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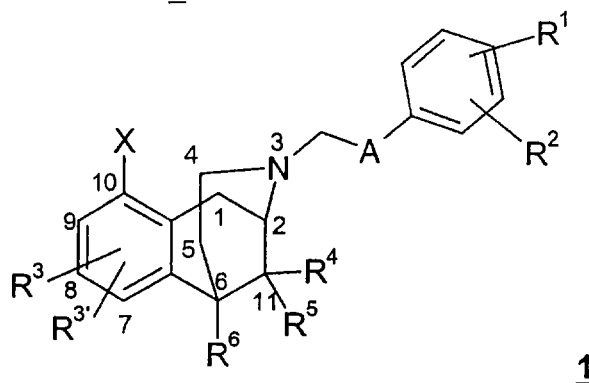


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Substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines and their use as pharmaceutical compositions

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The present invention relates to substituted 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocines of general formula 1

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wherein

10 R^1 and R^2 which may be identical or different denote hydrogen, C_1 - C_6 -alkyl, C_1 - C_6 -alkyloxy, OH, F, Cl or Br;

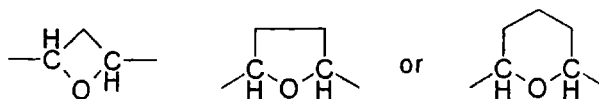
15 R^3 and $R^{3'}$ which may be identical or different denote hydrogen, F, Cl, Br, methyl, ethyl, OH, CF_3 , methoxy or phenyl, which may optionally be substituted by a group selected from among F, Cl, Br, methyl, ethyl, OH, CF_3 and methoxy;

R^4 , R^5 and R^6 which may be identical or different may denote hydrogen, methyl or ethyl,

20

X may denote NH_2 , $NH-(C_1-C_6-alkyl)$, $N(C_1-C_6-alkyl)_2$, the two C_1-C_6 -alkyl groups of which may be identical or different, $NH-COH$, $NH-CO(C_1-C_6-alkyl)$ or F;

25 A may denote $-(CH_2)_3-$, $-CH_2-CH_2-O-$, $-CH_2-O-CH_2-$, $-(CH_2)_4-$, $-CH(C_1-C_6-alkyl)-O-CH_2-$, $-(CH_2)_2-O-CH_2-$, $-(CH_2)_3-O-$, $-(CH_2)_5-$, $-CH_2-O-(CH_2)_3-$, $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_3-O-CH_2-$, $-(CH_2)_4-O-$, $-CH_2-O-CH_2-CH_2-O-$,



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optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

5 Preferred compounds are those of general formula 1 wherein

R^1 and R^2 which may be identical or different denote hydrogen, methyl, ethyl, methyloxy, ethyloxy, OH, F, Cl or Br;

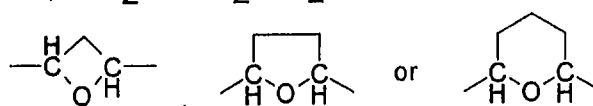
10 R^3 and $R^{3'}$ which may be identical or different denote hydrogen, F, Cl, Br, methyl, ethyl, OH, CF_3 , methoxy or phenyl, which is substituted by a group selected from among F, Cl, Br and preferably methyl;

R^4 , R^5 and R^6 which may be identical or different may denote hydrogen or methyl;

15

X may denote NH_2 , NH -(methyl), N (methyl) $_2$, NH -(ethyl), N (ethyl) $_2$, $NH-COH$, $NH-COMe$ or F;

A may denote $-CH_2-CH_2-O-$, $-CH_2-O-CH_2-$, $-CH$ (methyl)- $O-CH_2-$,
20 $-CH$ (ethyl)- $O-CH_2-$, $-CH$ (isopropyl)- $O-CH_2-$, $-(CH_2)_2-O-CH_2-$,
 $-(CH_2)_3-O-$, $-CH_2-O-(CH_2)_3-$, $-(CH_2)_2-O-(CH_2)_2-$, $-(CH_2)_3-O-CH_2-$,
 $-(CH_2)_4-O-$, $-CH_2-O-CH_2-CH_2-O-$,



optionally in the form of their racemates, their enantiomers, their diastereomers and
25 mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Particularly preferred are compounds of general formula 1

30 wherein

R^1 and R^2 which may be identical or different may denote hydrogen or F;

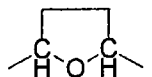
R^3 and $R^{3'}$ which may be identical or different may denote hydrogen, F, Cl, Br, CF_3 or methyl;

35

R^4 , R^5 and R^6 which may be identical or different may denote hydrogen or methyl;

X may denote NH_2 , $\text{NH}(\text{methyl})$, $\text{N}(\text{methyl})_2$, NH-COH , NH-COMe or F ;

A may denote $-\text{CH}(\text{methyl})-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{O}-\text{CH}_2-$ or



5 optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

Of particular importance according to the invention are compounds of general

10 formula 1, wherein

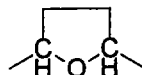
R^1 and R^2 which may be identical or different may denote hydrogen or F ;

R^3 and $\text{R}^{3'}$ which may be identical or different may denote hydrogen, F , Cl , Br , CF_3 or methyl;

R^4 , R^5 and R^6 which may be identical or different may denote hydrogen or methyl;

15 X may denote NH_2 , $\text{NH}(\text{methyl})$ or NH-COH ;

A may denote $-\text{CH}(\text{Methyl})-\text{O}-\text{CH}_2-$, $-\text{CH}_2-\text{O}-\text{CH}_2-$ or



optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts

20 thereof.

Of comparable importance according to the invention are compounds of general formula 1 wherein

25 R^1 and R^2 which may be identical or different may denote hydrogen or F ;

R^3 and $\text{R}^{3'}$ may denote hydrogen;

R^4 , R^5 and R^6 which may be identical or different may denote hydrogen or methyl;

X may denote F ;

A may denote $-\text{CH}(\text{methyl})-\text{O}-\text{CH}_2-$,

30 optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

In the abovementioned compounds of general formula 1, R^1 , if it is other than

35 hydrogen, is preferably in the *ortho* or *para* position, most preferably in the *ortho* position in relation to the bridge A. In the abovementioned compounds of general

formula 1, R², if it is other than hydrogen, is preferably in the *ortho* position in relation to the bridge A.

In the abovementioned compounds of general formula 1, R³, if it is other than hydrogen, is preferably in the 7-position, i.e. in the *para* position relative to the group X. In the abovementioned compounds of general formula 1, R^{3'}, if it is other than hydrogen, is preferably in the 9-position, i.e. in the *ortho* position relative to the group X.

Particularly preferred according to the invention are compounds of formula 1 wherein R^{3'} denotes hydrogen.

Of particular interest are compounds of general formula 1 selected from the group comprising:

- (2R,6S,2S')-10-amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,2S')-10-amino-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,11R,2"S)-10-amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,11S, 2"S)-10-amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S)-10-amino-3-[2(2,6-difluorophenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,2"S,5"S)-10-amino-3-[5"-phenyl-tetrahydrofuran-2"-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,2"S)-10-acetamino-3-[2(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride;
- (2R,6S,2"S)-10-acetamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride;
- (2R,6S,2"S)-10-formylamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride;
- (2R,6S,2"S)-10-methylamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,2"S)-10-dimethylamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,2"S)-10-ethylamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;

- (2R,6S,2"S)-10-amino-7-methyl-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,2"S)-10-amino-7-methyl-3-[2-(2,6-difluorophenyl-methoxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- 5 - (2R,6S, 2"S)-10-amino-7-chloro-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S, 2"S)-10-amino-7-chloro-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- 10 - (2R,6S, 2"S)-10-amino-7-bromo-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S, 2"S)-10-amino-7-bromo-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- 15 - (2R,6S,2"S)-10-amino-7-fluoro-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S,2"S,5"S)-10-amino-7-methyl-3-[5"-phenyl-tetrahydrofuran-2"-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride;
- 20 - (2R,6S, 2"S)-10-amino-7-trifluoromethyl-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-dihydrochloride;
- (2R,6S, 2"S)-10-amino-7-(4-methylphenyl)-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-dihydrochloride;
- 25

C₁-C₆-alkyl denotes a branched or unbranched hydrocarbon group having 1 to 6 carbon atoms which may optionally also contain ring systems. The alkyl substituents may be identical or different and may optionally be substituted with one or more halogen atoms, preferably fluorine. Examples include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, isopentyl, neopentyl, hexyl, cyclopropylmethyl, cyclobutyl, cyclopentyl and cyclohexyl. In some cases, common abbreviations are also used for the abovementioned alkyl groups, such as for example Me for methyl, Et for ethyl, prop for propyl etc.

- 35 C₁-C₆-alkyloxy denotes a branched or unbranched hydrocarbon group having 1 to 6 carbon atoms which is linked via an oxygen atom. The alkyloxy substituents may be identical or different. Examples include methyloxy, ethyloxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, pentyloxy, isopentyloxy, neopentyloxy, hexyloxy, cyclopropylmethyloxy, cyclobutyloxy, cyclopentyloxy, cyclohexyloxy. If desired, the

term alkoxy is used for the abovementioned alkyloxy groups. Thus, methoxy may be used instead of methyloxy, ethoxy instead of ethyloxy, propoxy instead of propyloxy, etc. In some cases, the abovementioned alkyloxy groups may be replaced by common abbreviations such as, for example, MeO for methyloxy, EtO for ethyloxy,

5 PropO for propyloxy, etc.

According to the invention, the double-bonded groups representing group A may be linked to the adjacent groups in both possible orientations.

- 10 If desired, the compounds of general formula (1) may be converted into the salts thereof, particularly, for pharmaceutical use, into the pharmacologically acceptable acid addition salts thereof with an inorganic or organic acid. Suitable acids for this purpose include, for example, succinic acid, hydrobromic acid, acetic acid, fumaric acid, maleic acid, methanesulphonic acid, lactic acid, phosphoric acid, hydrochloric acid, sulphuric acid, tartaric acid or citric acid. Mixtures of the abovementioned acids may also be used.
- 15

- The compounds according to the invention are blockers of the voltage-dependent sodium channel. They are compounds which competitively or non-competitively
- 20 displace batrachotoxin (BTX) with a high affinity ($K_i < 1000 \text{ nM}$) from the binding site on the sodium channel. Such substances exhibit "use-dependency" in blocking the sodium channels, i.e. in order for the substances to bind to the sodium channel the sodium channels first have to be activated. The maximum blockade of the sodium channels is only achieved after repeated stimulation of the sodium channels.
- 25 Consequently, the substances preferentially bind to sodium channels which are activated repeatedly.

- As a result, the substances are capable of acting preferentially in those parts of the body which are pathologically overstimulated. This includes diseases such as
- 30 arrhythmias, spasms, cardiac and cerebral ischaemia, pain and neurodegenerative diseases of various origins. The following may be mentioned, for example: epilepsy, hypoglycaemia, hypoxia, anoxia, brain trauma, brain oedema, cerebral stroke, perinatal asphyxia, degeneration of the cerebellum, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, cyclophrenia,
- 35 hypotonia, cardiac infarct, heart rhythm disorders, angina pectoris, chronic pain, neuropathic pain and local anaesthesia.

Another aspect of the invention therefore relates to the use of compounds of general formula 1 as pharmaceutical compositions, particularly as pharmaceutical

compositions in which the blockade of the voltage-dependent sodium channel may have a therapeutic value.

The compounds of general formula 1 according to the invention are preferably used
5 to prepare a pharmaceutical composition for the prevention or treatment of arrhythmias, spasms, cardiac and cerebral ischaemias, pain and neurodegenerative disorders.

The compounds of general formula 1 according to the invention are most preferably
10 used as hereinbefore to prepare pharmaceutical compositions for the prevention or treatment of epilepsy, hypoglycaemia, hypoxia, anoxia, brain trauma, brain oedema, cerebral stroke, perinatal asphyxia, degeneration of the cerebellum, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, cyclophrenia, hypotonia, cardiac infarct, heart rhythm disorders, angina pectoris,
15 chronic pain, neuropathic pain and local anaesthesia.

The test system used to detect the blocking effect on the sodium channel is the BTX binding to the sodium channel [S.W. Postma & W.A. Catterall, Mol. Pharmacol. 25, 219-227 (1984)] and patch-clamp experiments which can be used to show that the
20 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)]. The effect of the substances on various subtypes of sodium channel can be investigated by suitable selection of the cell system (e.g. neuronal, cardiac, DRG cells).

25

The sodium channel blocking property of the compounds according to the invention can be demonstrated by the blockade of the veratridine-induced glutamate release [S. Villanueva, P. Frenz, Y. Dragnic, F. Orrego, Brain Res. 461, 377-380 (1988)]. Veratridine is a toxin which permanently opens the sodium channel. As a result,
30 there is an increased influx of sodium ions into the cell. By means of the cascade described above, this sodium influx in the neuronal tissue leads to an increased glutamate release. The compounds according to the invention will antagonise this glutamate release.

35 The anticonvulsant properties of the substances according to the invention have been demonstrated by their protective effect against convulsions induced by a maximum electric shock in mice [M. A. Rogawski & R.J. Porter, Pharmacol. Rev. 42, 223-286 (1990)].

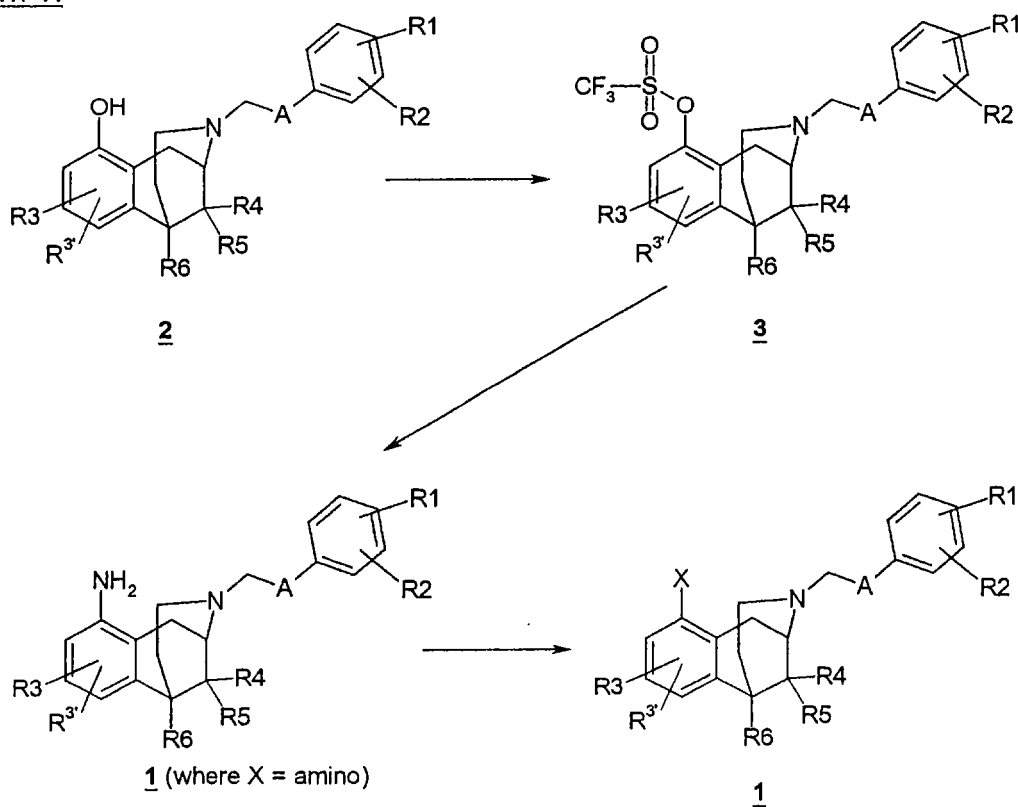
Neuroprotective properties have been demonstrated by the protective effect in a rat-MCAO model [U. Pschorn & A. J. Carter, J. Stroke Cerebrovascular Diseases, 6, 93-99 (1996)], a malonate-induced lesion model [M.F. Beal, Annals of Neurology, 38, 357-366 (1995) and J.B. Schulz, R.T. Matthews, D.R. Henshaw and M.F. Beal, Neuroscience, 71, 1043-1048 (1996)] and an MPTP-induced degeneration model [J.P. Steiner, et al. Proc. Natl. Acad. Sci. 94, 2019-2024 (1997)].

