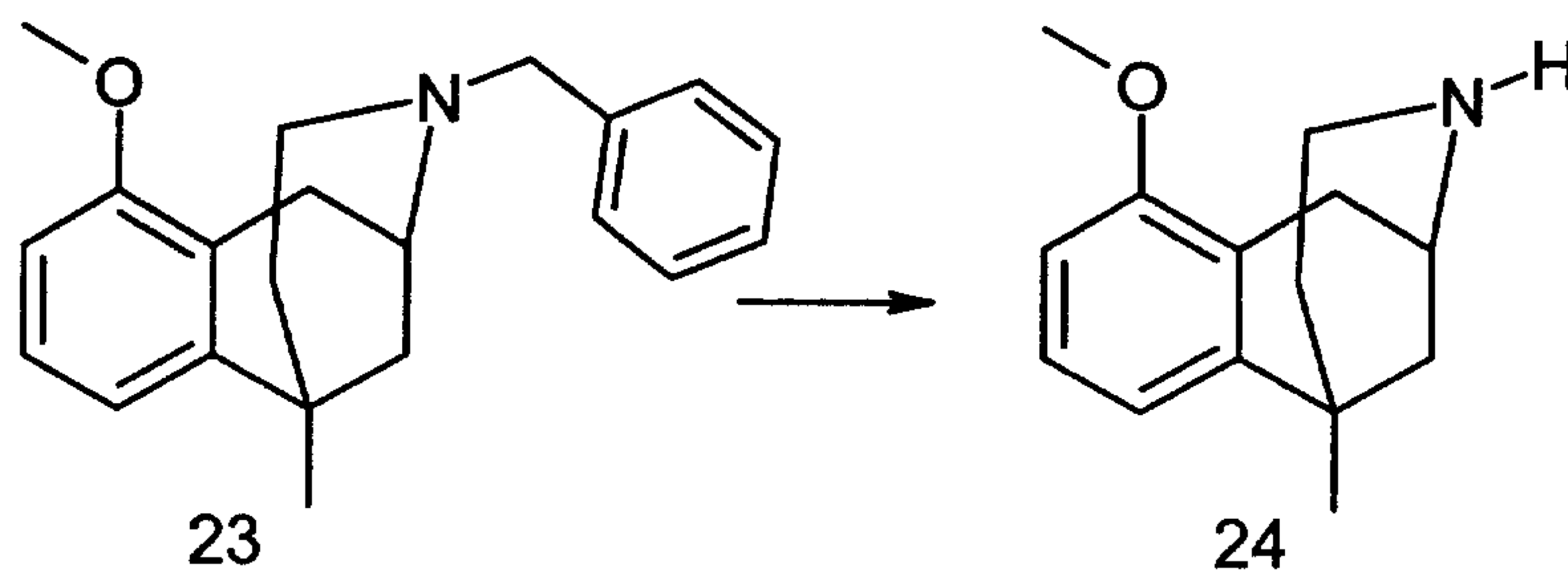


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and

c) the amino nitrogen is debenzylated to obtain the methoxybenzomorphan derivative 24

15

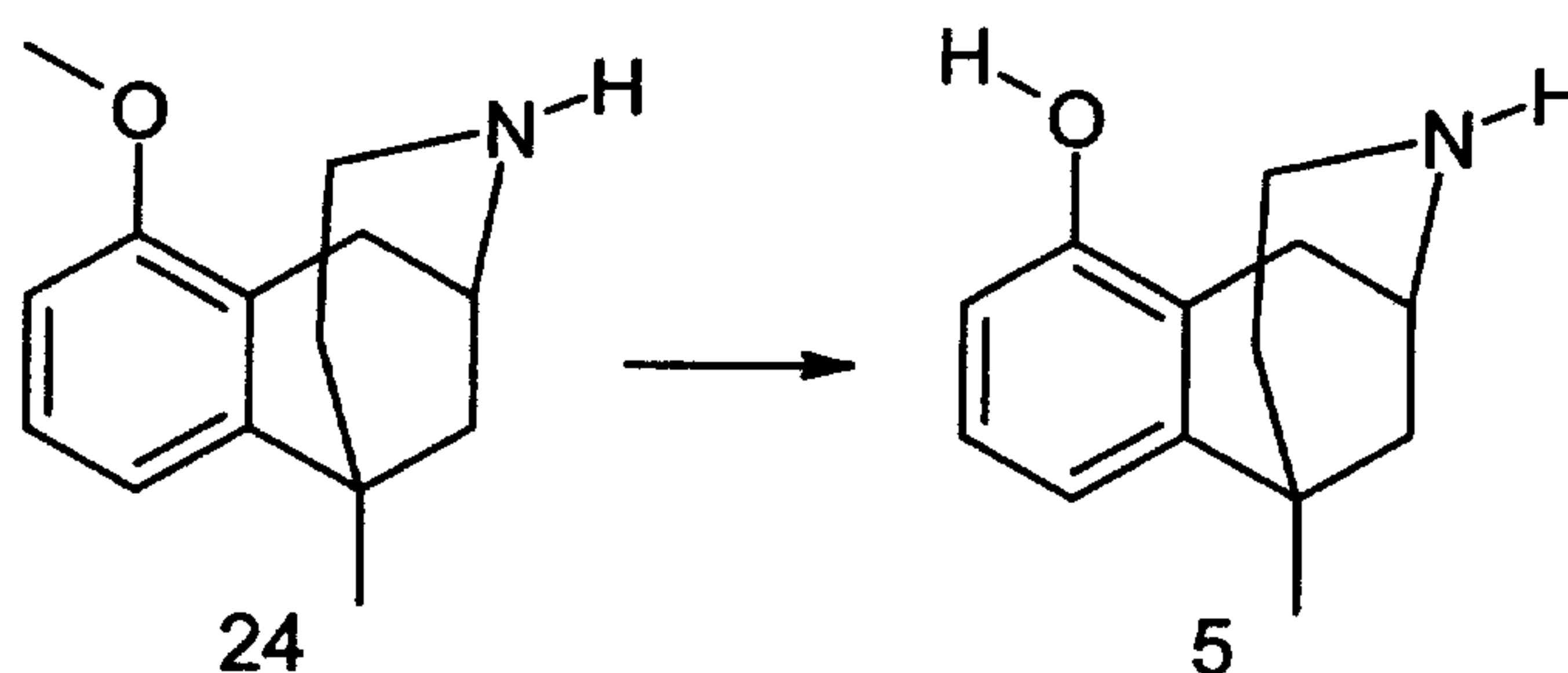


and

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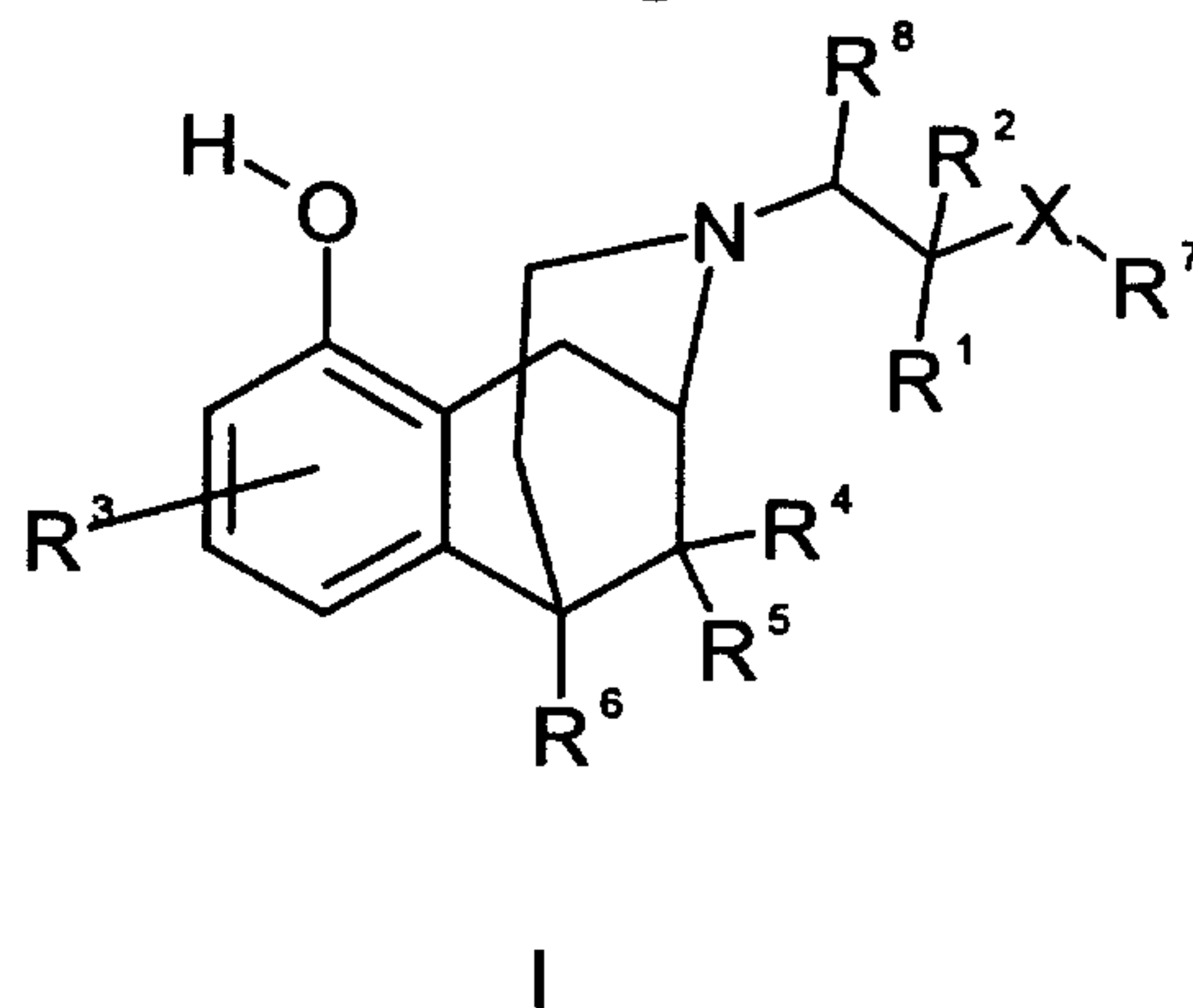
d) the phenolether 24 and the benzomorphan derivative 5 are isolated

