(11) Application No. AU 2001230192 B2

(19) AUSTRALIAN PATENT OFFICE

(54) Title
Method for the enzymatic resolution of the racemates of aminomethyl-aryl-cyclohexanol derivatives

(51)6 International Patent Classification(s)
C12P 41/00 060408BMEP
(2006.01) C12P 13/00
C12P 13/00 20060101ALI20
(2006.01) 060408BMEP
C12P 41/00 PCT/EP01/0052
20060101AFI20 2

(21) Application No: 2001230192 (22) Application Date: 2001.01.18

(87) WIPO No: WO01/57232

(30) Priority Data

(31) Number	(32) Date	(33) Country
10004926	2000.02.04	DE

(43) Publication Date : 2001.08.14
(43) Publication Journal Date : 2001.10.25

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(56) Related Art
Angew Chem., 1992, 104(9), pp. 1254-1255
Tetrahedron Asymmetry, 9, 19998, pp. 513-520
Bioflavour 95, 1995, pp. 345-349

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

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
9. August 2001 (09.08.2001)

PCT

(10) Internationale Veröffentlichungsnummer
WO 01/57232 A1

(51) Internationale Patentklassifikation[7]: C12P 41/00, 13/00 // C12N 9/18, 9/20

(21) Internationales Aktenzeichen: PCT/EP01/00522

(22) Internationales Anmeldedatum:
18. Januar 2001 (18.01.2001)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
100 04 926.5 4. Februar 2000 (04.02.2000) DE

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(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *mit internationalem Recherchenbericht*
— *mit geänderten Ansprüchen*

Veröffentlichungsdatum der geänderten Ansprüche:
10. Januar 2002

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT Gazette verwiesen.

WO 01/57232 A1

(54) **Title:** METHOD FOR THE ENZYMATIC RESOLUTION OF THE RACEMATES OF AMINOMETHYL-ARYL-CYCLOHEXANOL DERIVATIVES

(54) **Bezeichnung:** VERFAHREN ZUR ENZYMATISCHEN RACEMATSPALTUNG VON AMINOMETHYL-ARYL-CYCLOHEXANOL-DERIVATEN

(57) **Abstract:** The invention relates to a method for the enzymatic resolution of the racemates of aminomethyl-aryl-cyclohexanol derivatives.

(57) **Zusammenfassung:** Die Erfindung betrifft ein Verfahren zur enzymatischen Racematspaltung von Aminomethyl-Aryl-Cyclohexanol-Derivaten.

Patent Application by Grünenthal GmbH, D-52078 Aachen (in-house reference G 3004)

Process for the enzymatic cleavage of racemates of aminomethyl-aryl-cyclohexanol derivatives

The invention relates to a process for the enzymatic cleavage of racemates of aminomethyl-aryl-cyclohexanol derivatives.

Treatment of chronic and non-chronic states of pain is of great importance in medicine. There is a worldwide need for highly effective therapies of pain for the patient-specific, well-directed treatment of chronic and non-chronic states of pain which is to be understood as the successful and satisfactory pain treatment of the patient. This is documented in the large number of scientific papers which in the last few years have been published in the field of applied analgesics and basic research in nociception.

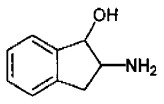
Tramadol hydrochloride -(1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride - is a well-known therapeutic for treatment of severe pain. Aminomethyl-aryl-cyclohexanol derivatives such as tramadol ((1RS,2RS)-2-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexanol hydrochloride) can accordingly have an analgesic effect, but this holds also for hydroxylated tramadol derivatives, as, e.g. in EP 753506 A1, or they can be used as intermediates for the preparation of substances having an analgesic effect (such as e.g. 4- or 5-substituted tramadol analogues, which are described in EP 753 506 A1 or EP 780 369 A1). It is tramadol which is peculiar among centrally effective analgesics as this active compound brings about extensive

inhibition of pain without the side effects known for opioids (J. Pharmacol. Exptl. Ther. 267, 331 (1993)); both the enantiomers of tramadol and the enantiomers of tramadol metabolites contribute to the analgesic effect (J. Pharmacol. Exp. Ther. 260, 275 (1992)).

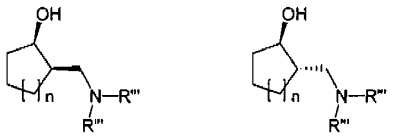
As can be seen from this, enantiomers can have significantly different effects, and it is very important in many respects to be able to separate racemates into enantiomerically pure forms as intermediates or in regard to approvals under drug legislation.

Enzymatic transformations now belong to the basic operations of preparative organic chemistry. Numerous industrial processes with enzymatic basic steps which now go far beyond enzymatic cleavage of racemates of amino acids have become established in the meantime. A more up-to-date review of the use of enzymes in the preparation of biologically active compounds is given by Roberts and Williamson (S.M. Roberts, N.M. Williamson, *Current Organic Chemistry*, **1997**, volume *1*, 1-20).

Luana et al. (A. Luna, A. Maestro, C. Astorga, V. Gotor, *Tetrahedron: Asymmetry* **1999**, *10*, 1969-1977) describe the enzymatic cleavage of racemates via transesterification of cyclic α-aminoalcohols using lipases and vinyl acetate as the acyl donor. This publication is of importance since it is shown that substrates with an aminoalcohol functionality can be used.