The analgesic effect was shown in a formalin-induced pain model [D. Dubuisson and S.G. Dennis, Pain, 4, 161-174 (1977)] and in a ligature model [G. J. Bennett & Y.-K. Xie, Pain 33, 87-107 (1988)].

It has also been shown that sodium channel blockers can be used to treat cyclophrenia (manic depressive disease) [J. R. Calabrese, C. Bowden, M.J. Woyshville; in: Psychopharmacology: The Fourth Generation of Progress (Eds.: D. E. Bloom and D. J. Kupfer) 1099-1111. New York: Raven Press Ltd.].

The compounds according to the invention 1 may be prepared analogously to methods of synthesis known *per se*. One possible method of synthesis is shown in diagram 1.

20 Diagram 1:

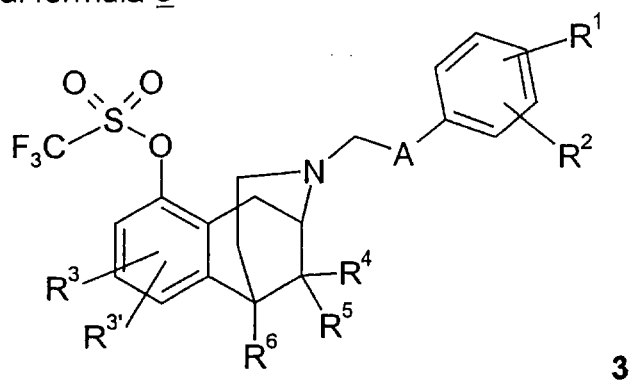


The key step is the conversion of the phenol 2 into the compound of formula 1 wherein $X = NH_2$, which is done by means of a Buchwald reaction [J. P. Wolfe, J. Ahman, J. P. Sadighi, R. A. Singer, S. L. Buchwald, THL 1997, 6367-6370].

The triflates 3 required for this reaction may be prepared from these compounds 2 with trifluoromethanesulphonic acid anhydride in the presence of an auxiliary base. Suitable auxiliary bases according to the invention include organic amines such as, for example, dimethylaminopyridine, pyridine or tert. amines such as trimethylamine, triethylamine, diisopropylethylamine or DBU (diazabicycloundecene). Of the abovementioned amines, the tert. amines are preferably used, and triethylamine is most preferably used as the auxiliary base. The reaction is carried out in aprotic, organic solvents, preferably in solvents selected from among dimethylformamide, dimethylacetamide, methylene chloride, toluene or tetrahydrofuran. Methylene chloride should be mentioned as being particularly preferred. The reactions to form the triflates 3 are preferably carried out at temperatures below ambient temperature, more preferably at $-50^{\circ}C$ to $0^{\circ}C$, most preferably at between $-30^{\circ}C$ and $-5^{\circ}C$. After 0.5 to 4 h stirring is continued at ambient temperature until the reaction is complete (about 1-12 h). After working up, the crude products 3 thus obtained are reacted, without further purification, in an aromatic organic solvent, preferably selected from among toluene, benzene or xylene, most preferably toluene, with palladium as catalyst, preferably in the presence of a phosphine ligand, with a nitrogen source, preferably with ketimines, most preferably with benzophenonimine. Suitable palladium catalysts according to the invention include tris(dibenzylidene-acetone)-dipalladium, palladium(II)acetate or tetrakis(triphenylphosphine)-palladium, for example. Suitable phosphine ligands which may be used include, for example, ligands selected from among DPPF, BINAP, p-tolBINAP, $PPh_2-CHMe-P(tBu)_2$, phosphine-substituted ferrocenes or triphenylphosphine. Tris(dibenzylidene-acetone)-dipalladium/BINAP is preferably used as the catalyst system. The reaction is preferably carried out with the exclusion of moisture and oxygen and preferably at elevated temperature. The solvent used is preferably refluxed during the reaction. The imine adduct obtained as an intermediate can be converted by acid hydrolysis, preferably with dilute inorganic acids, most preferably with dilute hydrochloric acid, into the compounds according to the invention 1 (where $X=NH_2$). The products are purified by chromatography on silica gel or by crystallisation, preferably by crystallisation of the pharmacologically acceptable acid addition salts, e.g. the hydrochlorides.

As can be seen from the above remarks, the triflates of general formula 3 are of central importance in the synthesis of the compounds of general formula 1 according to the invention.

Accordingly, another aspect of the present invention relates to the intermediate compounds of general formula 3



- 5 wherein the groups R^1 , R^2 , R^3 , $R^{3'}$, R^4 , R^5 , R^6 and A may be as hereinbefore defined.

In order to synthesise the compounds according to the invention of general formula 1 where $X \neq \text{NH}_2$ the following process may be used.

10

Compounds of formula 1 wherein $X = \text{NHC}_1\text{-C}_6\text{-alkyl}$ or $\text{N}(\text{C}_1\text{-C}_6\text{-alkyl})_2$ may be obtained by methods known *per se* by alkylation of 1 where $X = \text{NH}_2$, by reductive amination or by acylation, optionally in the presence of organic bases, with subsequent reduction.

- 15 For alkylation, the following method may be used. A compound of general formula 1 where $X = \text{NH}_2$ is dissolved in a polar organic solvent such as dimethylformamide, dimethylacetamide, methylene chloride, tetrahydrofuran, preferably dimethylformamide or methylene chloride. The resulting solution is mixed with a base and a corresponding alkylating agent. Suitable bases include alkali- and
- 20 alkaline earth metal hydrides, preferably sodium hydride. Suitable alkylating agents include alkyl halides, such as alkyl chloride, alkyl bromide, particularly alkyl iodide and alkyl tosylates, mesylates, triflates, dialkylsulphates. After conventional working up the alkylated compounds of general formula 1 may be purified by chromatography on silica gel or by crystallisation, optionally in the form of the
- 25 pharmacologically acceptable addition salts thereof, preferably as hydrochlorides. In order to prepare the compounds of general formula 1 by reductive amination the amines 1 where $X = \text{NH}_2$ are mixed with aldehydes or ketones in the presence of acids such as dilute hydrochloric acid, dilute acetic acid or dilute sulphuric acid, under otherwise conventional reaction conditions, with cooling, preferably at -50°C to
- 30 ambient temperature, most preferably between -30°C and 0°C , and the Schiff bases or iminium salts thus formed as intermediates are then reduced. The reduction is carried out using metal hydrides such as sodium borohydride, LiAlH_4 , Li-

alkoxyhydrides, NaBH_4 , NaBHCN_3 , $\text{NaBH}(\text{OAc})_3$; sodium borohydride is preferably used. After working up in the usual way, the alkylated compounds of general formula **1** may be purified by chromatography on silica gel or by crystallisation, optionally in the form of their pharmacologically acceptable acid addition salts thereof, preferably
 5 as hydrochlorides.

Compounds of formula **1** where $\text{X} = \text{NHCO}(\text{C}_1\text{-C}_6\text{-alkyl})$ may be prepared by methods known *per se* by acylating **1** where $\text{X} = \text{NH}_2$, preferably with acid chlorides or anhydrides. For this, the amino compound of formula **1** where $\text{X} = \text{NH}_2$ is suspended
 10 in an organic solvent, combined with an organic base and the desired acid chloride or anhydride is added. The mixture is kept at ambient temperature for 40 to 60 minutes, preferably 25 to 45 minutes at ambient temperature. Suitable organic solvents are dimethylformamide, dimethylacetamide, methylene chloride, toluene or tetrahydrofuran, methylene chloride being preferred. Suitable organic bases are
 15 dimethylaminopyridine, pyridine, tert. amines, e.g. trimethylamine, triethylamine, diisopropylethylamine, DBU (diazabicycloundecene). After working up, the products are purified by chromatography on silica gel or by crystallisation, preferably by crystallisation of the pharmacologically acceptable acid addition salts, e.g. the hydrochlorides.

20 Starting from the compounds of formula **1** with $\text{X} = \text{NHCO}(\text{C}_1\text{-C}_6\text{-alkyl})$ which may be obtained by the method described above, compounds of formula **1** with $\text{X} = \text{NH}(\text{C}_1\text{-C}_6\text{-alkyl})$, for example, may also be obtained by reduction with metal hydrides such as LiAlH_4 , Li-alkoxyhydrides, NaBH_4 , NaBHCN_3 , $\text{NaBH}(\text{OAc})_3$,
 25 preferably sodium borohydride. These reactions are preferably carried out in ethereal organic solvents, preferably in tetrahydrofuran or dioxan in the presence of Lewis acids, preferably boron trifluoride etherate, at elevated temperature, preferably above 50°C , most preferably at the reflux temperature of the solvent used. After working up, the products are purified by chromatography on silica gel or by
 30 crystallisation, preferably by crystallisation of the pharmacologically acceptable acid addition salts, e.g. the hydrochlorides.

The formylated compounds of formula **1** ($\text{X} = \text{NHCOH}$) may be obtained, for example, by reacting the compounds of formula **1** where $\text{X} = \text{NH}_2$ with formic acid at elevated
 35 temperature, preferably at reflux temperature. After working up, the products are purified by chromatography on silica gel or by crystallisation, preferably by crystallisation of the pharmacologically acceptable acid addition salts, e.g. the hydrochlorides.

- The fluorine-substituted compounds 1 (with X= F) may be obtained by methods known *per se* by diazotisation of 1 where X=NH₂ and subsequent decoction with BF₄⁻. Preferably, the reaction is carried out with NOBF₄ as the diazotisation and fluorination reagent in ethereal solvents, preferably in tetrahydrofuran or dioxan at
- 5 elevated temperature, preferably above 50°C, most preferably at the reflux temperature of the solvent used. After working up, the products are purified by chromatography on silica gel or by crystallisation, preferably by crystallisation of the pharmacologically acceptable acid addition salts, e.g. the hydrochlorides.
- 10 The 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-10-ols (2) designated as starting compounds in diagram 1 may be obtained using methods known from the prior art. In this context, reference is hereby made to European Patent Application EP 521422 and the International Patent Applications WO 97/06146 and WO 99/14199.
- 15 Compounds of general formula 2 wherein R³ denotes hydrogen, are prepared starting from the compounds of general formula 4 analogously to the methods of synthesis described in WO99/14199. In order to prepare compounds of general formula 1 wherein R³ does not denote hydrogen, the compounds of general formula 4 first have to be modified. This is done by analogously using methods of synthesis
- 20 known in principle as described in the following reaction plans.

For example, a p-methyl substituent (R³ equals methyl) may be introduced using the method given in Diagram 2.

- 25 In order to prepare the brominated compound of formula 5 the compounds of formula 4 are dissolved in a suitable solvent, preferably in acetic acid or trifluoroacetic acid, most preferably in a mixture of acetic acid and trifluoroacetic acid and NBS (N-bromosuccinimide) is added batchwise at 0-23°C, preferably at 10°C. The reaction is complete after about 1 to 5 hours. The product is worked up in the
- 30 usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies of the compounds 5.

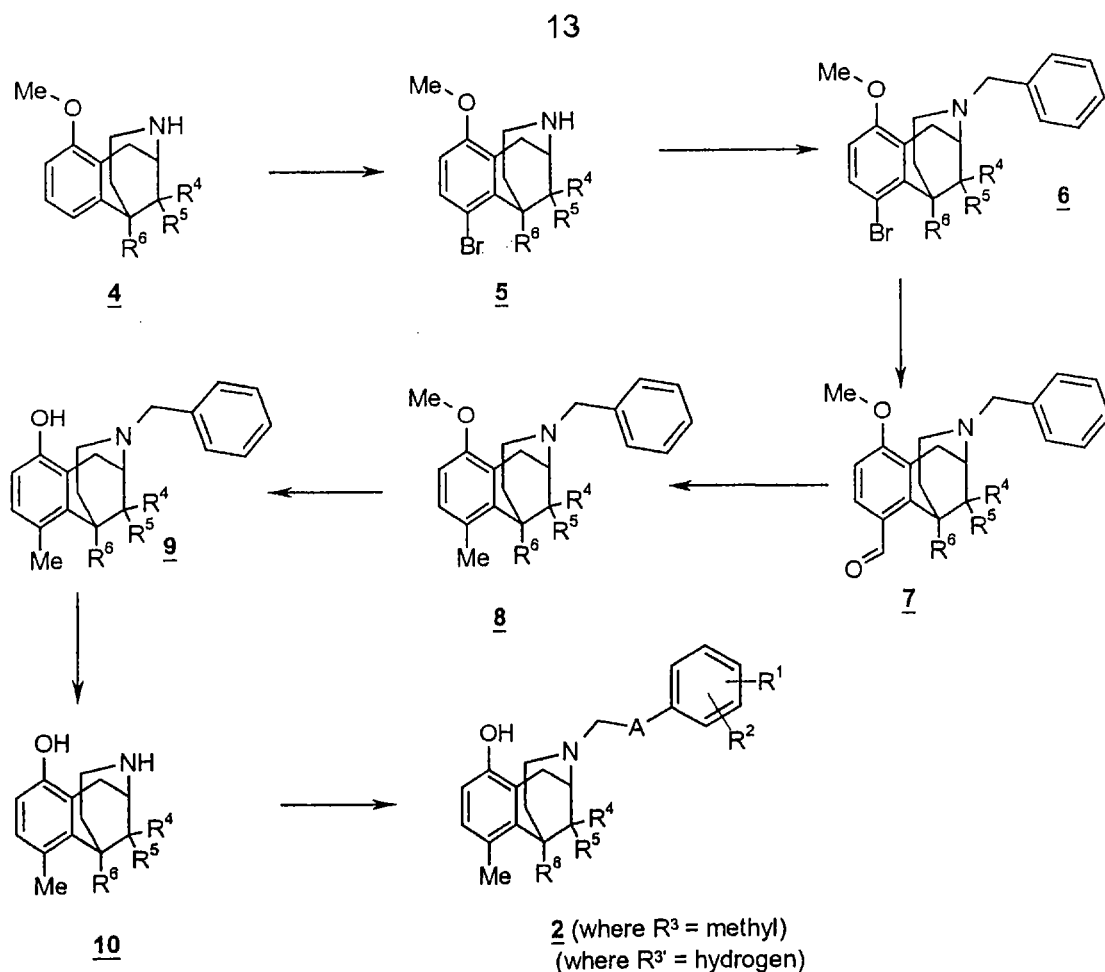


Diagram 2:

The benzylation of the compounds 5 to form the compounds 6 is preferably carried out in an organic solvent, preferably in a solvent selected from among

5 dichloromethane, dimethylformamide and dimethylacetamide, particularly preferably in dimethylacetamide. For this, the compounds 5 are dissolved in the solvent and benzyl chloride is added in the presence of a base at a temperature of 0-50°C, particularly preferably at ambient temperature (about 23°C). Suitable bases are organic or inorganic bases. Suitable inorganic bases are the alkali metal- or alkaline

10 earth metal carbonates of lithium, sodium, potassium, calcium such as sodium carbonate, lithium carbonate, potassium carbonate, calcium carbonate and preferably potassium carbonate. Suitable organic bases are preferably organic amines, particularly preferably diisopropylethylamine, triethylamine, cyclic amines such as DBU, or pyridine. After the benzyl chloride has all been added the mixture is

15 stirred for a further 1 to 6, preferably 2 to 4 hours at elevated temperature, preferably at about 50-120°C, particularly preferably at about 100°C, but at most at the boiling temperature of the solvent in question. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies of the compounds 6.