- 67 -



5

7. Process for preparing norbenzomorphans of general formula (I) according to claim 1



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wherein

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X denotes a single bond, -O-, C₁-C₄-alkylene, an alkylene bridge having 1 to 8 carbon atoms which may be branched or unbranched and may have one or two oxygen atom(s) anywhere in the bridge;

R¹ denotes hydrogen, methyl, ethyl, phenyl;

R² denotes hydrogen, methyl;

20

R³ denotes hydrogen, fluorine, chlorine, bromine, hydroxy, methyl, methoxy;

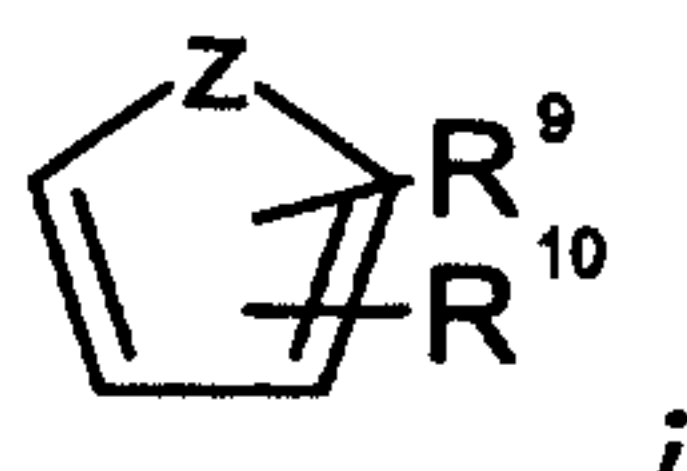
R⁴ denotes hydrogen, methyl, ethyl;

R⁵ denotes hydrogen, methyl, ethyl;

R⁶ denotes hydrogen, methyl, ethyl;

5

R⁷ denotes tert.-butyl, cyclohexyl, phenyl optionally substituted by R⁹ and R¹⁰, which may



be identical or different,

10

R⁸ denotes hydrogen, C₁-C₄-alkyl;

Z denotes oxygen, NH, sulphur;

15

R⁹ denotes hydrogen, methyl, fluorine, chlorine, bromine, methoxy;

R¹⁰ denotes hydrogen, methyl, fluorine, chlorine, bromine or methoxy,

20

characterised in that

a) a benzylcyanide of general formula 32 wherein R₃₀ denotes a C₁-C₄-alkyl group, is subjected to the conditions of a Reformatsky reaction with a halocarboxylate of general formula 33, wherein R₄₀ denotes C₁-C₈ -alkyl or benzyl, in the presence of an alkylhalosilane - preferably a trialkylchlorosilane and most preferably trimethylchlorosilane - and zinc powder in an inert solvent - preferably in an ether or in a halohydrocarbon and most preferably with dichloromethane and in the presence of a reducing agent which is selective with regard to the reduction of imino functions - preferably in the presence of an

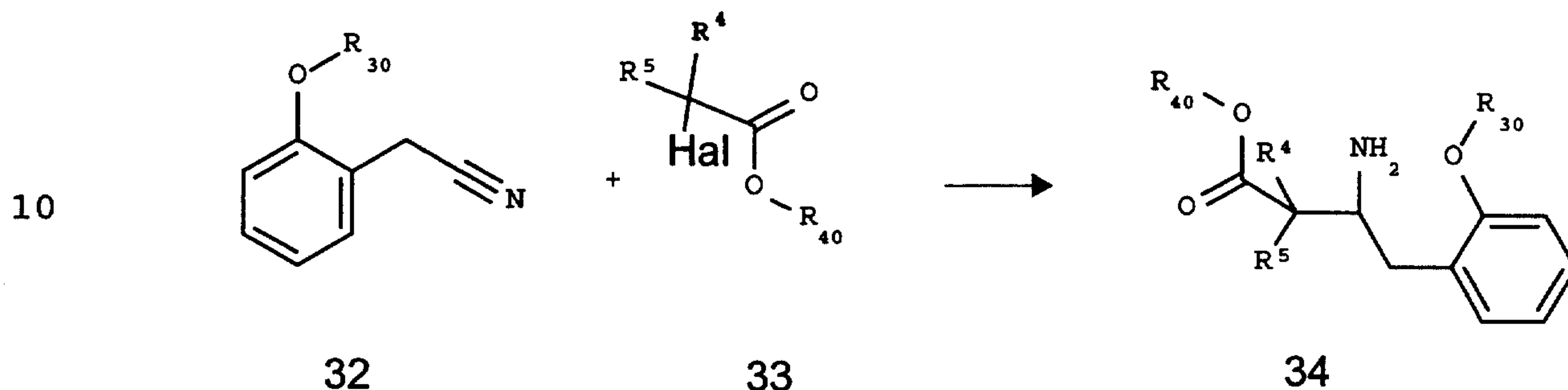
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alkali metal borohydride derivative and most preferably in the presence of sodium cyanoborohydride - and the resulting carboxylic acid ester derivative of general formula 34 is isolated

5

and



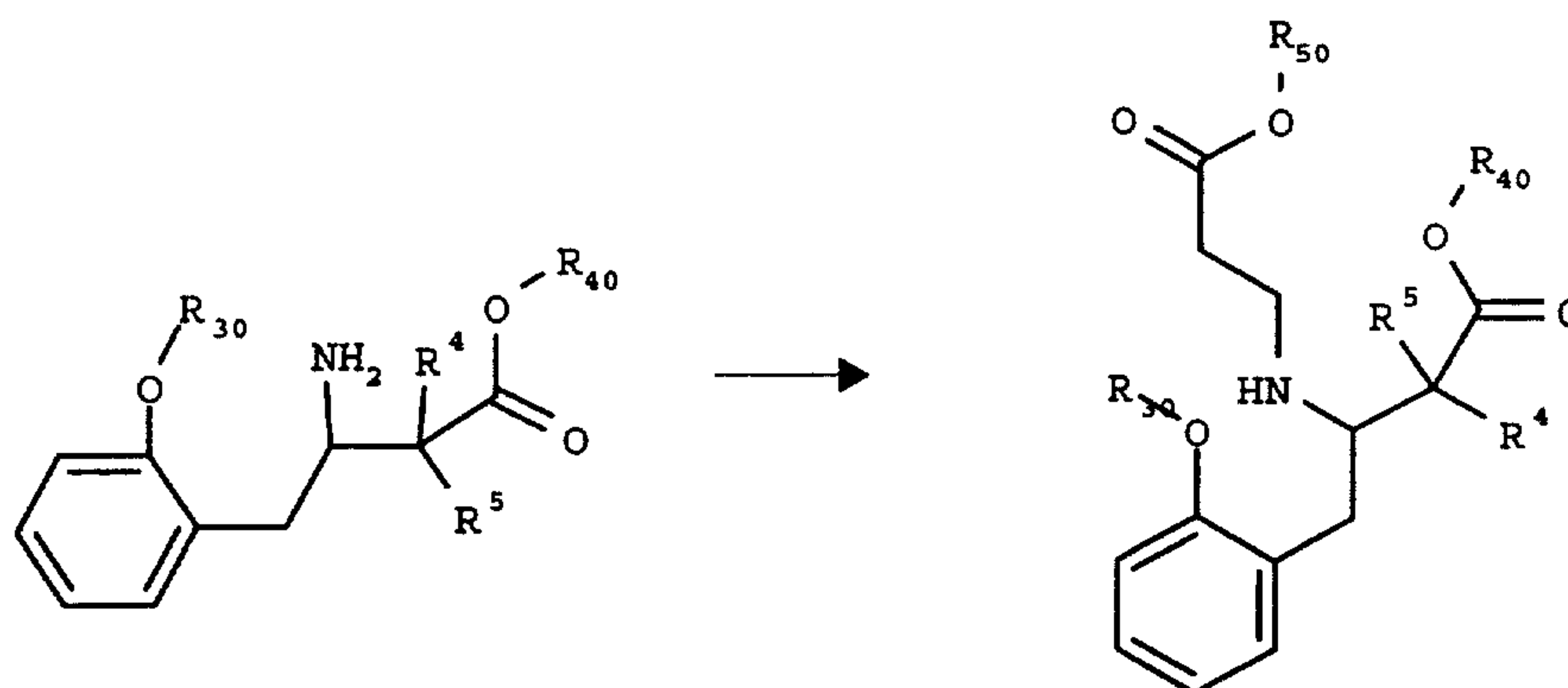
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b) the carboxylic acid ester derivative of general formula 34 is subjected to the conditions of a Michael addition reaction with an acrylic acid ester, wherein the alcohol component R₅₀ denotes a C₁-C₈-alkyl group or a benzyl group, in a solvent which is inert under the reaction conditions selected - preferably in an alkanol and most preferably in ethanol - and the resulting Michael addition product of general formula 35 is isolated