The compounds 7 are prepared from the compounds 6 by reacting with suitable formulating reagents. For this, the compounds 6 are dissolved in a suitable organic solvent, preferably in an anhydrous organic solvent, preferably in an ethereal solvent selected from among diethylether, tetrahydrofuran and dioxan, preferably in diethylether, and butyllithium, preferably dissolved in n-hexane, is added at low temperature, preferably at below -20°C , particularly preferably at a temperature between -50°C and -78°C . After about 0.5 to 2 hours stirring in the temperature range mentioned above, the formulating reagent, preferably dimethylformamide, is added and stirred for another 0.5 to 2 hours, optionally at slightly elevated temperature, preferably at -30°C to 0°C , particularly preferably at about -10°C . The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies of the compounds 7.

15

Reduction of the compounds 7 leads to the methyl compounds 8. For this the compounds 7 are dissolved in a suitable organic solvent, preferably in an anhydrous organic solvent, preferably in an ethereal solvent selected from among diethylether, tetrahydrofuran and dioxan, preferably in tetrahydrofuran, and a suitable reducing agent, preferably a metal salt hydride, particularly preferably NaBH_4 or NaCNBH_3 , preferably NaCNBH_3 , is added. It is also necessary to add boron trifluoride, or BF_3 -etherate. After the addition of the reducing agent the mixture is stirred for another 1 to 6 hours, preferably 2 to 4 hours at constant temperature, preferably at ambient temperature. After the addition of a protic solvent, particularly preferably a lower alcohol selected from among methanol, ethanol or isopropanol, particularly preferably methanol and hydrolysis with an aqueous acid, preferably with aqueous hydrochloric acid, the mixture is stirred for a further 0.5 to 4 hours, optionally at elevated temperature, preferably at a temperature above 50°C , particularly preferably at the reflux temperature of the solvent. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies of the compounds 8.

The cleaving of the methoxy group in 8 leads to the hydroxy compounds 9 and is carried out with the use of strong acids, such as HI and HBr , particularly preferably concentrated HBr at elevated temperature, preferably at more than 50°C , particularly preferably at reflux temperature. There is no need to use a solvent if HBr is used, for example. The reaction is complete after about 1 to 6, preferably 2 to 4 hours. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies of

the compounds 9. The cleaving of the methoxy group in 8 to yield the hydroxy compounds 9 may alternatively be carried out using BBr_3 analogously to the procedure described for reacting the compounds 17 to obtain the hydroxy compounds 18.

5

The compounds 10 may be obtained from the compounds 9 by hydrogenolytic cleaving of the benzyl group. This reduction is preferably carried out by catalytic hydrogenation, preferably on palladium catalysts or on Raney nickel, particularly preferably on palladium catalysts in alcoholic solvents, preferably in methanol, at
10 ambient temperature. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on their crystallisation tendencies.

The compounds of general formula 2 may be prepared starting from the compounds
15 of general formula 10 analogously to the methods of synthesis described in WO99/14199.

A p-fluoro substituent is introduced by the method shown in diagram 3. To do this, a compound of formula 6 is dissolved in a suitable organic solvent, preferably in an
20 anhydrous organic solvent, preferably in an ethereal solvent selected from among diethylether, tetrahydrofuran and dioxan, preferably in diethylether, and butyllithium, preferably dissolved in n-hexane, is added at low temperature, preferably at below -20°C , particularly preferably at a temperature between -50°C and -78°C . After about 0.5 to 2 hours stirring in the temperature range specified above, a suitable
25 fluorinating agent, preferably N-fluorobenzenesulphonimide, dissolved in one of the solvents mentioned above, is slowly added and stirring is continued for another 0.5 to 2 hours at constant temperature. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on their crystallisation tendencies.

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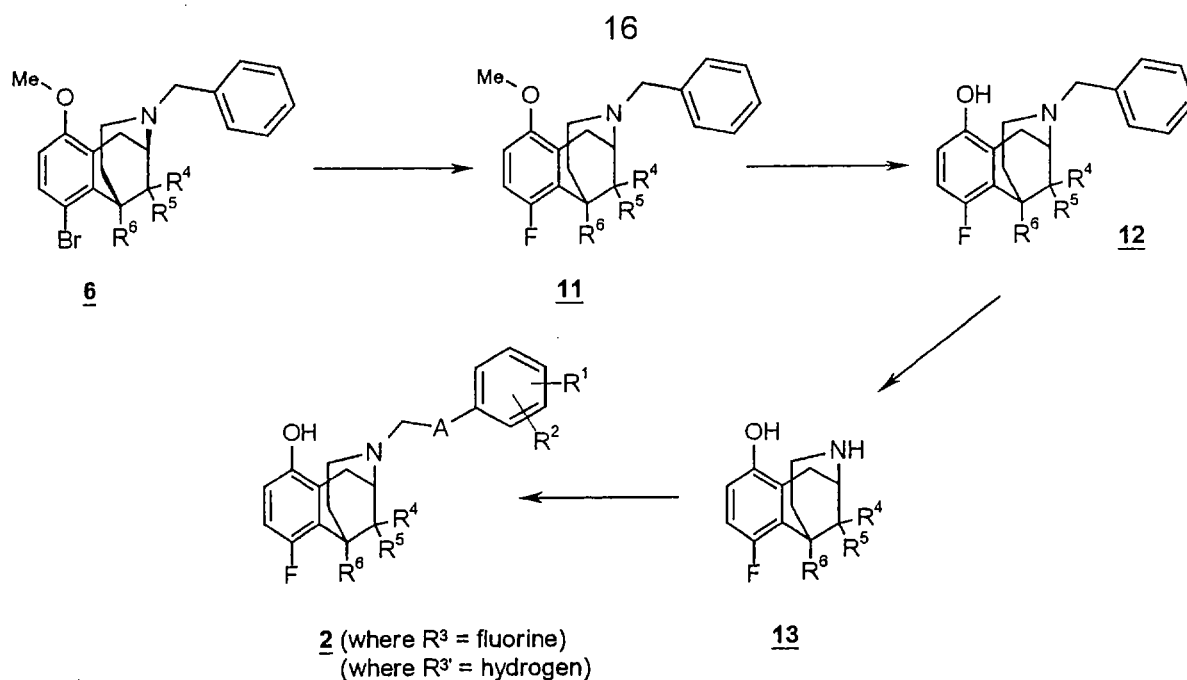


Diagram 3:

The compounds **11** are converted into the hydroxy compounds **12** as described for the reaction of the compounds **8** to form the compounds **9**. The conversion of the compounds **12** into the debenzylated compounds **13** is carried out as described for the reaction of the compounds **9** to form the compounds **10**.

The compounds of general formula **2** may be prepared starting from the compounds of general formula **13** analogously to the methods of synthesis described in WO99/14199.

A p-CF₃ substituent is introduced according to the method of synthesis shown in diagram 4.

In a first step, a compound of formula **4** is converted into an iodide of formula **14**. This reaction is carried out analogously to the procedure described for reacting **4** to **5** using NIS (N-iodosuccinimide).

From the compounds **14** it is possible to obtain the N-protected compounds **15** wherein PG denotes an amino protecting group. The protecting group used may be any of the groups commonly used to protect the amino function. Examples include the benzyl group, the benzyloxycarbonyl and tert.-butoxycarbonyl group, the latter being preferred. The following method is used to introduce the tert.-butoxycarbonyl group. The reaction is preferably carried out in an organic solvent, preferably in a solvent selected from among dichloromethane, dimethylformamide and dimethylacetamide, particularly preferably in dichloromethane. For this, the compounds **14** are dissolved in the solvent and in the presence of a base at a

temperature of -50°C to 10°C, preferably at -20°C to 0°C, and an inorganic base is added. The inorganic base may be, for example, an alkali metal- or alkaline earth metal hydroxide of lithium, sodium, potassium, calcium such as sodium hydroxide, lithium hydroxide, potassium hydroxide, calcium hydroxide and preferably potassium hydroxide, optionally in aqueous solution. Then di-t-butyl dicarbonate, optionally dissolved in one of the abovementioned organic solvents, is added. After it has all been added, the mixture is stirred for another 0.5 to 6, preferably 1 to 3 hours, optionally at fairly elevated temperature, preferably at ambient temperature. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies of the compounds **15**.

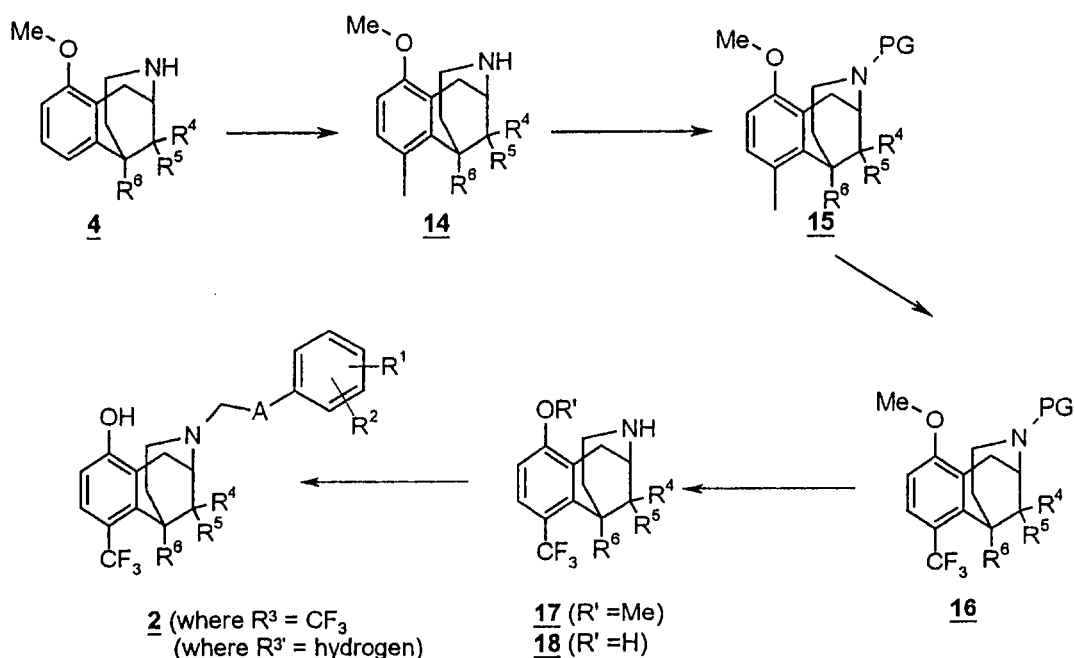


Diagram 4:

The trifluoromethyl compounds **16** may be prepared from the compounds **15**. For this, a compound **15** is dissolved in a suitable organic solvent, preferably in a polar organic solvent selected from among dimethylacetamide, dimethylsulphoxide or dimethylformamide, particularly preferably dimethylformamide, and methyl fluorosulphonyl-difluoroacetate and CuI, preferably anhydrous CuI, are added. Then the reaction mixture is heated to a temperature in the range from 50-90°C, particularly preferably to 70°C. It is stirred at constant temperature for between 1 day and 4 days, preferably about 2 days. Depending on the progress of the reaction it may be necessary to add more methyl fluorosulphonyl-difluoroacetate and CuI. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies of the compounds **16**.

The cleaving of the amino protecting group starting from the compounds **16** yields the compounds **17**. The processes for cleaving the protecting groups used are known from the prior art. At this point, we should mention a possible alternative
5 method of cleaving the tert.-butoxycarbonyl protecting group, solely by way of example. This is done by reacting **16** with trifluoroacetic acid in a suitable organic solvent, preferably in dichloromethane at ambient temperature within a period of 1 to 3 hours. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies
10 of the compounds **17**.

The cleaving of the methoxy group starting from the compounds **17** yields the compounds **18** and is carried out by reacting with BBr_3 solution in the presence of trifluoroacetic acid in a suitable organic solvent, preferably in dichloromethane at low
15 temperature, preferably at below -50°C , particularly preferably between -75°C and -60°C . After the reactants have all been added at the temperature specified above the reaction is completed by stirring at a temperature in the range from -20°C to 20°C , preferably at about 0°C , over a period of 4 to 12 hours. The product is worked up in the usual way. The products are purified either by crystallisation or by
20 chromatography depending on the crystallisation tendencies of the compounds **18**. Alternatively to the method described above, the cleaving of the methoxy group in **17** to form the hydroxy compounds **18** may also be carried out using strong acids. On this subject we refer the reader to the corresponding remarks regarding the reaction of the compounds **8** to form the hydroxy compounds **9**.

25

The compounds of general formula **2** may be prepared starting from the compounds of general formula **18** analogously to the methods of synthesis described in WO99/14199.

30 A p-phenyl substituent may also be introduced as illustrated in diagram 5.

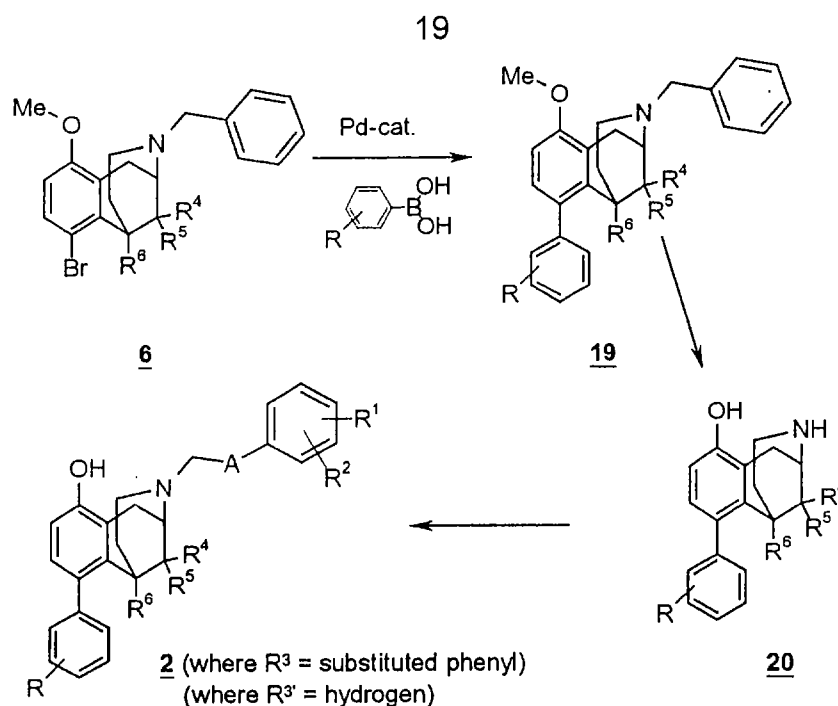


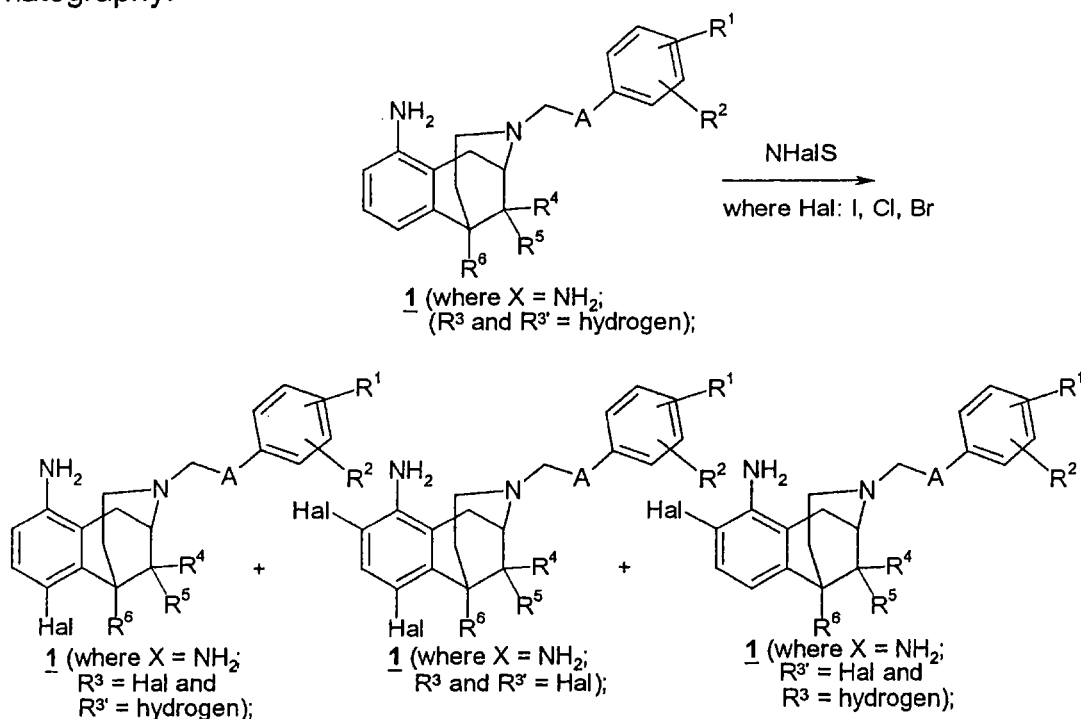
Diagram 5:

Starting from the compounds **6**, the compounds **19** are obtained by reacting with suitably substituted borates and subsequent transmetalisation with palladium(0) compounds. Phenylboric acids substituted with the group R are used as the borates. For the reaction, **6** is dissolved in a suitable organic solvent, preferably in an anhydrous, oxygen-free organic solvent, preferably in an ethereal solvent selected from among diethylether, tetrahydrofuran and dioxan, preferably in dioxan, and the abovementioned boric acid derivative, potassium phosphate and a suitable palladium(0) catalyst are added successively. The Pd(0) catalyst according to the invention may be tris(dibenzylidene-acetone)-dipalladium, palladium(II)acetate or tetrakis(triphenylphosphine) palladium, for example, preferably tris(dibenzylidene-acetone)-palladium(0). Phosphines or phosphites also have to be added. The phosphine ligands may be, for example, ligands selected from among DPPF, BINAP, p-tolBINAP, PPh₂-CHMe-P(tBu)₂, phosphine-substituted ferrocenes, triphenylphosphine or trimethylphosphite, preferably trimethylphosphite. After all the reaction components have been added, the mixture is stirred at elevated temperature, preferably at a temperature above 50°C, particularly preferably at the reflux temperature of the solvent, for 0.5 to 2 hours. The product is worked up in the usual way. The products are purified either by crystallisation or by chromatography depending on the crystallisation tendencies of the compounds **19**.

The compounds **19** are converted into the hydroxy compounds **20** as described for the reaction of the compounds **8** into the compounds **10** (via **9**).

The compounds of general formula 2 may be prepared starting from the compounds of general formula 20 analogously to the methods of synthesis described in WO99/14199.

- 5 Halogen-substituted derivatives may be obtained, for example, by reacting the compounds 1 according to the invention wherein X denotes NH₂ and R³ denotes hydrogen, with NIS, NBS or NCS (Diagram 6). As a rule, mixtures of the para-, ortho- and para-/ortho-disubstituted compounds are obtained, which can be separated by chromatography.



10

Diagram 6:

The compounds of general formula 2 wherein R³ denotes hydrogen may be prepared starting from the compounds of general formula 4 analogously to the methods of synthesis described in WO99/14199. In order to prepare the compounds

- 15 2 wherein R³ denotes hydrogen, the compounds of formula 21 are used as starting material (diagram 7). These may be obtained from the compounds 4. The compounds 21 are disclosed in WO99/14199.

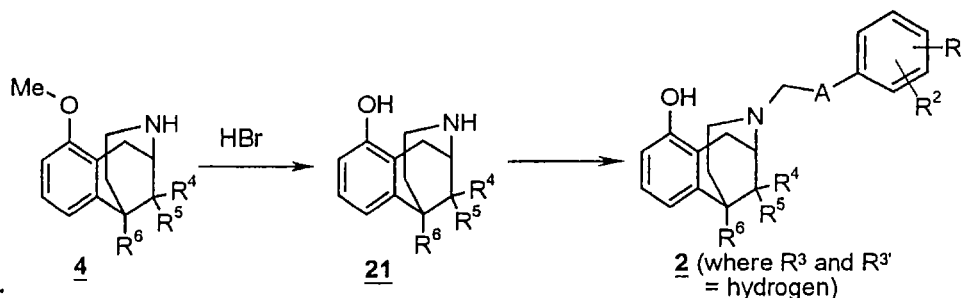
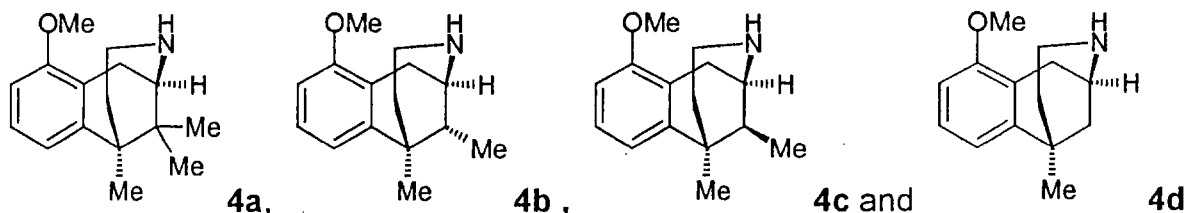


Diagram 7:

The Examples that follow serve to illustrate the invention, without restricting it to the compounds and processes disclosed by way of example.

I. Synthesis of the precursors 4 to 20:

5 The compounds of formula



are known, for example, from WO99/14199.

10 Compounds of formula 5:

(2R,6S)-7-bromo-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride 5a:

24.7 g (0.1 mol) (2R,6S)-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine (**4a**) are dissolved in 220 mL of acetic acid and 22 mL of trifluoroacetic acid, cooled to 10 °C, and 19.6 g of NBS (N-bromosuccinimide) is added batchwise. The mixture is stirred for 3 h at 10 °C, the solvent is eliminated *in vacuo* and the residue is combined with ice-cooled ammonia solution. Then it is extracted twice with 200 mL of ethyl acetate, the combined organic phase is dried and the solvent is eliminated *in vacuo*. The residue is dissolved in acetone and the hydrochloride is precipitated with ethereal HCl.

Yield: 32,6 g (91%), melting point: 203 °C.

Compounds of formula 6:

(2R,6S)-3-Benzyl-7-bromo-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 6a:

32.6 g (91 mmol) of (2R,6S)-7-bromo-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride **5a** are dissolved in 160 mL of dimethylacetamide, combined with 28 g of K₂CO₃ and 18.9 g of benzyl chloride and stirred for 3h at 100 °C. Then the solvent is eliminated *in vacuo*, the residue is combined with water and twice with 200 mL aliquots of ethyl acetate. The combined organic phase is dried, the solvent is eliminated *in vacuo* and the residue chromatographed on silica gel. The appropriate fractions are evaporated down *in vacuo*. Yield: 24.5 g (73%); oil.

Compounds of formula 7:

(2R,6S)-3-Benzyl-7-formyl-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 7a:

- 24.5 g (59 mmol) of (2R,6S)-3-benzyl-7-bromo-10-methoxy-1,2,3,4,5,6-hexahydro-
 5 6,11,11-trimethyl-2,6-methano-3-benzazocine **6a** are dissolved in 250 mL of abs.
 ether, cooled to – 70 °C and 40.7 mL of BuLi (1.6 M in hexane) are added dropwise.
 Then the mixture is stirred for 1 h at –60 °C, 10 mL of DMF are added dropwise
 thereto and after another hour the resulting mixture is allowed to come up slowly to
 -10 °C. It is then added to 500 mL of water and extracted twice with 300 mL aliquots
 10 of ether. The combined organic phase is dried, the solvent is eliminated *in vacuo* and
 the residue chromatographed on silica gel. The appropriate fractions are evaporated
 down *in vacuo*. Yield: 18.3 g (85%); oil.

Compounds of formula 8:

- 15 (2R,6S)-3-Benzyl-7-methyl-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 8a:

- 8 g (22mmol) of (2R,6S)-3-benzyl-7-formyl-10-methoxy-1,2,3,4,5,6-hexahydro-
 6,11,11-trimethyl-2,6-methano-3-benzazocine **7a** are dissolved in 80 mL of THF,
 mixed with 4 g of NaCNBH₃ and 20 mL of BF₃-etherate and stirred for 3 h at RT.
 20 Then 100 mL of methanol are carefully added dropwise, 100 mL of 2 N HCl are
 added and the mixture is refluxed for 1 h. The solvent is eliminated *in vacuo*,
 ammonia is added to the residue and it is then extracted twice with 100 mL aliquots
 of ethyl acetate. The combined organic phase is dried, the solvent is eliminated *in*
vacuo and the residue chromatographed on silica gel. The appropriate fractions are
 25 evaporated down *in vacuo*. Yield: 5.5 g (72%); oil.

Compounds of formula 9:

(2R,6S)-3-Benzyl-7-methyl-10-hydroxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 9a:

- 30 5.3 g (15 mmol) of (2R,6S)-3-benzyl-7-methyl-10-methoxy-1,2,3,4,5,6-hexahydro-
 6,11,11-trimethyl-2,6-methano-3-benzazocine **8a** are dissolved in 54 mL of conc.
 HBr and refluxed for 2 h. The mixture is evaporated down *in vacuo*, the residue is
 combined with ice and conc. ammonia and extracted twice with 50 mL of ethyl
 acetate. The combined organic phase is dried and the solvent is eliminated *in vacuo*.
 35 The residue is dissolved in acetone and the hydrochloride is precipitated with
 ethereal HCl. Yield: 3.7 g (66%),

Compounds of formula 10:

(2R,6S)-3-Benzyl-7-methyl-10-hydroxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 10a:

- 3.6 g (10 mmol) of (2R,6S)-3-benzyl-10-hydroxy-7-methyl-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine **9a** are hydrogenated on 0.4 g of PdC in 60 mL of methanol at 5 bar for 4 hours. The mixture is then filtered and the solvent is eliminated *in vacuo*. Yield 2.6 g (92%); oil.

Compounds of formula 11:

- 10 (2R,6S)-3-Benzyl-7-fluoro-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 11a:

- 8 g (20mmol) of (2R,6S)-3-benzyl-7-bromo-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine **6a** are dissolved in 100 mL of ether, cooled to -65 °C and under nitrogen 15 mL of BuLi (1.6 M in hexane) are added dropwise. After 1 h, 8 g of N-fluorobenzenesulphonimide in 100 mL of THF are added dropwise and the mixture is stirred for 1 h at -60 °C. It is then heated to RT, any insoluble matter is removed by suction filtering and the solvent is eliminated *in vacuo*. The residue is taken up in 100 mL of water, combined with 10 mL of conc. ammonia and extracted twice with 150 mL of ether. The combined organic phase is dried, the solvent is eliminated *in vacuo* and the residue chromatographed on silica gel. The appropriate fractions are evaporated down *in vacuo*. Yield: 3.4 g (48%); oil.

Compounds of formula 12:

- 25 (2R,6S)-3-Benzyl-7-fluoro-10-hydroxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 12a:

Prepared analogously to the preparation of compound **9** starting from **11**;oil;

Compounds of formula 13:

- 30 (2R,6S)-7-Fluor-10-hydroxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 13a:

Prepared analogously to the preparation of compound **10** starting from **12**;oil;

Compounds of formula 14:

- 35 (2R,6S)-7-iodo-10-hydroxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 14a:

32.5 g (0.13 mol) of (2R,6S)-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine **4a** are dissolved in 330 mL of acetic acid and 110 mL of trifluoroacetic acid, cooled to 5 °C and 32.9 g of NIS is added batchwise. The mixture is stirred for 3 h at 10 °C, the solvent is eliminated *in vacuo* and the residue

is combined with ice-cooled ammonia solution. It is then extracted twice with 200 mL aliquots of ethyl acetate, the combined organic phase is dried and the solvent is eliminated *in vacuo*. The residue is dissolved in ethyl acetate and the hydrochloride is precipitated with ethereal HCl. Yield: 31.7 g (59%), melting point: 231 °C.

5

Compounds of formula 15:

(2R,6S)-3-t-Butyloxycarbonyl-7-iodo-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 15a:

31.6 g (78 mmol) of (2R,6S)-7-iodo-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride **14a** are suspended in 350 mL of dichloromethane, cooled to -5 °C, combined with 9 g of KOH in 18 mL of water and 17.7 g of di-t-butylidicarbonate in 50 mL of dichloromethane are added dropwise. The mixture is then allowed to come slowly up to RT, is stirred for 2 h at room temperature and 200 mL of water are added. The organic phase is separated off, dried, and the solvent is eliminated *in vacuo*. Yield: 36.7 g (100%) of viscous oil.