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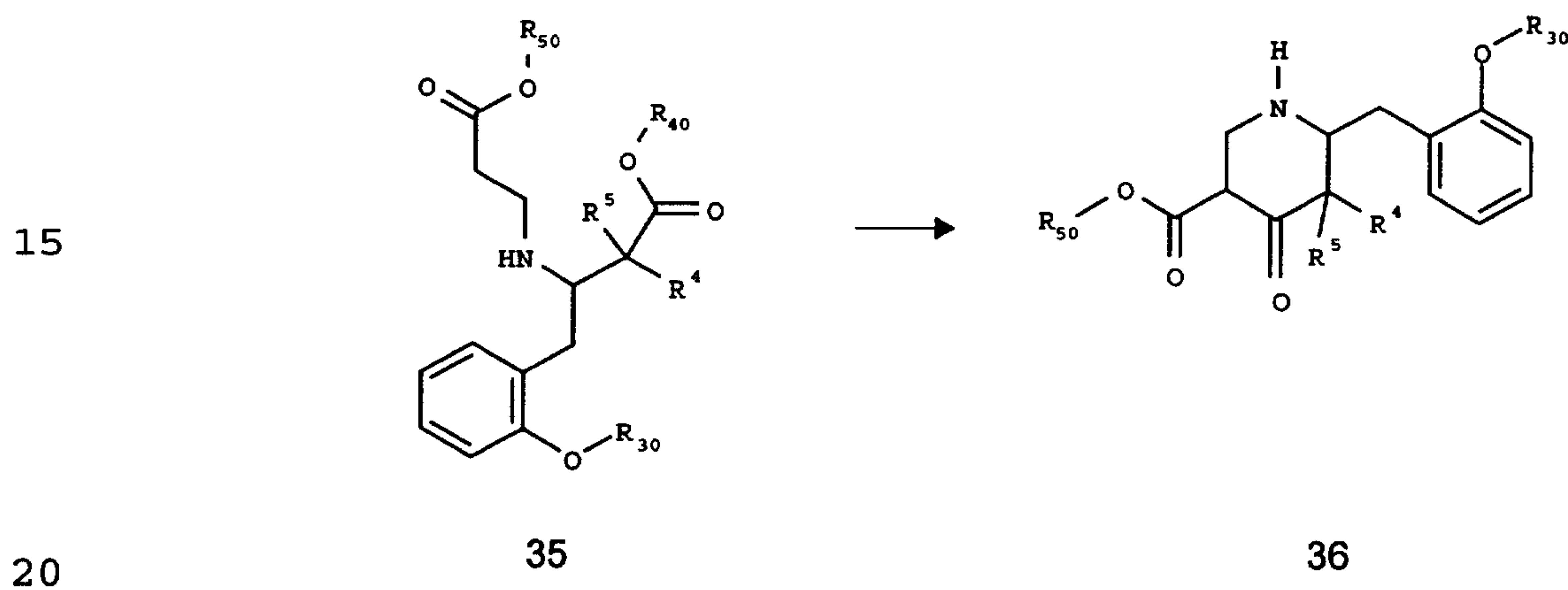
and

34

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- 70 -

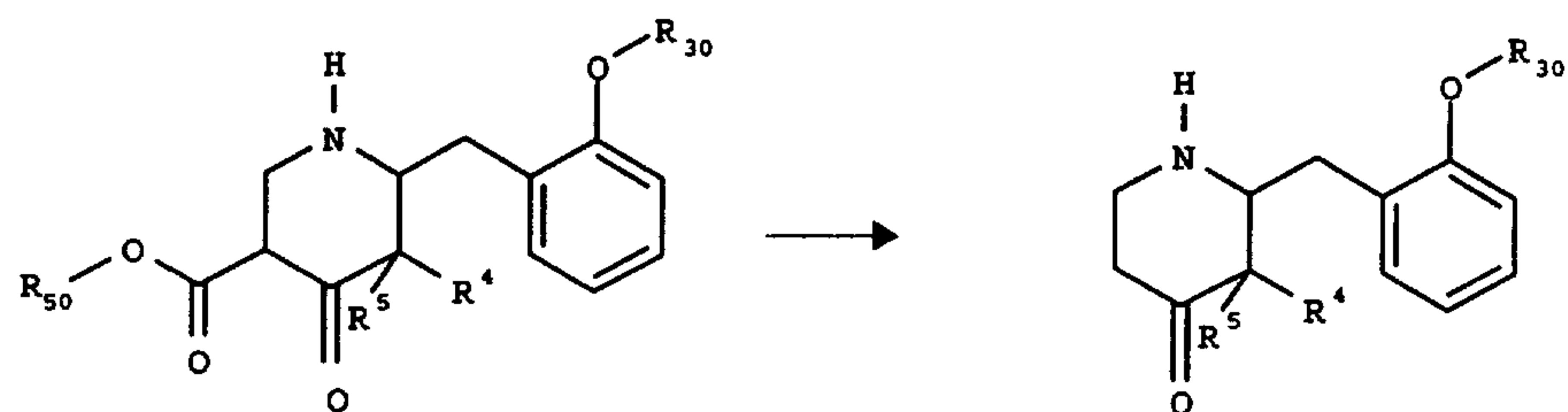
c) the carboxylic acid diester derivative of general formula 35 thus prepared is subjected to the conditions of Dieckmann's ester condensation in an inert solvent - preferably in an aliphatic or aromatic hydrocarbon and most preferably in toluene - in the presence of a basically reacting compound - preferably in the presence of an alkali metal alkoxide, a branched or unbranched C₁-C₄-alkanol and most preferably in the presence of potassium-tert.-butoxide - and the resulting piperidone derivative of general formula 36 is isolated



and

d) the piperidone derivative 36 is saponified and decarboxylated under acid or alkaline conditions - preferably in the presence of an alkali hydroxide or an inorganic acid and most preferably in the presence of sodium hydroxide - in a polar solvent or solvent mixture - preferably in a mixture of a straight-chained or branched C₁-C₄-alkanol and water and most preferably in an ethanol/water mixture - with heating, to obtain the corresponding piperidone ester derivative of general formula 37, which is isolated, and optionally the corresponding acid addition salt is prepared with an acid and isolated

5



36

37

and

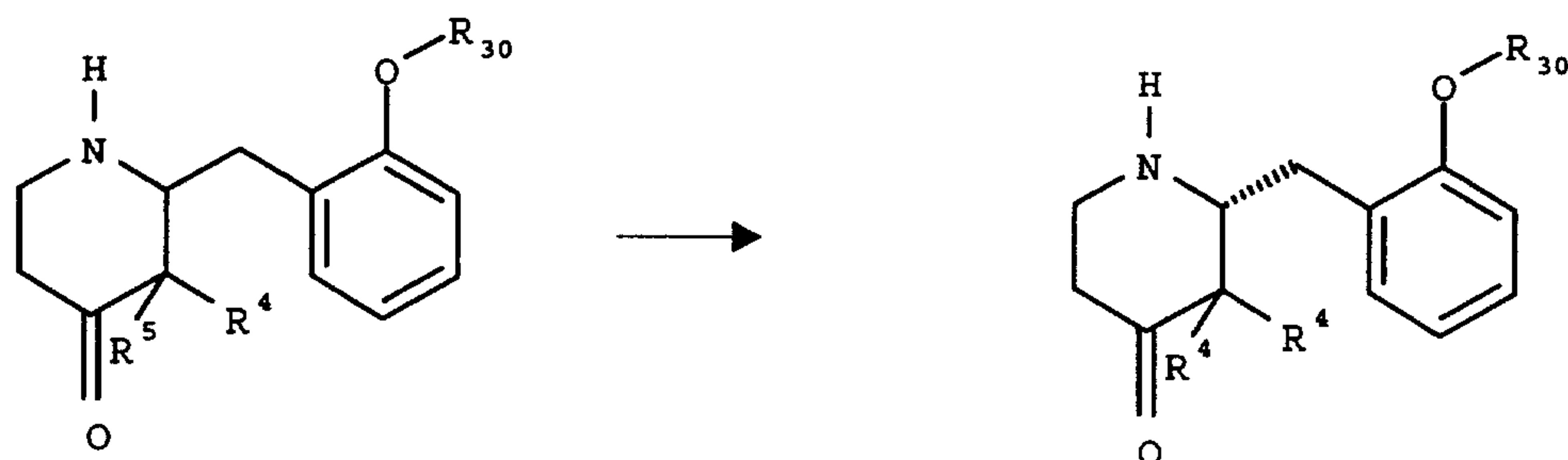
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e) if desired, the mixture of stereoisomers thus obtained is dissolved in a reaction medium which is inert with regard to the enantiomer separation, optionally after the release of the enantiomeric free bases, combined with a suitable stereoisomer of an organic acid suitable for salt formation with a stereoisomer of the enantiomer mixture, and the desired stereoisomer is isolated in the form of its addition salt with the optically active acid