Compounds of formula 16:

(2R,6S)-3-t-Butyloxycarbonyl-7-trifluoromethyl-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 16a:

15.8 g (34 mmol) of (2R,6S)-3-t-butyloxycarbonyl-7-iodo-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine **15a** is dissolved in 120 mL of DMF, 10 g of methyl fluorosulphonyl-difluoroacetate and 2.3 g of CuI are added and the mixture is heated to 70 °C. After 24 h another 3 g of methyl fluorosulphonyl-difluoroacetate and 0.7 g of CuI are added and stirring is continued for another 18 h at 70 °C. The mixture is cooled, combined with 500 mL of ether and suction filtered to remove any insoluble matter. The filtrate was washed twice with dilute ammonia solution and with water. The organic phase was dried and the solvent eliminated *in vacuo*. Yield: 13.6 g (98%); orange resin.

Compounds of formula 17:

(2R,6S)-7-Trifluoromethyl-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 17a:

13.6 g (33 mmol) of (2R,6S)-3-t-butyloxycarbonyl-7-trifluoromethyl-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine **16a** are dissolved in 250 mL of dichloromethane, 25 mL of trifluoroacetic acid are added dropwise and the mixture is stirred for 2 h at RT. It is then added to ice water and ammonia solution, the organic phase is separated off, dried and the solvent is eliminated *in vacuo*. Yield: 10.7 g (100%) orange resin.

Compounds of formula 18:

(2R,6S)-7-trifluoromethyl-10-hydroxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 18a:

1.0 g (3.2 mmol) of (2R,6S)-7-trifluoromethyl-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine **17a** are dissolved in 10 mL of dichloromethane, cooled to -65 °C and 7 mL of BBr₃ solution (1M in dichloromethane) are added dropwise. The mixture is then allowed to come up to 0 °C and stirred for 8 h at this temperature. 10 mL of MeOH are added, while cooling with ice, and the solvent is eliminated *in vacuo*. Yield: 1.2 g (100%), brown resin.

10

Compounds of formula 19:

(2R,6S)-3-Benzyl-7-(4-methyl)phenyl-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine 19a:

4.1 g (10 mmol) of (2R,6S)-3-Benzyl-7-bromo-10-methoxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine **6a** are dissolved in 100 mL of degassed dioxan under N₂, combined with 12.6 g of K₂PO₄, 2.9 g of 4-methylphenylboric acid, 0.92 g of tris(dibenzylideneacetone)-palladium(0) and 0.25 g of trimethylphosphite and refluxed for 1 h. Then the mixture is cooled, the salts are removed by suction filtering and the solvent is eliminated *in vacuo*. The residue is chromatographed on silica gel. The appropriate fractions are evaporated down *in vacuo*.

20

Yield: 3.8 g (89%); oil.

Compounds of formula 20:

(2R,6S)-10-Hydroxy-7-(4-methyl)phenyl-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrobromide 20a:

Prepared from **19a** analogously to the preparation of **10a**;

melting point: >250 °C.

Compounds of formula 21:

(2R,6S)-10-Hydroxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrobromide 21a:

Prepared from **4a** analogously to the preparation of **9a**;

(2R,6S, 11R)-10-Hydroxy-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-hydrobromide 21b:

35

Prepared from **4b** analogously to the preparation of **9a**;

(2R,6S, 11S)-10-Hydroxy-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-hydrobromide **21c**:

Prepared from **4c** analogously to the preparation of **9a**;

5 (2R,6S)-10-Hydroxy-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-hydrochloride **21d**:

Prepared from **4d** analogously to the preparation of **9c**;

II. Synthesis of the compounds of formula 2:

10 (2R,6S,2"S)-10-Hydroxy-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2a**:

1.6 g (6.9 mmol) of (2R,6S)-10-hydroxy-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrobromide **21a** are suspended in 30 mL of dichloromethane and 6 mL of N-methylmorpholine is added. After 30 min. the mixture is cooled to -5°C and a solution of 2.3 g (11.6 mmol) of (-)-S-2-bBenzyloxy-propionic acid chloride in 20 mL of dichloromethane is slowly added dropwise thereto. The mixture is stirred for a further 30 min. at -5 °C, 40 mL of 2 N hydrochloric acid are added and the organic phase is separated off. The organic phase is dried over MgSO₄, the solvent is eliminated *in vacuo* and the residue is taken up in 80 mL of THF. To this solution are added 1.0 g (26 mmol) of LiAlH₄ whereupon the temperature rises to 35 °C. The solution is left to react for 30 min, 0.8 mL of water and 0.4 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 evaporated down *in vacuo*. The residue is taken up in 200 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: 2.1 g (73%), melting point: 254 °C, $[\alpha]_D^{25} = (-) 20.7^\circ$ (C=1 in methanol);

30 The following compounds **2** were also obtained using the corresponding carboxylic acids:

(2R,6S,2S')-10-Hydroxy-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2b**

35 Prepared from **21a** analogously to the preparation of **2a**;

(2R,6S,11R,2S')-10-Hydroxy-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-dihydrochloride **2c**

Prepared from **21b** analogously to the preparation of **2a**;

(2R,6S,11S,2S')-10-Hydroxy-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-dihydrochloride **2d**

Prepared from **21c** analogously to the preparation of **2a**;

5

(2R,6S,2S')-10-Hydroxy-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-dihydrochloride **2e**

Prepared from **21d** analogously to the preparation of **2a**;

10 (2R,6S)-10-Hydroxy-3-[2(2,6-difluorophenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2f**

Prepared from **21a** analogously to the preparation of **2a**;

15 (2R,6S,2S')-10-Hydroxy-3-[2(2,6-difluorophenyl-methoxy)-isopentyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2g**

Prepared from **21a** analogously to the preparation of **2a**;

(2R,6S)-10-Hydroxy-3-[2(benzyloxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2h**

20 Prepared from **21a** analogously to the preparation of **2a**;

(2R,6S)-10-Hydroxy-3-[2(2-fluorophenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2i**

Prepared from **21a** analogously to the preparation of **2a**;

25

(2R,6S)-10-Hydroxy-3-[2(2,4-difluorophenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2j**

Prepared from **21a** analogously to the preparation of **2a**;

30 (2R,6S)-10-Hydroxy-3-[2(2,6-dimethylphenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2k**

Prepared from **21a** analogously to the preparation of **2a**;

35 (2R,6S,2S')-10-Hydroxy-3-[2(benzyloxy)-butyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2l**

Prepared from **21a** analogously to the preparation of **2a**;

(2R,6S,2S')-10-Hydroxy-3-[2(2,6-difluorophenyl-methoxy)-butyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2m**

Prepared from **21a** analogously to the preparation of **2a**;

(2R,6S,2S')-10-Hydroxy-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-dihydrochloride **2n**

Prepared from **21d** analogously to the preparation of **2a**;

5

(2R,6S,2"R,5"S)-10-Hydroxy-3-[5"-phenyl-tetrahydrofuran-2"-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2o**:

Prepared from **21a** analogously to the preparation of **2a**;

10 (2R,6S,2"S,5"S)-10-Hydroxy-3-[5"-phenyl-tetrahydrofuran-2"-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2p**:

Prepared from **21a** analogously to the preparation of **2a**;

(2R,6S)-10-Hydroxy-3-[3(2,6-difluorophenyloxy)-propyl]-1,2,3,4,5,6-hexahydro-

15 6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2q**

Prepared from **21a** analogously to the preparation of **2a**;

(2R,6S)-10-Hydroxy-3-[4(2,6-difluorophenyl)-butyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2r**

20 Prepared from **21a** analogously to the preparation of **2a**;

(2R,6S,2S')-10-Hydroxy-7-methyl-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2s**

25 Prepared from **10a** analogously to the preparation of **2a**;

(2R,6S,2S')-10-Hydroxy-7-methyl-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2t**

Prepared from **10a** analogously to the preparation of **2a**;

30

(2R,6S,2"S,5"S)-10-Hydroxy-7-methyl-3-[5"-phenyl-tetrahydrofuran-2"-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2u**: Prepared from **10a** analogously to the preparation of **2a**;

35 (2R,6S,2S')-10-Hydroxy-7-fluoro-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride **2v**

Prepared from **13a** analogously to the preparation of **2a**;

(2R,6S,2S')-10-Hydroxy-7-trifluoromethyl-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride 2w
Prepared from 18a analogously to the preparation of 2a;

5 (2R,6S,2S')-10-Hydroxy-7-(4-methylphenyl)-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride 2x

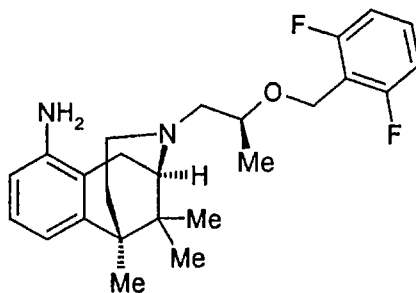
Prepared from 20a analogously to the preparation of 2a;

10 (2R,6S)-10-Hydroxy-7-methyl-3-[2(2,6-difluorophenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride 2y
Prepared from 10a analogously to the preparation of 2a;

III. Synthesis of the compounds of formula 1 according to the invention:

15

Example 1: (2R,6S,2S')-10-Amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



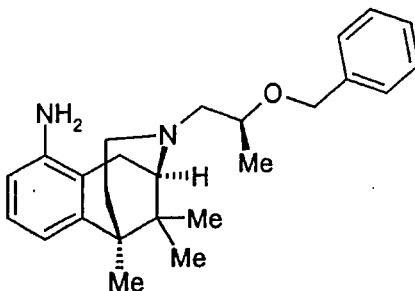
13.5 g (0.03 mol) of (2R,6S,2"S)- 3-[2(2,6-difluorophenyl-methoxy)-propyl]-
20 1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-10-ol 2d are
dissolved in 135 mL of dichloromethane, combined with 30 mL of triethylamine and a
spatula tip of 4-dimethylaminopyridine and cooled to -10 °C. Then 6.8 mL of
trifluoromethanesulphonic acid anhydride are added dropwise, the mixture is stirred
for 1h at -10 °C and for a further 2 h at room temperature. The reaction mixture is
25 poured onto ice, combined with 50 mL of ammonia, the organic phase is separated
off and washed once with 50 mL of water. The organic phase is dried, the solvent is
eliminated *in vacuo*, the residue is taken up in 350 mL of toluene, and 21.6 g of
CsCO₃ and 10.8 g of benzophenone-imine are added. Then nitrogen is bubbled
through the suspension for 30 min., 1.2 g of BINAP and 0.6 g of tris(dibenzylidene-
30 acetone)-dipalladium are added and the mixture is refluxed for 6 h. After cooling, it is
washed with 200 mL of water, the organic phase is dried and the solvent is
eliminated *in vacuo*. The residue is taken up in ethanol and the hydrochloride is

precipitated with ethereal HCl. Yield: 13.7 g (88%), melting point: 266 °C, $[\alpha]_D^{20} = (-) 37.0^\circ$ (c=1 in MeOH).

The following compounds were also obtained, *inter alia*:

5

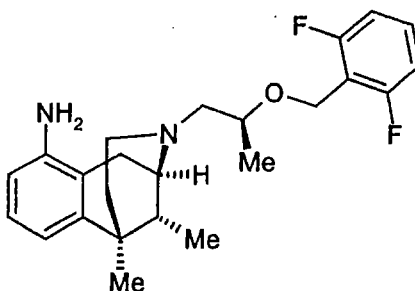
Example 2: (2R,6S,2"S)-10-Amino-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



Prepared from compound **2a** analogously to Example 1;

10 melting point: 257 °C, $[\alpha]_D^{20} = (-) 29.3^\circ$ (c=1 in MeOH).

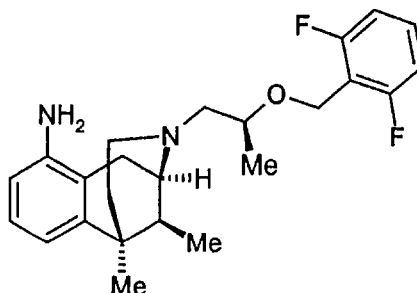
Example 3: (2R,6S,11R,2"S)-10-Amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-dihydrochloride:



15 Prepared from compound **2c** analogously to Example 1;

melting point: 232 °C, $[\alpha]_D^{20} = (-) 4.1^\circ$ (c=1 in MeOH).

Example 4: (2R,6S, 11S, 2"S)-10-Amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11-dimethyl-2,6-methano-3-benzazocine-dihydrochloride:

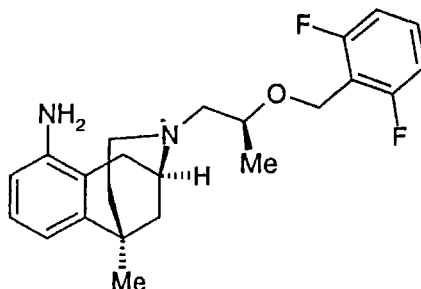


20

Prepared from compound **2d** analogously to Example 1;

melting point: 267 °C, $[\alpha]_D^{20} = (-) 2.4^\circ$ (c=1 in MeOH).

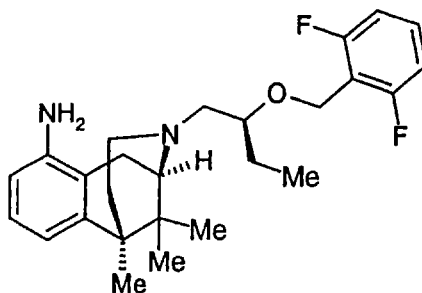
Example 5: (2R,6S, 2"S)-10-Amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-dihydrochloride:



Prepared from compound **2n** analogously to Example 1;

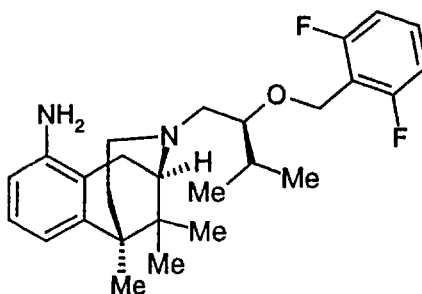
5 melting point: 187 °C, $[\alpha]_D^{20} = 19.7^\circ$ (c=1 in MeOH).

Example 6: (2R,6S,2S')-10-Amino-3-[2(2,6-difluorophenyl-methoxy)-butyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



10 Prepared from compound **2m** analogously to Example 1;
melting point: 200°C.

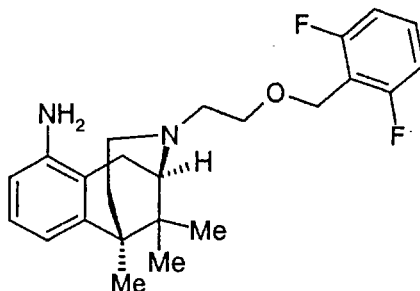
Example 7: (2R,6S,2S')-10-Amino-3-[2(2,6-difluorophenyl-methoxy)-isopentyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



15

Prepared from compound **2g** analogously to Example 1;
melting point: 274 °C, $[\alpha]_D^{20} = (-) 21.8^\circ$ (c=1 in MeOH).

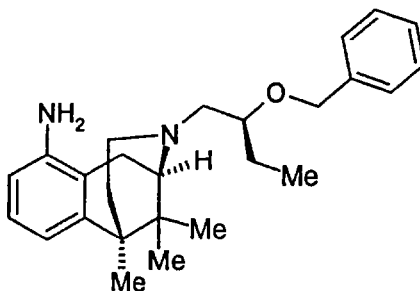
Example 8: (2R,6S)-10-Amino-3-[2(2,6-difluorophenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



Prepared from compound **2f** analogously to Example 1;

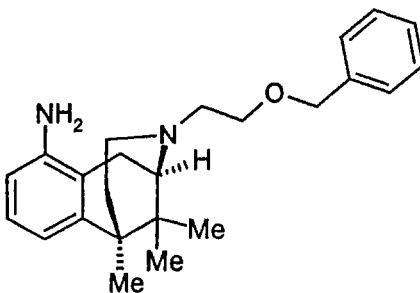
5 melting point: 270 °C, $[\alpha]_D^{20} = (-) 77.4^\circ$ (c=1 in MeOH).

Example 9: (2R,6S,2S')-10-Amino-3-[2(benzyloxy)-butyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



10 Prepared from compound **2l** analogously to Example 1;
melting point: >190 °C (decomposition);.

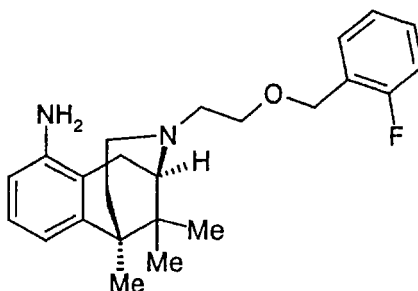
Example 10: (2R,6S)-10-Amino-3-[2(benzyloxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



15

Prepared from compound **2h** analogously to Example 1;
melting point: 220 °C;.

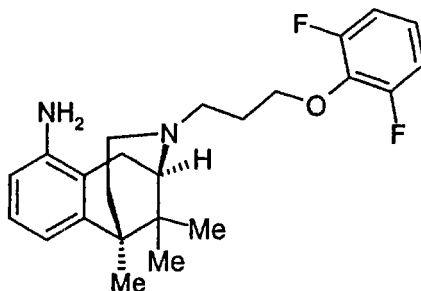
Example 11: (2R,6S)-10-Amino-3-[2(2-fluorophenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



Prepared from compound **2i** analogously to Example 1;

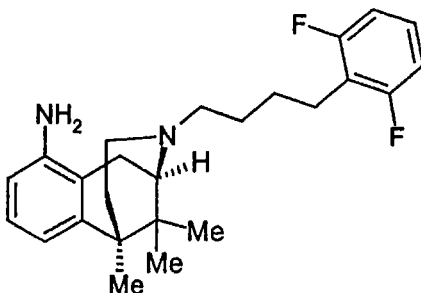
5 melting point: 220 °C;.

Example 12: (2R,6S)-10-Amino-3-[3(2,6-difluorophenyl)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



10 Prepared from compound **2g** analogously to Example 1;
melting point: 250 °C;.

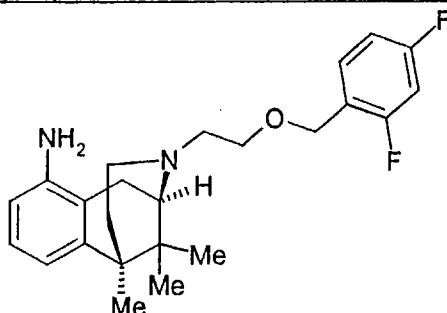
Example 13: (2R,6S)-10-Amino-3-[4(2,6-difluorophenyl)-butyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



15

Prepared from compound **2r** analogously to Example 1;
melting point: 250 °C;.

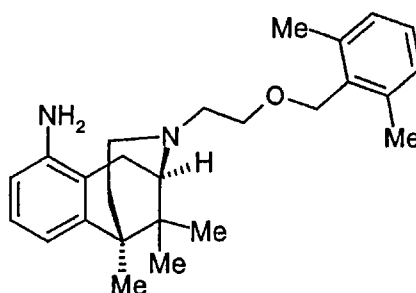
Example 14: (2R,6S)-10-Amino-3-[2(2,4-difluorophenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride



Prepared from compound **2j** analogously to Example 1;

5 melting point: 220 °C;.

Example 15: (2R,6S)-10-Amino-3-[2(2,6-dimethylphenyl-methoxy)-ethyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride

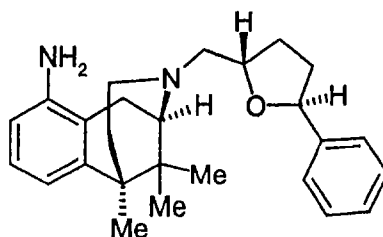


10 Prepared from compound **2k** analogously to Example 1;

melting point: 245 °C;.

Example 16: (2R,6S,2''S,5''S)-10-Amino-3-[5''-phenyl-tetrahydrofuran-2''-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-

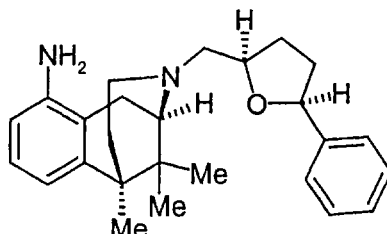
15 dihydrochloride:



Prepared from compound **2p** analogously to Example 1;

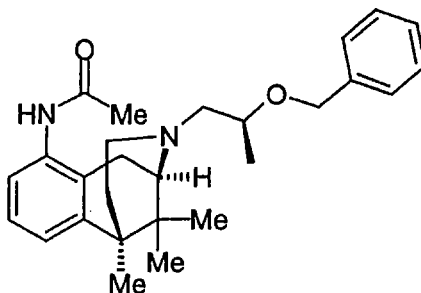
melting point: 253 °C, $[\alpha]_D^{20} = (-) 135.4^\circ$ (c=1 in MeOH).

Example 17: (2R,6S,2''R,5''S)-10-Amino-3-[5''-phenyl-tetrahydrofuran-2''-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



- 5 Prepared from compound **2o** analogously to Example 1;
melting point: 255 °C;.

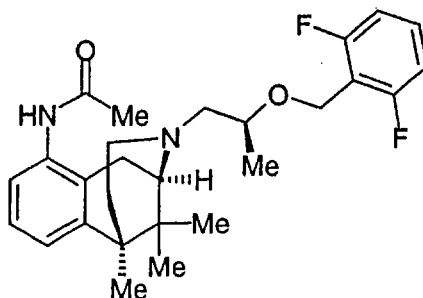
Example 18: (2R,6S,2''S)-10-Acetamino-3-[2(2,6-benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride:



10

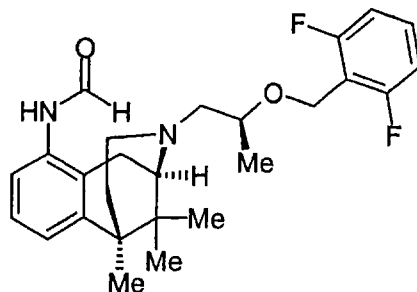
- 2 mL of acetic anhydride are added to 1.1 g (2.4 mmol) of (2R,6S,2''S)-10-amino-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride (Example 2) and 5 mL of triethylamine in 50 mL of dichloromethane and the mixture is stirred for 0.5 h at room temperature. It is then
15 evaporated down *in vacuo*, combined with 100 mL of ether and washed twice with 50 mL of water. The organic phase is dried, the solvent is eliminated *in vacuo*, the residue is taken up in ether and the hydrochloride is precipitated with ethereal HCl.
Yield: 0.8 g (73%), melting point: >100 °C, $[\alpha]_D^{20} = (-) 56.5^\circ$ (c=1 in MeOH).

- 20 **Example 19:** (2R,6S,2''S)-10-Acetamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride:



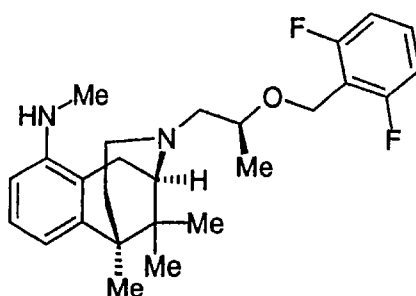
Prepared from Example 1 analogously to Example 18;
melting point: 125 °C, $[\alpha]_D^{20} = (-) 58.7^\circ$ (c=1 in MeOH).

Example 20: (2R,6S,2"S)-10-Formylamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride:



- 5 0.5 g (1.2 mmol) of (2R,6S,2"S)-10-amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine (Example 1) are combined with 10 mL of 97% formic acid and refluxed for 1 h. The mixture is then evaporated down *in vacuo*, the residue is combined with ice and 50 mL of ammonia and extracted twice with 50 mL of ethyl acetate. The combined organic
10 phase is washed with 30 mL of water, dried and the solvent is eliminated *in vacuo*. The residue is taken up in ether and the hydrochloride is precipitated with ethereal HCl. Yield: 0.3 g (52%), melting point: amorphous, $[\alpha]_D^{20} = (-) 41.6^\circ$ (c=1 in MeOH).

Example 21: (2R,6S,2"S)-10-methylamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:

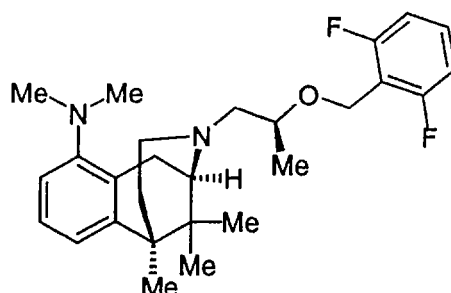


- 1.0 g (2.4 mmol) of (2R,6S,2"S)-10-amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine (Example 1)
20 are dissolved in 10 mL of ethyl acetate, and 1 mL of triethylamine and 1 mL of trifluoroacetic acid anhydride is added. After 10 min the mixture is washed twice with 10 mL of water, the organic phase is dried and the solvent is eliminated *in vacuo*. The residue is taken up in 10 mL of dimethylacetamide and 0.5 g of NaH is added. After 15 min. 1 mL of methyl iodide is added and the mixture is stirred for 1 h at 50°C.
25 Then the solvent is eliminated *in vacuo*, the residue is combined with 20 mL of methanol and 2 mL of 20% NaOH and stirred for 30 min. at 60°C. The solution is once more evaporated down *in vacuo*, the residue is combined with 50 mL of water and extracted twice with 100 mL of ether. The combined organic phase is dried, the

solvent is eliminated *in vacuo* and the residue is chromatographed on silica gel. The appropriate fractions are combined and the hydrochloride is precipitated with ethereal HCl. Yield: 0.4 g (35%), melting point: 243 °C, $[\alpha]_D^{20} = (-) 20.5^\circ$ (c=1 in MeOH).

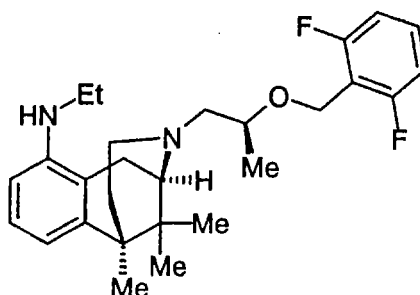
5

Example 22: (2R,6S,2"S)-10-dimethylamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



- 10 A suspension of 0.4 g (1 mmol) of (2R,6S,2"S)-10-amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine (Example 1) and 0.3 g of NaBH₄ in 7 mL of THF is added batchwise to a solution of 0.6 mL of 37% formalin and 1.2 mL of 3N H₂SO₄ cooled to -10°C. After it has all been added, the mixture is left to react for 10 min, ammonia is added and
- 15 the resulting mixture is extracted twice with 20 mL of ethyl acetate. The organic phase is dried, the solvent is eliminated *in vacuo*, the residue is taken up in ether and the hydrochloride is precipitated with ethereal HCl. Yield: 0.5 g (97%), melting point: 125 °C, $[\alpha]_D^{20} = (-) 20.0^\circ$ (c=1 in MeOH).

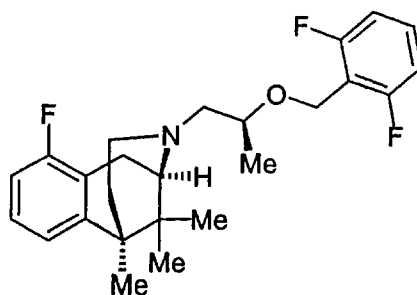
- 20 **Example 23:** (2R,6S,2"S)-10-ethylamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



- 1.1 g (2.4 mmol) of (2R,6S,2"S)-10-acetamino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine (Example 1) are dissolved in 30 mL of THF, combined with 0.5 g of NaBH₄ and 1.5 mL of BF₃-etherate and refluxed for 6 h. The mixture is allowed to cool, 30 mL of MeOH and 60 mL of 2 N HCl are added and the resulting mixture is refluxed for a
- 25

further 30 min. Then the solvent is eliminated *in vacuo*, the residue is combined with conc. ammonia and extracted twice with 30 mL of ethyl acetate. The combined organic phase is washed once with 20 mL of water, dried and the solvent is eliminated *in vacuo*. The residue is taken up in acetone and the hydrochloride is precipitated with ethereal HCl. Yield: 0.95 g (89%), melting point: 242 °C, $[\alpha]_D^{20} = (-)$ 24.8° (c=1 in MeOH).

Example 24: (2R,6S,2"S)-10-Fluoro-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-hydrochloride:



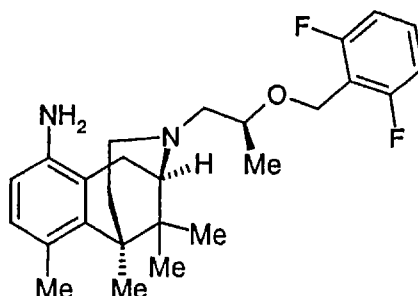
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1.5 g (3.6 mmol) of (2R,6S,2"S)-10-amino-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine (Example 1) are placed in 30 mL of dioxan, combined with 3 g of NOBF₄ in 30 mL of dioxan and stirred for 1 h at 90°C. Then the solvent is eliminated *in vacuo*, the residue is combined with 50 mL of ethyl acetate and washed once with 30 mL of dilute ammonia and once with 30 mL of water. The combined organic phase is dried, the solvent is eliminated *in vacuo* and the residue is chromatographed on silica gel. The appropriate fractions are combined and the hydrochloride is precipitated with ethereal HCl. Yield: 0.5 g (33%), melting point: 190 °C, $[\alpha]_D^{20} = (-)$ 27.3° (c=1 in MeOH).

20

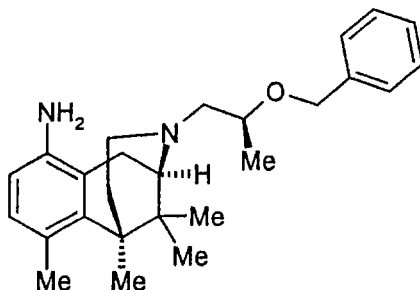
Example 25: (2R,6S,2"S)-10-Amino-7-methyl-3-[2-(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:

25



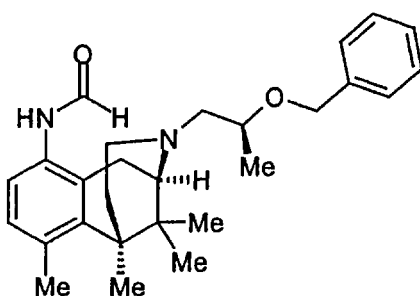
Prepared from **2s** analogously to Example 1;
melting point: 236 °C;.