20

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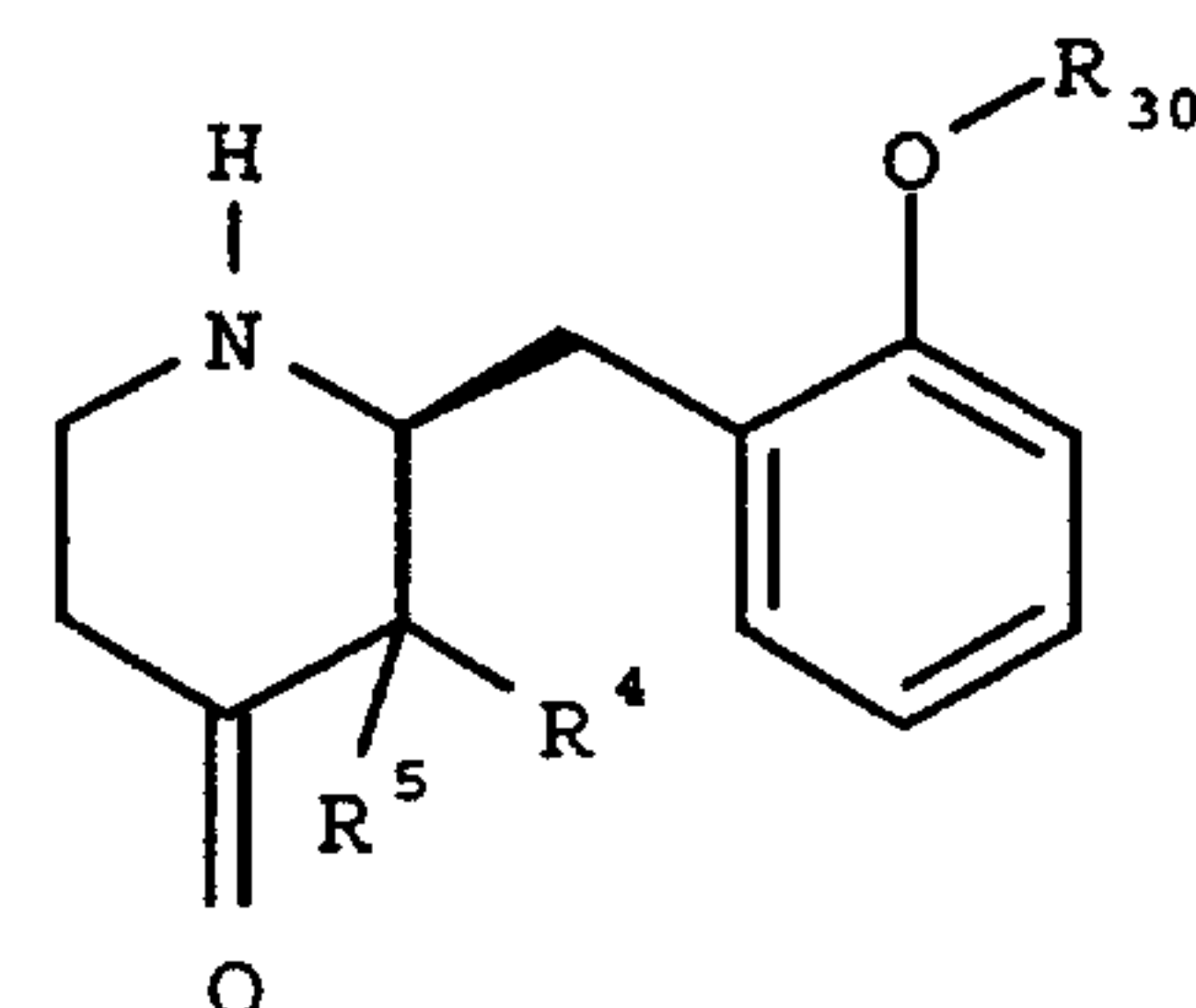


30

37

38'

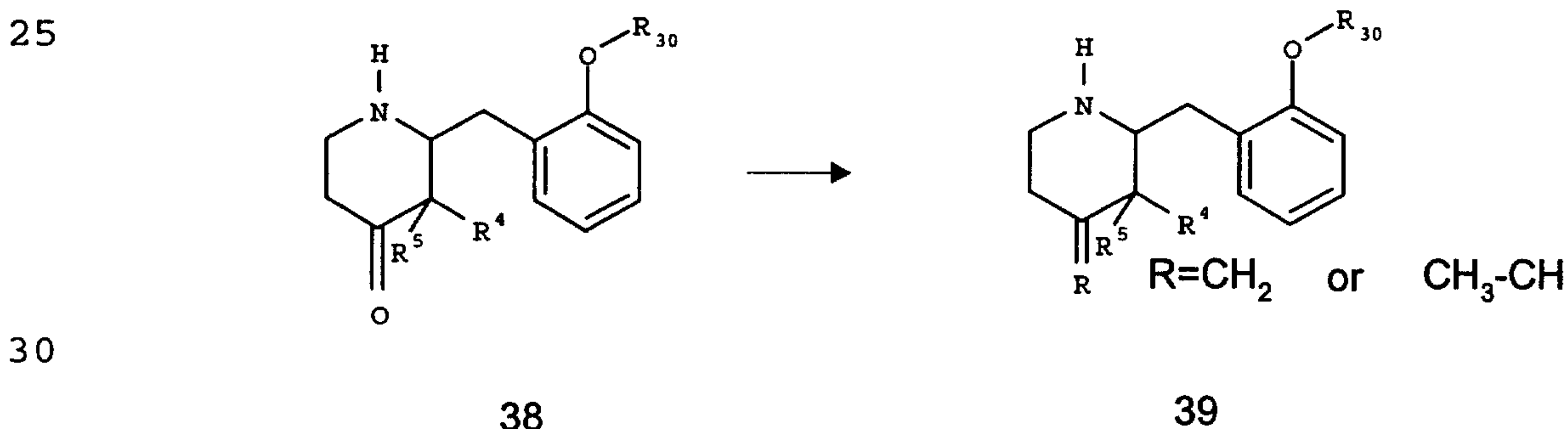
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38''

and

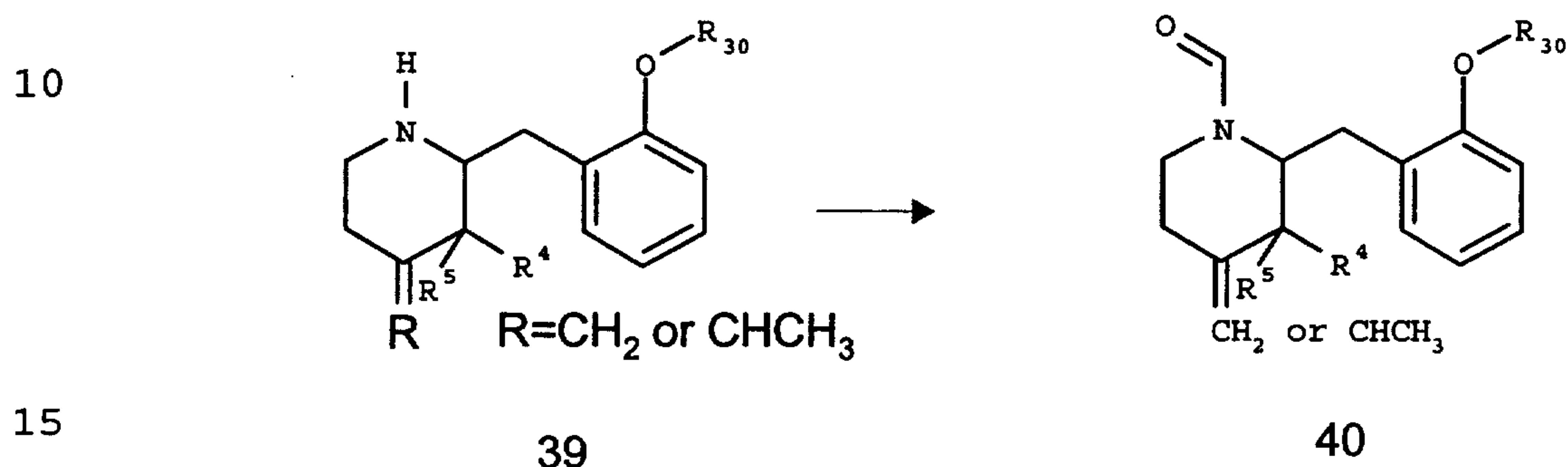
5 f) the pure stereoisomer 38' or 38" or the isomer
mixture 38 thus obtained is subjected to a Wittig
reaction after liberation from the enantiomerically
pure acid addition salt in an inert solvent with a
10 Wittig reagent generating a $\text{CH}_2=$ or $\text{CH}_3\text{-CH=}$
grouping, preferably with an
ethyltriphenylphosphonium halide or with a
methyltriphenylphosphonium halide, most preferably
with methyltriphenylphosphonium bromide or
ethyltriphenylphosphonium bromide in the presence
15 of a basically reacting compound - preferably in
the presence of an alkali metal alkoxide, most
preferably potassium tert.-butoxide - in an inert
reaction medium - preferably in a cyclic ether,
most preferably in tetrahydrofuran - and the
20 reaction product of type 39 or the corresponding
stereoisomer is optionally isolated in the form of
its acid addition salt