Example 26: (2R,6S,2''S)-10-Amino-7-methyl-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



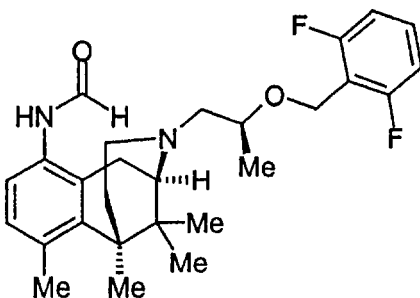
- 5 Prepared from **2t** analogously to Example 1;
melting point: 227 °C, $[\alpha]_D^{20} = (-) 31,8^\circ$ (c=1 in MeOH).

Example 27: (2R,6S,2''S)-10-Formylamino-7-methyl-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



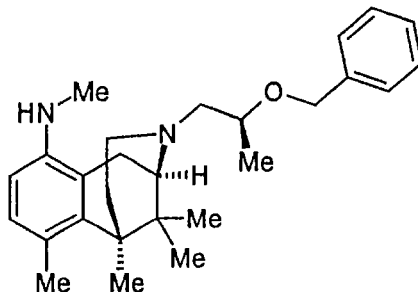
Prepared from Example 26 analogously to Example 20;
melting point: 141 °C;.

15 **Example 28:** (2R,6S,2''S)-10-Formylamino-7-methyl-3-[2-(2,6-difluorophenyl-methoxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



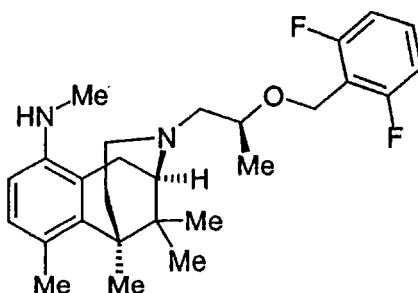
- Prepared from Example 28 analogously to Example 20;
20 melting point: >105°C °C (decomposition), $[\alpha]_D^{20} = (-)42,2^\circ$ (c=1 in MeOH);.

Example 29: (2R,6S,2"S)-10-methylamino-7-methyl-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



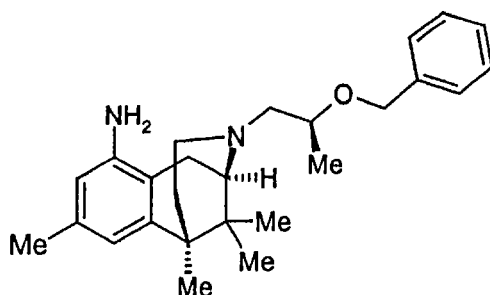
- 5 Prepared from Example 26 analogously to Example 21;
melting point: >100 °C (decomposition);.

Example 30: (2R,6S,2"S)-10-methylamino-7-methyl-3-[2-(2,6-difluorophenyl-methoxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrobromide:



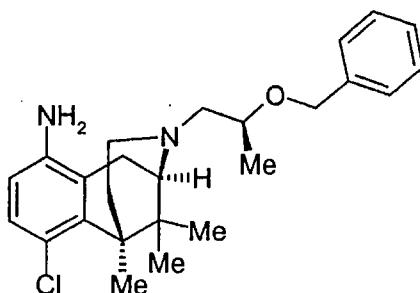
Prepared from Example 25 analogously to Example 21;
melting point: 221 °C (decomposition), $[\alpha]_D^{20} = (-)29,4^\circ$ (c=1 in MeOH);.

15 **Example 31:** (2R,6S,2"S)-10-Amino-8-methyl-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



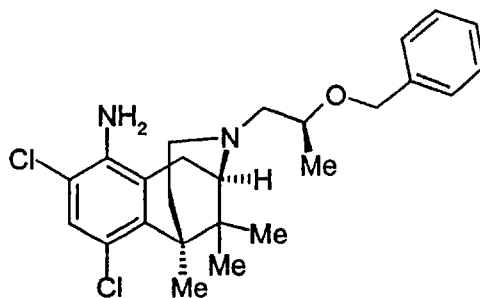
Prepared analogously to Example 1; melting point: 250 °C;.

Example 32: (2R,6S, 2"S)-10-Amino-7-chloro-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



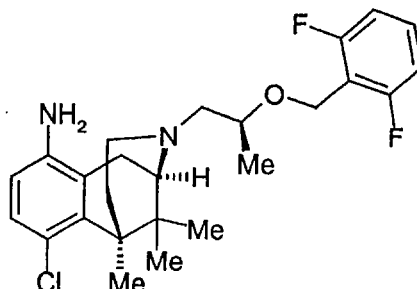
- 4.5 g (10 mmol) of (2R,6S,2"S)-10-amino-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride (Example 2) are dissolved in 90 mL of MeOH and 90 mL of glacial acetic acid, 1.45 g of NCS (N-chloro-succinimide) are added and the mixture is stirred for 4 h at room temperature. Then the solvent is eliminated *in vacuo*, the residue is taken up in 100 mL of aqueous ammonia solution and extracted twice with 50 mL of ethyl acetate.
- 10 The combined organic phase is dried, the solvent is eliminated *in vacuo* and the residue is chromatographed on silica gel. The appropriate fractions are evaporated down *in vacuo* and the hydrochloride is precipitated with ethereal HCl.
- Yield: 1.3 g (27%); melting point: 222 °C, $[\alpha]_D^{20} = (-)17.4^\circ$ (c=1 in MeOH);.

- 15 **Example 33:** (2R,6S, 2"S)-10-Amino-7,9-dichloro-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



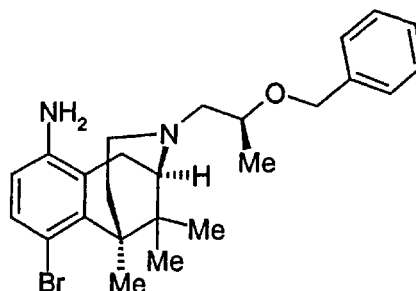
- Prepared together with Example 32;
- 20 Separation by chromatography produces:
- Yield: 0.6 g (12%); melting point: 197 °C, $[\alpha]_D^{20} = 11,0^\circ$ (c=1 in MeOH);.

Example 34: (2R,6S, 2"S)-10-Amino-7-chloro-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



- 5 Prepared from Example 1 analogously to Example 32;
melting point: 247 °C;.

Example 35: (2R,6S, 2"S)-10-Amino-7-bromo-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:

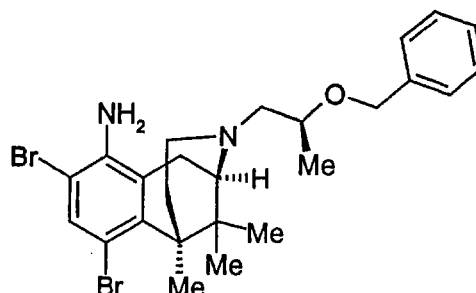


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- Prepared from Example 2 analogously to Example 32 using NBS;
melting point: 215 °C, $[\alpha]_D^{20} = (-)17.3^\circ$ (c=1 in MeOH);.

Example 36: (2R,6S, 2"S)-10-Amino-7,9-dibromo-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:

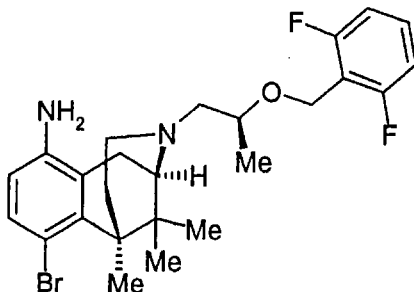
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- Prepared together with Example 35 analogously to Example 33;
melting point: 177 °C, $[\alpha]_D^{20} = 11.5^\circ$ (c=1 in MeOH);.

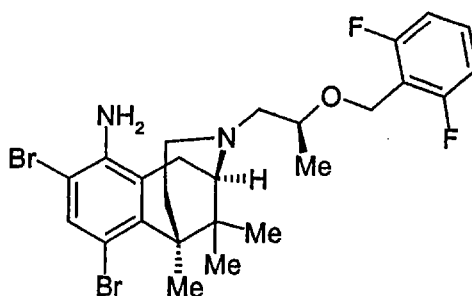
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Example 37: (2R,6S, 2"S)-10-Amino-7-bromo-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



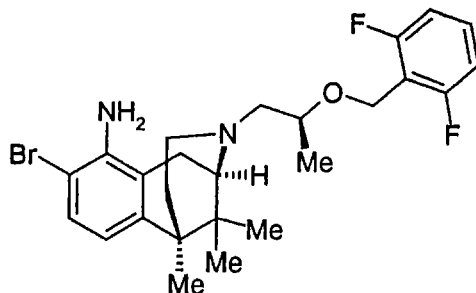
- 5 Prepared from Example 1 analogously to Example 32 using NBS;
melting point: 233 °C, $[\alpha]_D^{20} = (-)20.5^\circ$ ($c=1$ in MeOH);.

Example 38: (2R,6S, 2"S)-10-Amino-7,9-dibromo-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-
10 dihydrochloride:



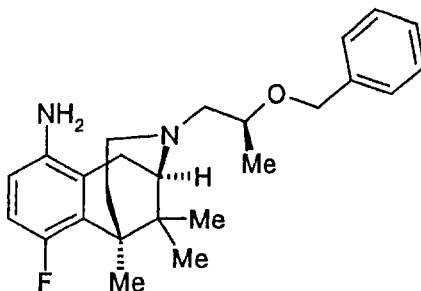
Prepared together with Example 37 analogously to Example 36;
melting point: 236 °C, $[\alpha]_D^{20} = 5.9^\circ$ ($c=1$ in MeOH);.

15 **Example 39:** (2R,6S, 2"S)-10-Amino-9-bromo-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-
dihydrochloride:



Prepared together with Example 37 analogously to Example 32;
20 melting point: 252 °C, $[\alpha]_D^{20} = (-)14.6^\circ$ ($c=1$ in MeOH);.

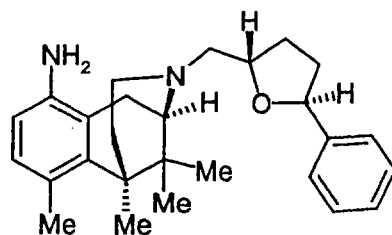
Example 40: (2R,6S,2''S)-10-Amino-7-fluoro-3-[2-(benzyloxy)propyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



Prepared from **2v** analogously to Example 1;

5 melting point: 150 °C;.

Example 41: (2R,6S,2''S,5''S)-10-Amino-7-methyl-3-[5''-phenyl-tetrahydrofuran-2''-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



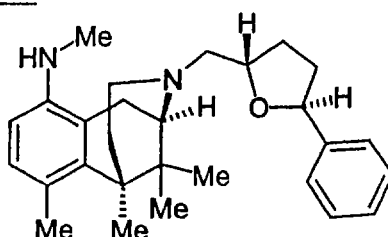
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Prepared from **2u** analogously to Example 1;

melting point: 250 °C;.

Example 42: (2R,6S,2''S,5''S)-10-methylamino-7-methyl-3-[5''-phenyl-

15 tetrahydrofuran-2''-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:



Prepared from Example 41 analogously to Example 21;

melting point: 250 °C;.

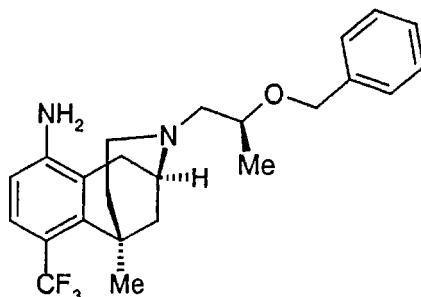
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Example 43: (2R,6S,2''S,5''S)-10-Formylamino-7-methyl-3-[5''-phenyl-tetrahydrofuran-2''-yl)methyl]-1,2,3,4,5,6-hexahydro-6,11,11-trimethyl-2,6-methano-3-benzazocine-dihydrochloride:

Prepared from Example 41 analogously to Example 20;

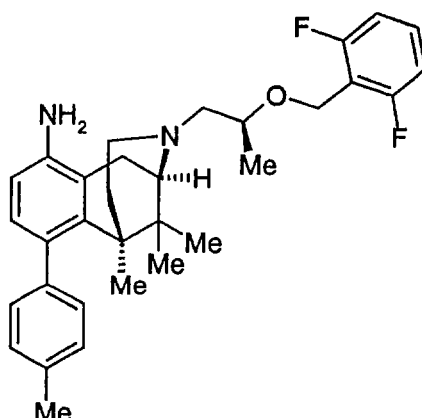
25 melting point: 250 °C;.

Example 44: (2R,6S, 2"S)-10-Amino-7-trifluoromethyl-3-[2(benzyloxy)-propyl]-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-dihydrochloride:



- 5 Prepared from **2w** analogously to Example 1;
melting point: 165 °C;.

Example 45: (2R,6S, 2"S)-10-Amino-7-(4-methylphenyl)-3-[2(2,6-difluorophenyl-methoxy)-propyl]-1,2,3,4,5,6-hexahydro-6-methyl-2,6-methano-3-benzazocine-dihydrochloride:



Prepared from **2x** analogously to Example 1;
melting point: 219 °C, $[\alpha]_D^{20} = (-)19.5^\circ$ (c=1 in MeOH).

15

The compounds according to the invention may be administered orally, transdermally, nasally, by inhalation or parenterally. The compounds according to the invention occur as active ingredients in conventional preparations, for example in compositions which consist essentially of an inert pharmaceutical carrier and an effective dose of the active substance, such as for example tablets, coated tablets, capsules, lozenges, powders, solutions, suspensions, emulsions, syrups, suppositories, transdermal systems etc.. An effective dose of the compounds according to the invention is between 1 and 1000, preferably between 1 and 500, most preferably between 5-300 mg/dose for oral administration, and between 0.001 and 50, preferably between 0.1 and 10 mg/dose for intravenous, subcutaneous or

20

25

intramuscular administration. For inhalation, according to the invention, solutions containing 0.01 to 1.0, preferably 0.1 to 0.5 % active substance are suitable. For administration by inhalation the use of powders is preferred. It is also possible to use the compounds according to the invention as a solution for infusion, preferably in a physiological saline or nutrient saline solution.

The compounds according to the invention may be used on their own or in conjunction with other active substances according to the invention, optionally also in conjunction with other pharmacologically active substances. Suitable preparations include for example tablets, capsules, suppositories, solutions, elixirs, emulsions or dispersible powders.

Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example collidone or shellac, gum arabic, talc, titanium dioxide or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavour enhancer, e.g. of a flavouring such as vanilline or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

Solutions for injection are prepared in the usual way, e.g. of. with the addition of preservatives such as p-hydroxybenzoates, or stabilisers such as alkali metal salts of ethylenediamine tetraacetic acid, and transferred into injection vials or ampoules.