and

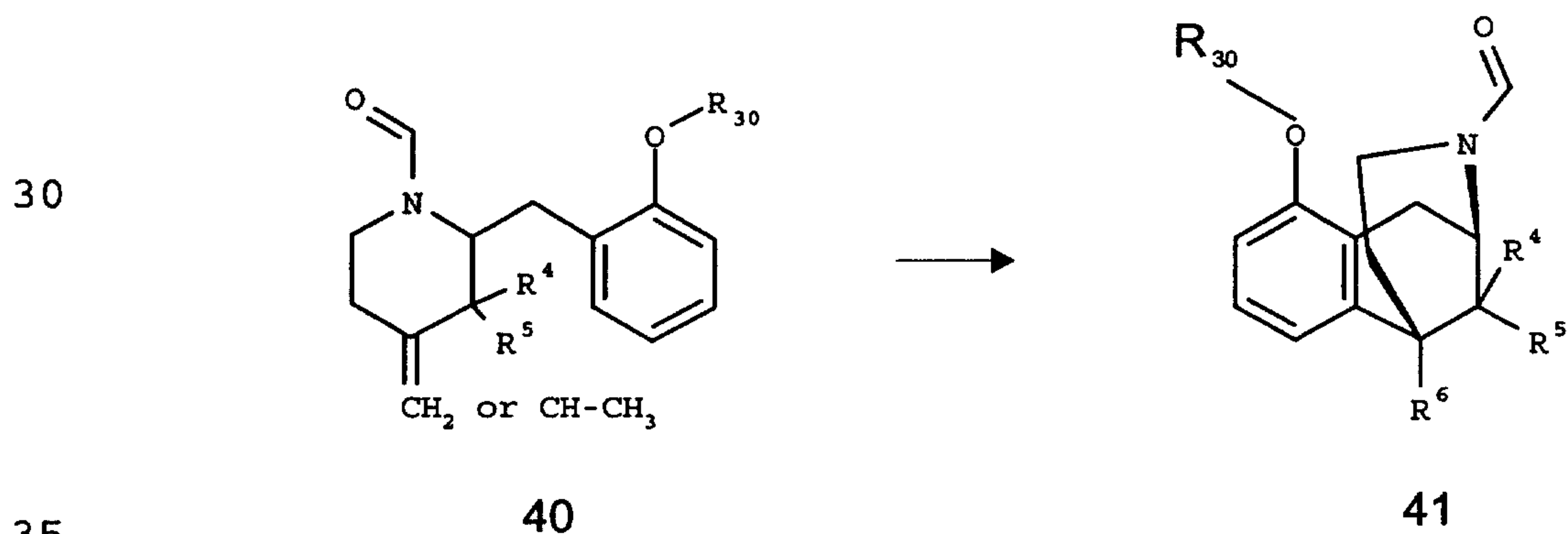
35 g) the alkene 39 obtained from the Wittig reaction is
optionally first liberated from the acid addition
salt thereof and the free base of type 39 is

dissolved in an organic solvent - preferably in a halogenated hydrocarbon and most preferably in dichloromethane - and subjected to a formylation reaction with a formylating agent - preferably n-butylformate - at the piperidine nitrogen and the reaction product of type 40 or the corresponding stereoisomer is isolated



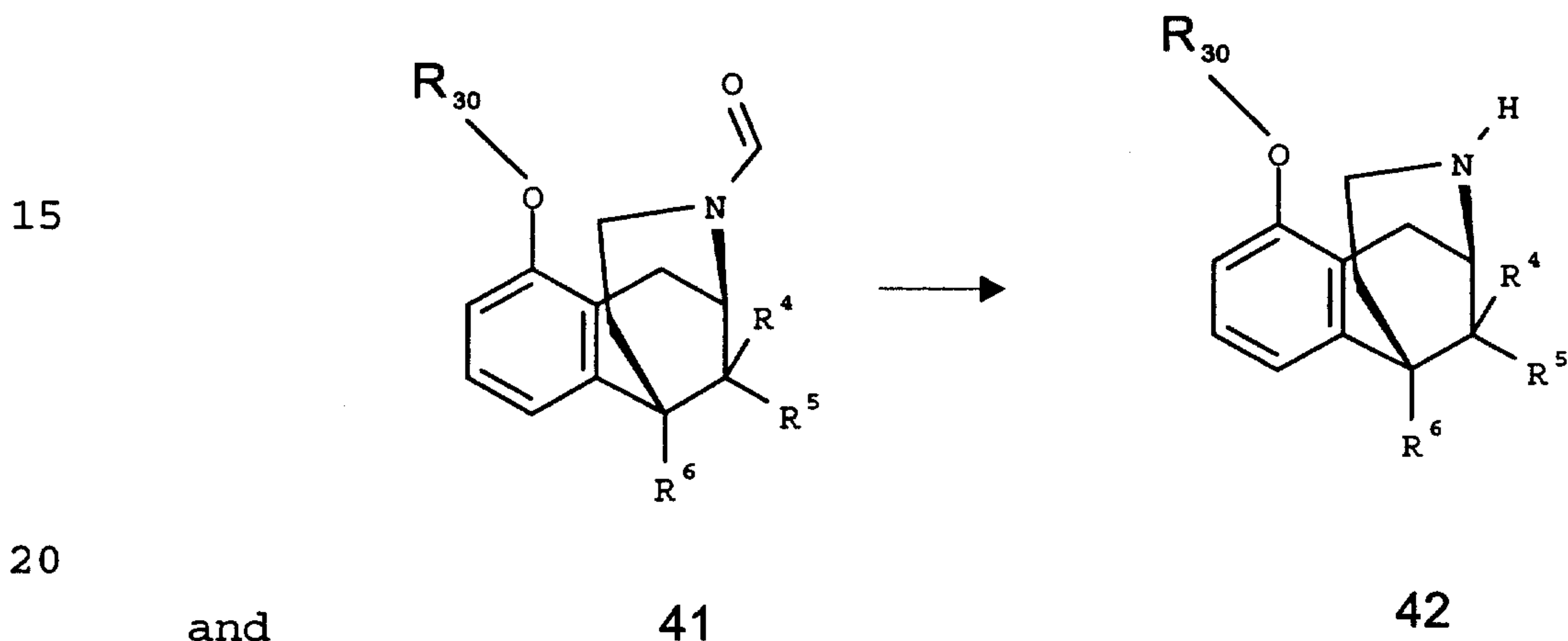
and

h) the formyl compound 40 thus obtained - or the corresponding stereoisomer - is reacted with an inorganic acid or with a Lewis acid - preferably aluminium(III)chloride - dissolved in an inert solvent - preferably in a halogenated hydrocarbon and most preferably in dichloromethane - and the cyclisation product of type 41 resulting from this reaction is isolated

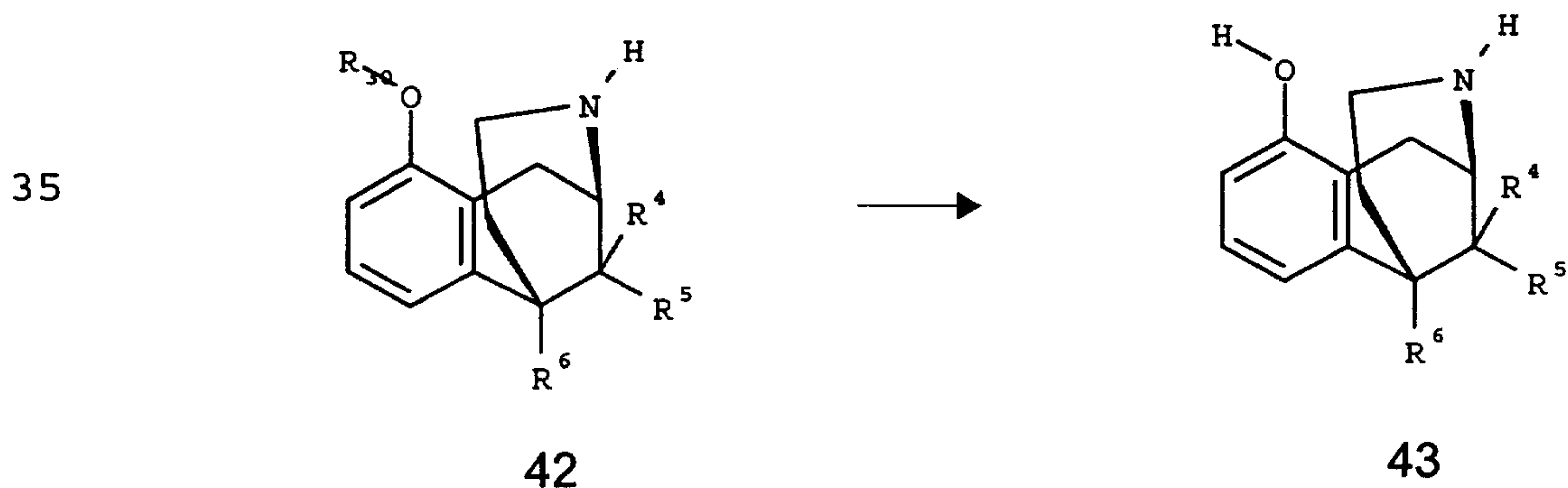


and

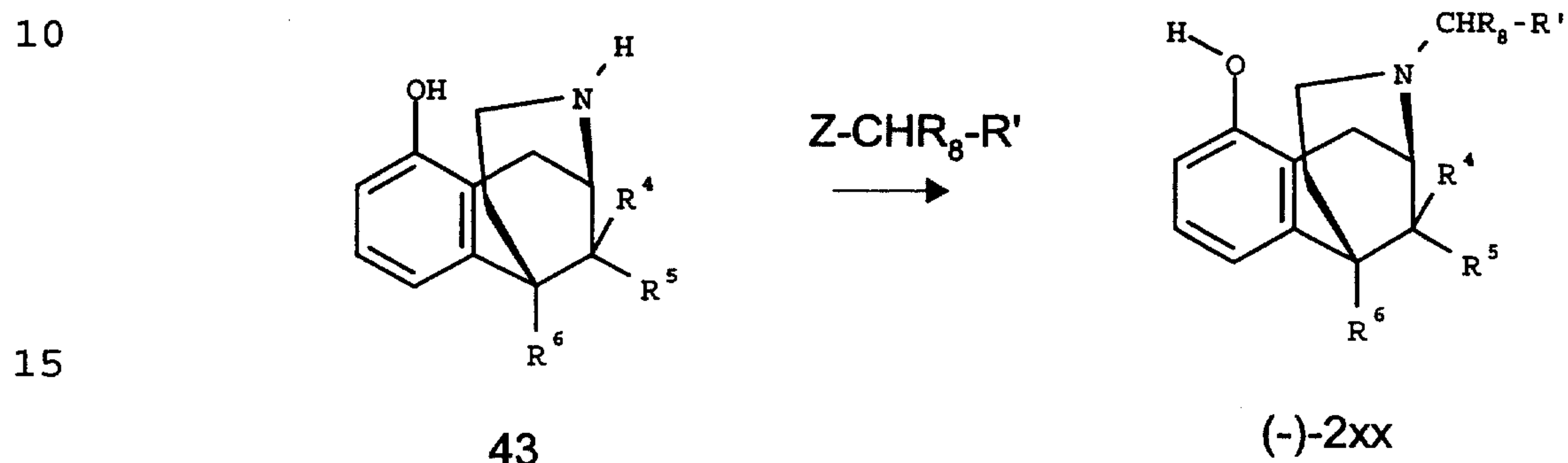
i) the benzomorphan derivative resulting from the cyclisation reaction is dissolved in a polar solvent - preferably in a C₁-C₄-alkanol, most preferably in n-propanol - and reacted with an acidically reacting compound - preferably with the aqueous solution of an inorganic acid and most preferably with concentrated hydrochloric acid - and the deformylated norbenzomorphan of type 42 resulting from this reaction is isolated, optionally in the form of its acid addition salt



j) if the stereoisomers have not yet been separated, at this stage the stereoisomers are separated in a manner known *per se* and after the release of the free benzomorphan base the phenolether is cleaved with an acidically reacting compound - preferably with an inorganic acid and most preferably with hydrobromic acid - and the cleavage product of type 43 is isolated

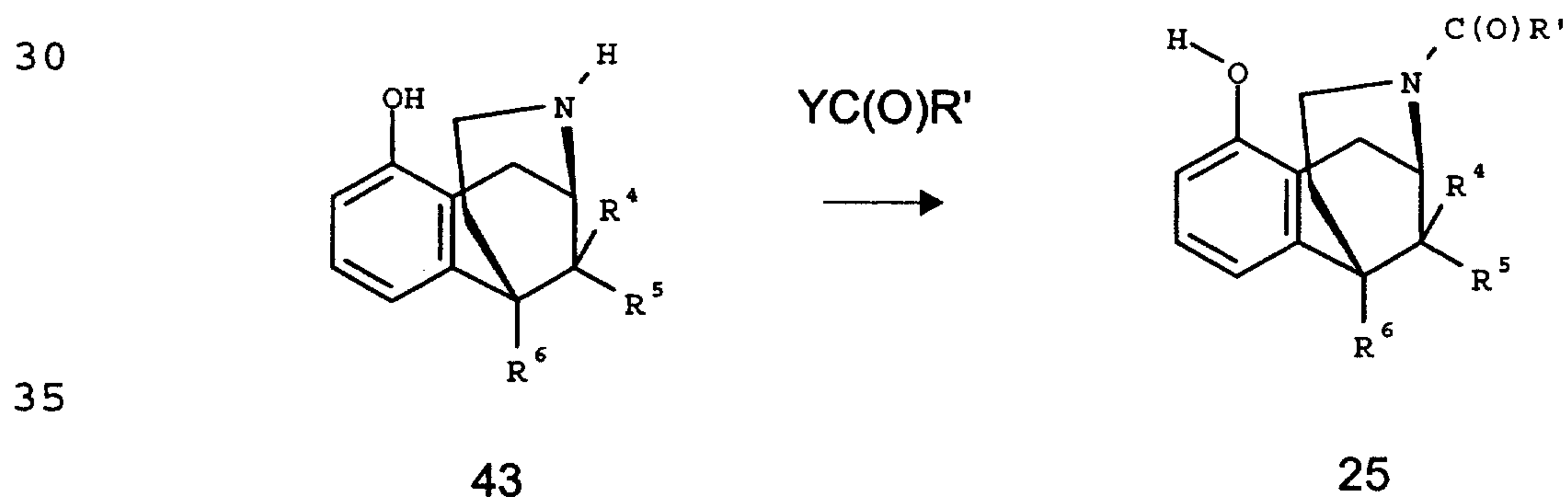


- k) reacted with a compound of type $Z-CHR_8-R'$ wherein Z denotes a secondary amino nitrogen substituted leaving group, preferably a halogen such as chlorine, bromine, iodine or an organic sulphonate, preferably trifluoromethanesulphonate and R' denotes $-CR^1R^2XR^7$,



or

- 20 is reacted with a compound of type $YC(O)R'$ wherein Y denotes a secondary amino nitrogen substituted leaving group which may be preferably a halogen such as chlorine, bromine, iodine or an organic sulphonate, preferably trifluoromethanesulphonate, and R' denotes $-CR^1R^2XR^7$, and subsequently the carbonyl compound is reduced to the compound (-)-2xx
- 25