Capsules containing one or more active substances or combinations of active substances may for example be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

- 5 Sutable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

A therapeutically effective daily dose is between 1 and 1000 mg, preferably 10 - 500 mg per adult.

10

The Examples which follow illustrate the present invention without restricting its scope:

15 Examples of pharmaceutical formulations

A)	<u>Tablets</u>	<u>per tablet</u>
20	active substance	300 mg
	lactose	240 mg
	corn starch	340 mg
	polyvinylpyrrolidone	45 mg
	magnesium stearate	15 mg
25		
		940 mg

- The finely ground active substance, lactose and some of the corn starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet-granulated and dried. The granules, the
 30 remaining corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B)	<u>Tablets</u>	<u>per tablet</u>
5	active substance	80 mg
	corn starch	190 mg
	lactose	55 mg
	microcrystalline cellulose	35 mg
	polyvinylpyrrolidone	15 mg
	sodium-carboxymethyl starch	23 mg
	magnesium stearate	<u>2 mg</u>
10		400 mg

The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium-carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

C)	<u>Coated tablets</u>	<u>per coated tablet</u>
20	Active substance	5 mg
	Corn starch	41.5 mg
	Lactose	30 mg
	Polyvinylpyrrolidone	3 mg
25	Magnesium stearate	<u>0.5 mg</u>
		80 mg

The active substance, corn starch, lactose and polyvinylpyrrolidone are thoroughly mixed and moistened with water. The moist mass is pushed through a screen with a 1 mm mesh size, dried at about 45°C and the granules are then passed through the same screen. After the magnesium stearate has been mixed in, convex tablet cores with a diameter of 6 mm are compressed in a tablet-making machine. The tablet cores thus produced are coated in known manner with a covering consisting essentially of sugar and talc. The finished coated tablets are polished with wax.

D) Capsules

per capsule

5	Active substance	1.50	mg
	Corn starch	268.5	mg
	Magnesium stearate	<u>1.5</u>	mg
		420	mg

The substance and corn starch are mixed and moistened with water. The moist mass is screened and dried. The dry granules are screened and mixed with magnesium stearate. The finished mixture is packed into size 1 hard gelatine capsules.

E) Ampoule solution

15	active substance	50	mg
	sodium chloride	50	mg
	water for inj.	5	ml

20 The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make it isotonic. The solution obtained is filtered free from pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilised and sealed by fusion. The ampoules contain 5 mg, 25 mg and 50 mg of active substance.

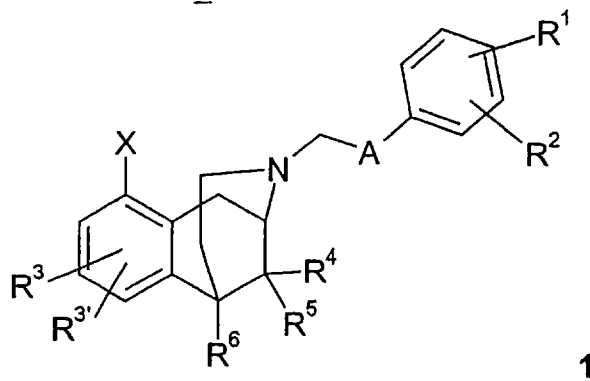
F) Suppositories

	Active substance	50	mg
	Solid fat	<u>1650</u>	<u>mg</u>
30		1700	mg

The hard fat is melted. At 40°C the ground active substance is homogeneously dispersed. It is cooled to 38°C and poured into slightly chilled suppository moulds.

Patent Claims

1) Compounds of general formula 1



5 wherein

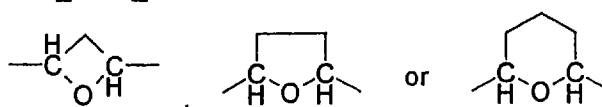
R¹ and R² which may be identical or different denote hydrogen, C₁-C₆-alkyl, C₁-C₆-alkyloxy, OH, F, Cl or Br;

10 R³ and R^{3'} which may be identical or different denote hydrogen, F, Cl, Br, methyl, ethyl, OH, CF₃, methoxy or phenyl, which may optionally be substituted by a group selected from among F, Cl, Br, methyl, ethyl, OH, CF₃ and methoxy;

15 R⁴, R⁵ and R⁶ which may be identical or different may denote hydrogen, methyl or ethyl,

20 X may denote NH₂, NH-(C₁-C₆-alkyl), N(C₁-C₆-alkyl)₂, the two C₁-C₆-alkyl groups of which may be identical or different, NH-COH, NH-CO(C₁-C₆-alkyl) or F;

25 A may denote -(CH₂)₃-, -CH₂-CH₂-O-, -CH₂-O-CH₂-, -(CH₂)₄-, -CH(C₁-C₆-alkyl)-O-CH₂-, -(CH₂)₂-O-CH₂-, -(CH₂)₃-O-, -(CH₂)₅-, -CH₂-O-(CH₂)₃-, -(CH₂)₂-O-(CH₂)₂-, -(CH₂)₃-O-CH₂-, -(CH₂)₄-O-, -CH₂-O-CH₂-CH₂-O-,



optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts
30 thereof.

2) Compounds of general formula 1 according to claim 1,
wherein

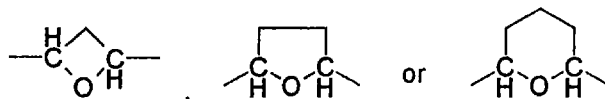
R¹ and R² which may be identical or different denote hydrogen, methyl, ethyl,
methyloxy, ethyloxy, OH, F, Cl or Br;

R³ and R^{3'} which may be identical or different denote hydrogen, F, Cl, Br, methyl,
ethyl, OH, CF₃, methoxy or phenyl, which may optionally be substituted
by a group selected from among F, Cl, Br and preferably methyl;

R⁴, R⁵ and R⁶ which may be identical or different may denote hydrogen or methyl;

X may denote NH₂, NH-(methyl), N(methyl)₂, NH-(ethyl), N(ethyl)₂,
NH-COH, NH-COMe or F;

A may denote -CH₂-CH₂-O-, -CH₂-O-CH₂-, -CH(methyl)-O-CH₂-,
-CH(ethyl)-O-CH₂-, -CH(isopropyl)-O-CH₂-, -(CH₂)₂-O-CH₂-,
-(CH₂)₃-O-, -CH₂-O-(CH₂)₃-, -(CH₂)₂-O-(CH₂)₂-, -(CH₂)₃-O-CH₂-,
-(CH₂)₄-O-, -CH₂-O-CH₂-CH₂-O-,



optionally in the form of their racemates, their enantiomers, their diastereomers and
mixtures thereof, and optionally the pharmacologically acceptable acid addition salts
thereof.

3) Compounds of general formula 1 according to one of claims 1 or 2,
wherein

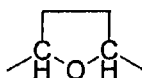
R¹ and R² which may be identical or different may denote hydrogen or F;

R³ and R^{3'} which may be identical or different may denote hydrogen, F, Cl, Br, CF₃
or methyl;

R⁴, R⁵ and R⁶ which may be identical or different may denote hydrogen or methyl;

X may denote NH₂, NH-(methyl), N(methyl)₂, NH-COH, NH-COMe or F;

A may denote -CH(methyl)-O-CH₂-, -CH₂-O-CH₂- or



optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

- 5 4) Compounds of general formula 1 according to claim 1, 2 or 3, wherein

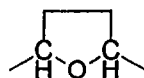
R^1 and R^2 which may be identical or different may denote hydrogen or F;

R^3 and $R^{3'}$ which may be identical or different may denote hydrogen, F, Cl, Br, CF_3 or methyl;

- 10 R^4 , R^5 and R^6 which may be identical or different may denote hydrogen or methyl;

X may denote NH_2 , NH -(methyl) or $NH-COH$;

A may denote $-CH(methyl)-O-CH_2-$, $-CH_2-O-CH_2-$ or



- 15 optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

- 5) Compounds of general formula 1 according to claim 1, 2 or 3, wherein

20

R^1 and R^2 which may be identical or different may denote hydrogen or F;

R^3 and $R^{3'}$ may denote hydrogen;

R^4 , R^5 and R^6 which may be identical or different may denote hydrogen or methyl;

X may denote F;

- 25 A may denote $-CH(methyl)-O-CH_2-$,

optionally in the form of their racemates, their enantiomers, their diastereomers and mixtures thereof, and optionally the pharmacologically acceptable acid addition salts thereof.

30

- 6) Pharmaceutical preparation, characterised in that it contains one of the compounds of formula 1 according to one of claims 1 to 5 together with conventional excipients and carriers.

- 35 7) Use of one of the compounds of formula 1 according to one of claims 1 to 5 as a pharmaceutical composition.

8) Use of one of the compounds of formula 1 according to one of claims 1 to 5 for preparing a pharmaceutical composition for the prevention or treatment of diseases or disorders in which blockade of the voltage-dependent sodium channel may be of therapeutic value.

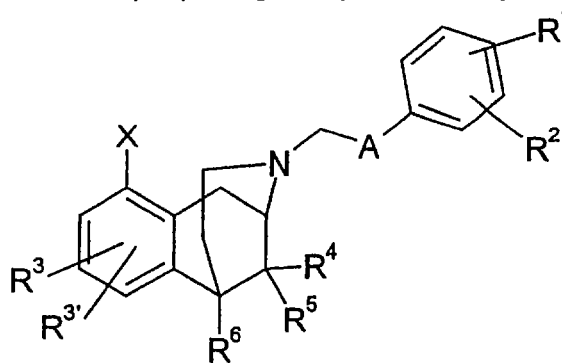
5

9) Use of one of the compounds of formula 1 according to one of claims 1 to 5 for preparing a pharmaceutical composition for the prevention or treatment of arrhythmias, spasms, cardiac and cerebral ischaemia, pain and neurodegenerative diseases.

10

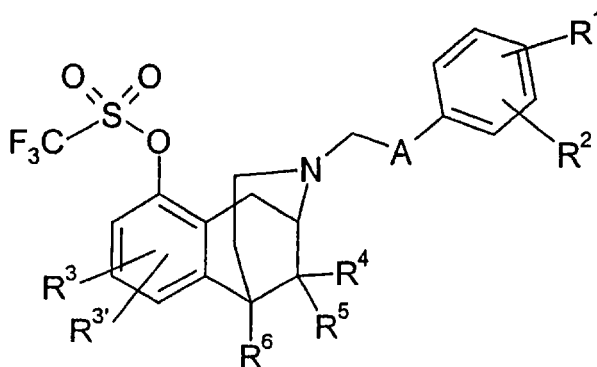
10) Use of one of the compounds of formula 1 according to one of claims 1 to 5 for preparing a pharmaceutical composition for the prevention or treatment of epilepsy, hypoglycaemia, hypoxia, anoxia, brain trauma, brain oedema, cerebral stroke, perinatal asphyxia, degeneration of the cerebellum, amyotrophic lateral sclerosis, Huntington's disease, Alzheimer's disease, Parkinson's disease, cyclophrenia, hypotonia, cardiac infarct, cardiac rhythm disorders, angina pectoris, chronic pain, neuropathic pain or local anaesthesia.

11) Process for preparing compounds of general formula 1

1

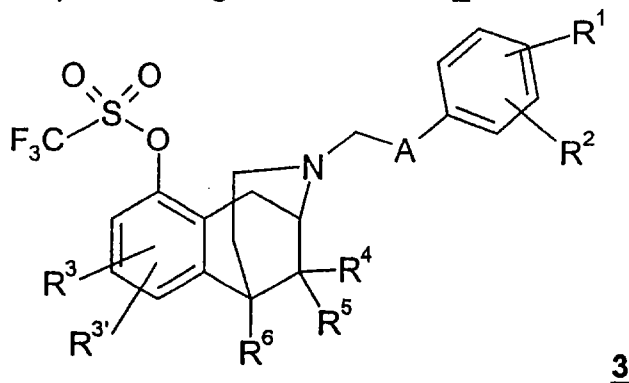
20

wherein the groups R¹, R², R³, R^{3'}, R⁴, R⁵, R⁶ and A may have the meanings given in claims 1-5 and X denotes NH₂, characterised in that compounds of general formula 3

3

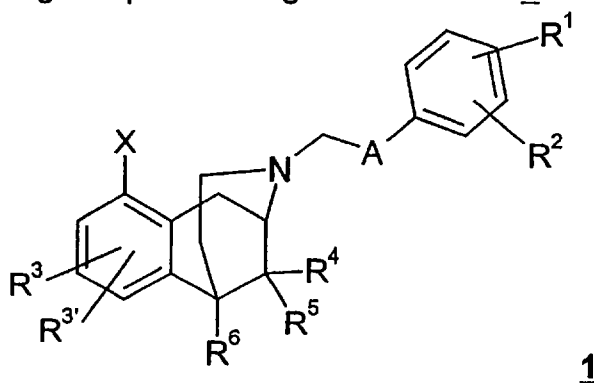
wherein the groups R^1 , R^2 , R^3 , $R^{3'}$, R^4 , R^5 , R^6 and A may have the meanings given in claims 1-5,
are reacted with a source of nitrogen in an aromatic solvent with palladium catalysis.

- 5 12) Intermediate compounds of general formula 3



wherein the groups R^1 , R^2 , R^3 , $R^{3'}$, R^4 , R^5 , R^6 and A may have the meanings given in claims 1-5.

- 10 13) Process for preparing compounds of general formula 1



wherein the groups R^1 , R^2 , R^3 , $R^{3'}$, R^4 , R^5 , R^6 and A may have the meanings given in claims 1-5, characterised in that compounds of general formula 1 wherein X denotes NH_2

- 15 a) are reacted with a base and a corresponding alkylating agent, in a polar organic solvent, to form compounds of general formula 1 wherein X denotes $NH-(C_1-C_6\text{-alkyl})$ or $N(C_1-C_6\text{-alkyl})_2$, or
- b) are reacted with aldehydes or ketones, with cooling, in the presence of acids,
20 and the Schiff bases or iminium salts thus formed as intermediates are subsequently reduced with metal hydrides to form compounds of general formula 1 wherein X denotes $NH-(C_1-C_6\text{-alkyl})$ or $N(C_1-C_6\text{-alkyl})_2$, or
- c) are reacted, in the presence of a base, with an acid chloride or anhydride to
25 form compounds of general formula 1 wherein X denotes $NHCO(C_1-C_6\text{-alkyl})$,

or

- d) the compounds of formula 1 wherein X denotes $\text{NHCO}(\text{C}_1\text{-C}_6\text{-alkyl})$, obtained according to step c), are then optionally reduced with metal hydrides, using Lewis acids as catalysts, to obtain compounds of general formula 1 wherein X denotes $\text{NH}-(\text{C}_1\text{-C}_6\text{-alkyl})$ or $\text{N}(\text{C}_1\text{-C}_6\text{-alkyl})_2$, or
- e) are converted at elevated temperature into the compounds of general formula 1 wherein X denotes NHCOH by reacting with formic acid, or
- f) are reacted by diazotisation and subsequent decoction with BF_4^- to form the compounds of formula 1 wherein X denotes F.