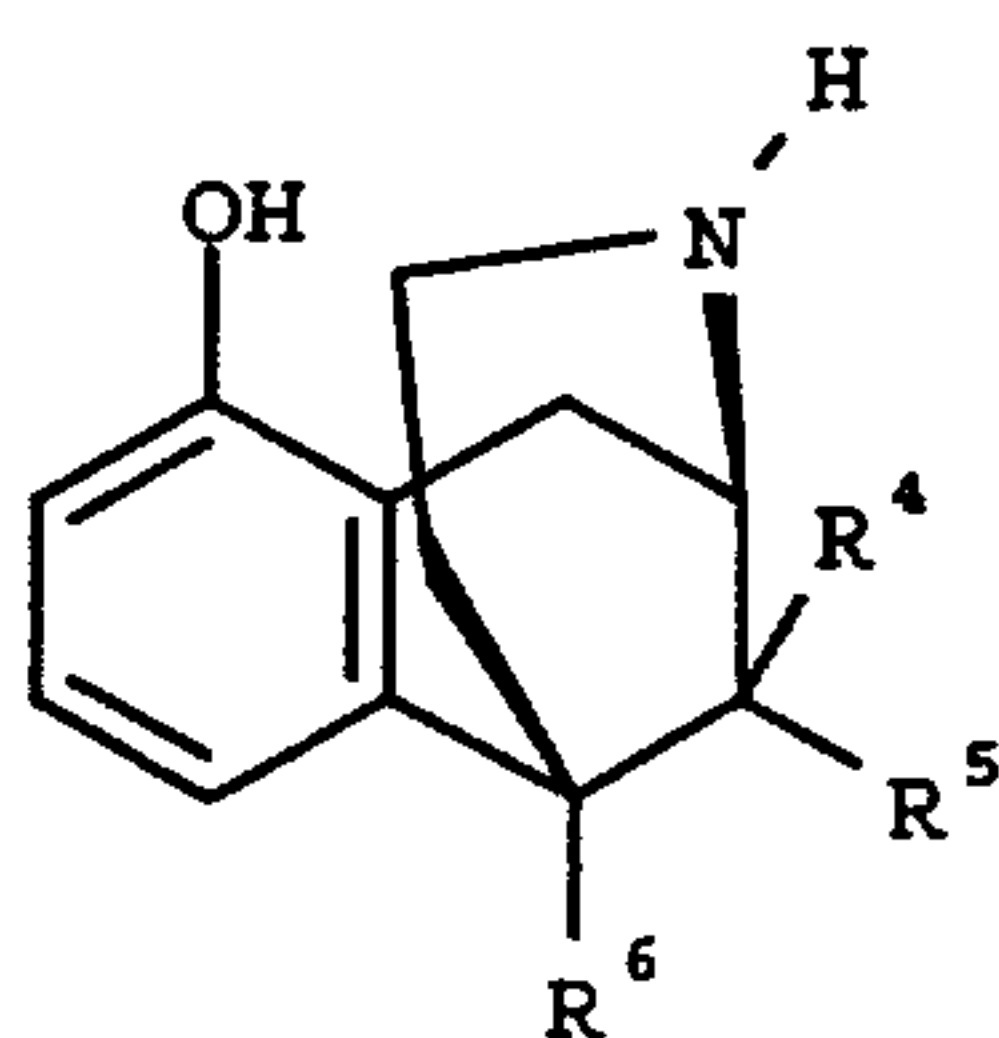


or

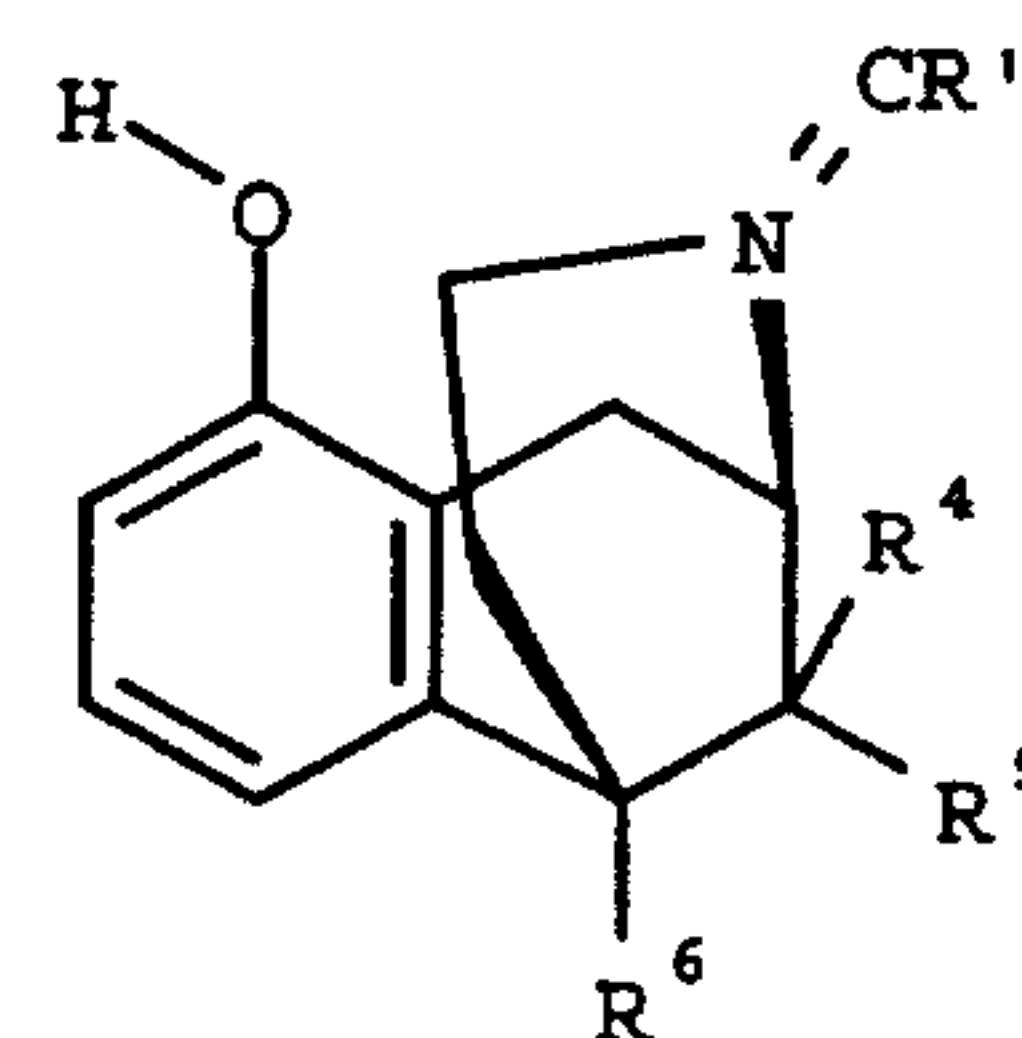
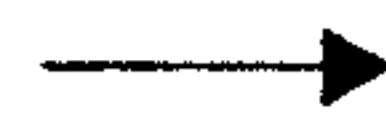
reacted with an aldehyde of general formula
 5 HC(O)-R' , wherein R' denotes $-\text{CR}^1\text{R}^2\text{XR}^7$, and the
 resulting Schiff base 26 is reduced to the
 compound $(-)-2\text{xx}$

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43



26

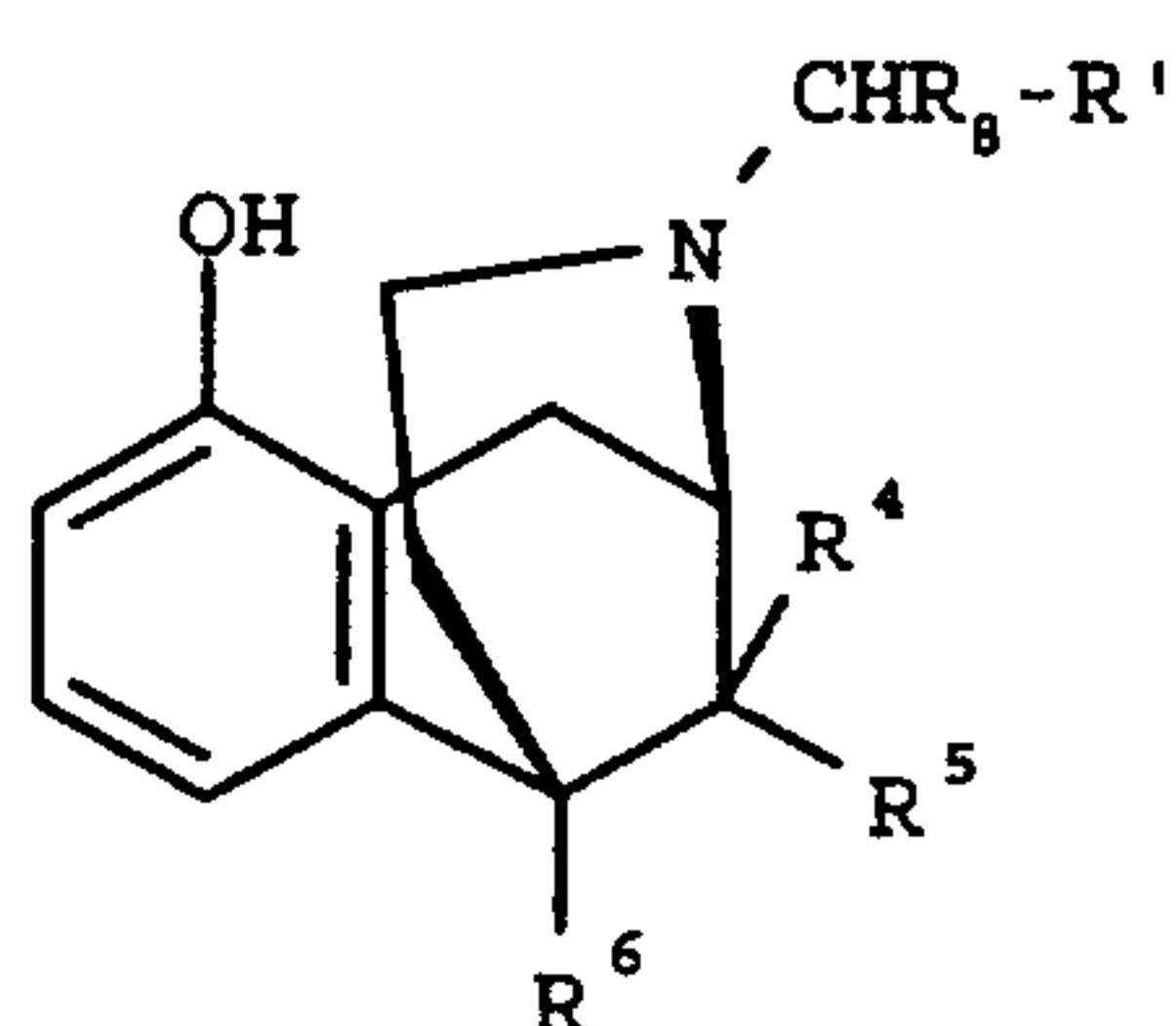
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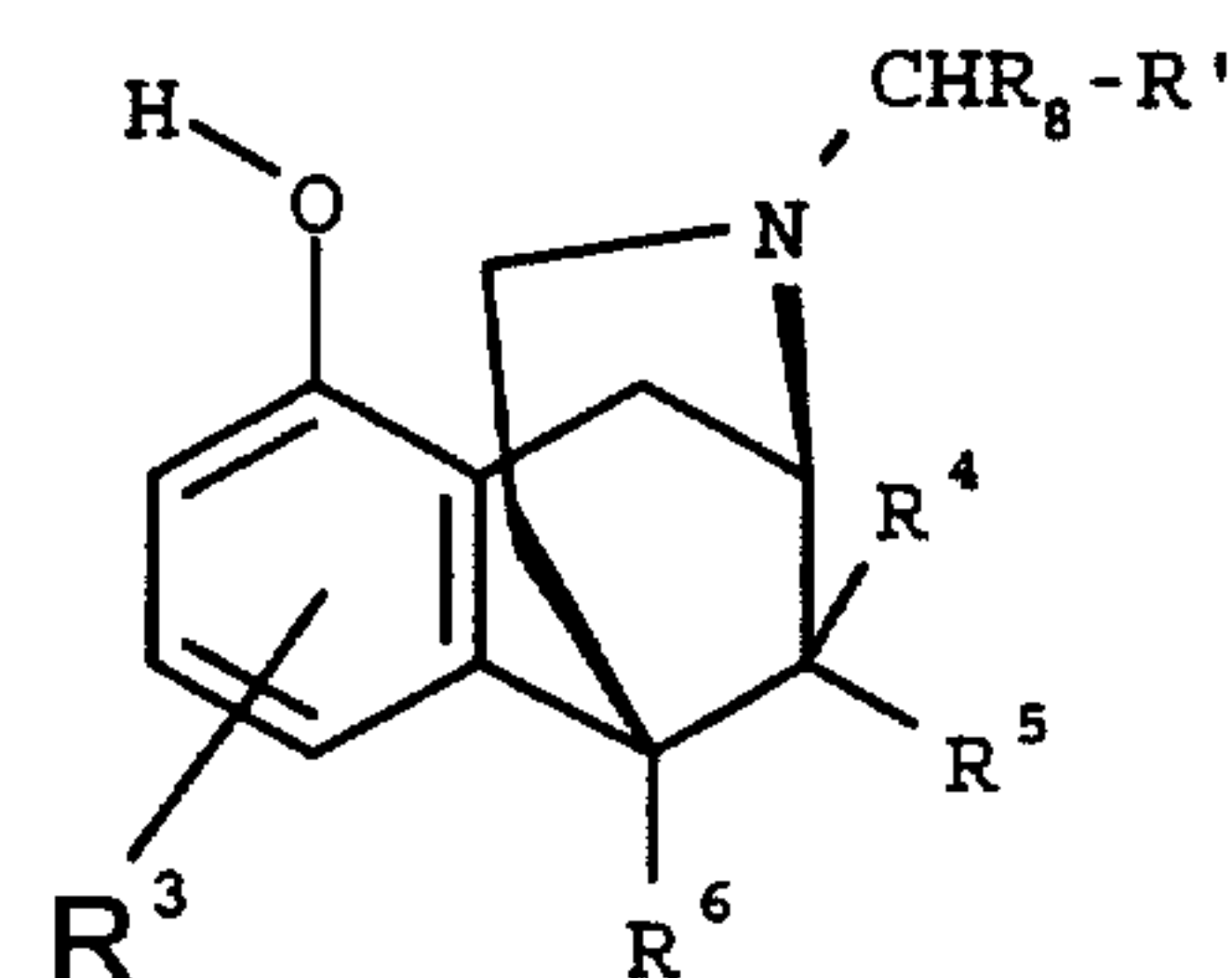
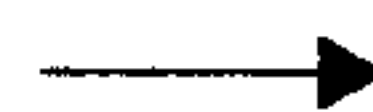
1) optionally within the framework of an
 electrophilic substitution the substituent R^3 is
 introduced

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$(-)-2\text{xx}$



$\text{R}_8 = \text{H}$

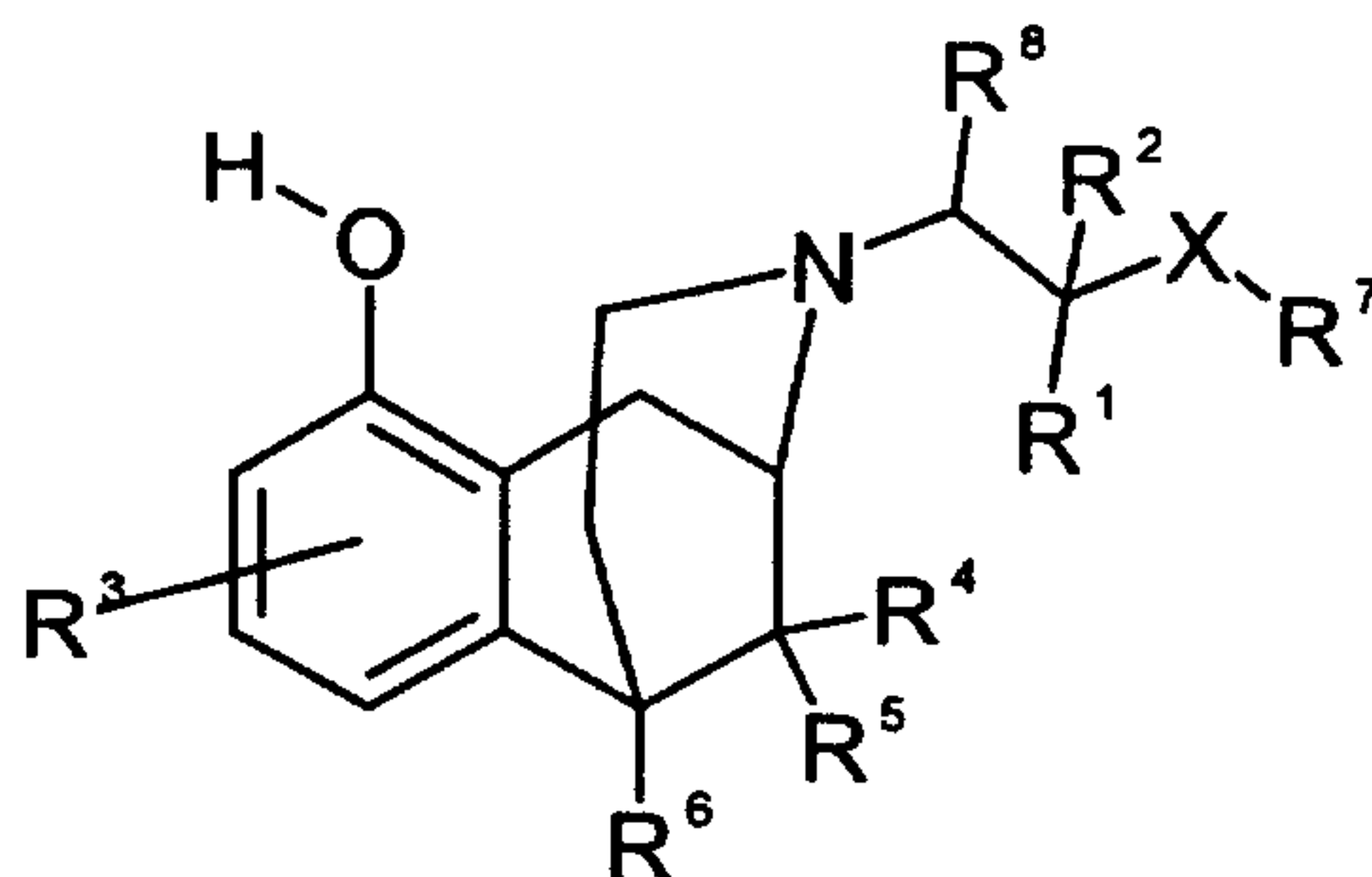
I

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8. Pharmaceutical preparation characterised in that it
 contains one of the compounds according to one of

claims 1 to 4 and the acid addition salts thereof together with conventional adjuvants and carriers.

- 5 9. Pharmaceutical preparation according to claim 7, characterised in that it is formulated as a solution for infusion.
- 10 10. Pharmaceutical preparation according to claim 8, characterised in that the content of active substance, based on the total mass of the pharmaceutical preparation, is in a range from 0.001 to 20 % by weight.
- 15 11. Pharmaceutical preparation according to claim 9, characterised in that the content of active substance, based on the total mass of the pharmaceutical preparation, is in a range from 0.001 to 10 % by weight.
- 20 12. Pharmaceutical preparation according to claim 10, characterised in that the content of active substance, based on the total mass of the pharmaceutical preparation, is in a range from 0.01 to 5 % by weight.
- 25 13. Use of compounds of general formula (I)



wherein

5 X denotes a single bond, -O-, C₁-C₄-alkylene,
an alkylene bridge having 1 to 8 carbon atoms
which may be branched or unbranched and may have
one or two oxygen atom(s) anywhere in the bridge;

R¹ denotes hydrogen, methyl, ethyl, phenyl;

10 R² denotes hydrogen, methyl;

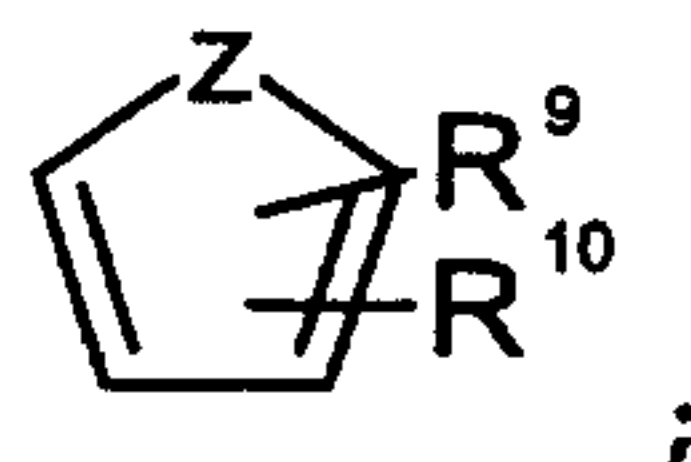
R³ denotes hydrogen, fluorine, chlorine, bromine,
hydroxy, methyl, methoxy;

15 R⁴ denotes hydrogen, methyl, ethyl;

R⁵ denotes hydrogen, methyl, ethyl;

20 R⁶ denotes hydrogen, methyl, ethyl;

R⁷ denotes tert.-butyl, cyclohexyl, phenyl
optionally substituted by R⁹ and R¹⁰, which may



be identical or different,

25 R⁸ denotes hydrogen, C₁-C₄-alkyl;

Z denotes oxygen, NH, sulphur;

30 R⁹ denotes hydrogen, methyl, fluorine, chlorine,
bromine, methoxy;

R¹⁰ denotes hydrogen, methyl, fluorine, chlorine,
bromine, methoxy,

as sodium channel blockers.

- 5 13[sic] Use of compounds according to one of claims 1 to
4 for preparing a pharmaceutical composition for
the therapeutic treatment of cerebral ischaemias of
various origins, neurodegenerative disorders,
epilepsy, hypoglycaemia, hypoxia, anoxia, brain
10 trauma, cerebral oedema, cerebral stroke, perinatal
asphyxia, amyotrophic lateral sclerosis,
Huntington's disease, Alzheimer's disease,
Parkinson's disease, bipolar disorders,
cyclophrenia, hypotonia, cardiac infarct, cardiac
15 rhythm disorders, angina pectoris, pain, for
anaesthesia and local anaesthesia.

**Fetherstonhaugh & Co.,
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Patent Agents**