Forró and Fülöp (E. Forró, F. Fülöp, *Tetrahedron: Asymmetry* **1999**, *10*, 1985-1993, E. Forró, L. Kanerva, F. Fülöp, *Tetrahedron: Asymmetry* **1998**, *9*, 513-520) describe the enzymatic cleavage of racemates of reduced cyclic Mannich bases of the following type:



cis trans

where n = 1,2,3 and R''' = alkyl, alkylaryl, cycloalkyl

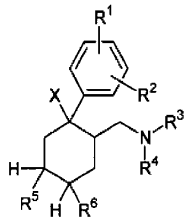
The authors make reference to tramadol in the introduction, and in the introductory text refer to the use of these compounds as units for substances possibly having an analgesic effect.

In the development of enzymatic processes, in addition to the suitable enzyme system, finding suitable reaction parameters is decisive for the success of the process.

Preparation of enantiomerically pure aminomethyl-aryl-hexanol derivatives, in particular 4- or 5-hydroxylated tramadol derivatives, via fractional crystallization of diastereomeric salts, such as e.g. tartrates, dibenzoyltartrates or dobenzoyltartrates, to date has not been successful. Preparative chromatographic processes can be employed only in certain cases for providing enantiomerically pure compounds on a multigram scale. Also suitable chromatographic conditions of preparative separation have not yet been found.

The object of the present invention was therefore to determine suitable processes for enantiomerically pure separation of the enantiomers of aminomethyl-aryl-hexanol derivatives, in particular 4- or 5-hydroxylated tramadol derivatives - and this also on a larger scale.

The invention therefore relates to processes for the enzymatic cleavage of racemates of aminomethyl-aryl-cyclohexanol derivatives of the general formula I



I

wherein X is chosen from

H, F, Cl, Br, I, CF_3, $O\text{-}S(O_2)\text{-}C_6H_4\text{-}pCH_3$, OR^{14} or $OC(O)R^{14}$, wherein R^{14} is chosen from

H; C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by N, S or O; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

R^3, R^4 independently of one another are chosen from

H, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by N, S or O; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

or

R^3 and R^4 together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or NR^{15}, where R^{15} is chosen from

H, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted;

R^1 and R^2 independently of one another are either H or any desired substituent

and

in each case one of the substituents R^5 and R^6 corresponds to H and the other corresponds to OH, characterized in that, depending on the desired enantiomer of the aminomethyl-aryl-cyclohexanol derivatives of the general formula I

either in reaction alternative I,

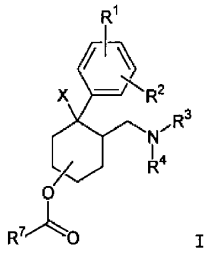
the racemate of compounds according to formula I is first esterified and then converted enzymatically and the enantiomerically pure compounds formed are separated,

or in reaction alternative II,

the racemate of compounds according to formula I is converted enzymatically in the presence of an ester and the resulting enantiomerically pure compounds are separated.

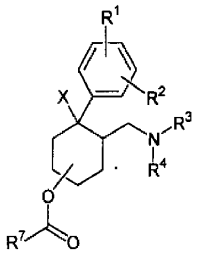
These processes utilize in particular the fact that reaction alternatives I and II are to be regarded as complementary processes, since in the enzymatic conversion of the racemic mixture, the respective opposite stereochemistry is induced.

In reaction alternative I, a racemic compound according to formula II

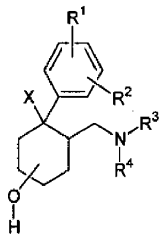


II

in which the substituent $OC(O)R^7$ corresponds to the position of R^5 or R^6 in formula I and R^7 is chosen from C_1-C_6-alkyl, unsubstituted or mono- or polysubstituted; as the free base or in the form of its salt, is converted enzymatically in a solvent with a lipase or esterase and the resulting enantiomerically pure compounds of formulae III and Ia are separated



III



Ia

wherein compounds according to formula Ia correspond to compounds according to formula I and the substituent OH corresponds to the position of R^5 or R^6 in formula I.

It is particularly preferable in reaction alternative I if R^7 in formulae II and III is chloroacetyl, butyl or pentyl.

An esterase, in particular a pig liver esterase, is preferably used as the enzyme in reaction alternative I.

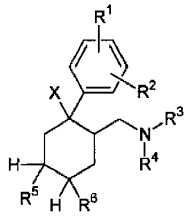
The preferred solvent in reaction alternative I is an aqueous buffer system, which preferably has a pH between 6.0 and 8.0 - preferably a pH between 7.0 and 7.5. It is also advantageous in this context if the solvent is an aqueous buffer system with a physiological pH for the enzyme used. It is particularly advantageous if one or more organic solvents, preferably acetone or butanol, are added to the aqueous buffer system up to a percentage content by volume of between 1 and 50%, preferably 5 and 20%, in particular 20%.

It is furthermore preferable, in particular in the case of an aqueous buffer system, to use the compound according to formula II as hydrochloride salt in reaction alternative I.

It is of particular importance in this context that particularly in the enzymatic hydrolysis of the butyric acid ester of 4-hydroxytramadol, but also in other cases involving reaction alternative I - specifically with an aqueous buffer system -, the use of the salt, in particular the hydrochloride, rather than the base can lead to better results. A sufficient amount of the base is often not soluble in the aqueous buffer system. It is furthermore particularly noteworthy that a significant improvement of the process, particularly with the hydrochloride, can be observed if acetone and butanol are added. This holds particularly for the reaction rate. In particular, addition of acetone or butanol to the aqueous buffer in an amount as high as 5 to 20%, preferably 20%, of the total volume is often optimal in regard to selectivity and reaction rate.

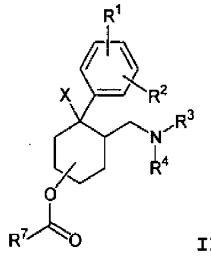
The use of amino-hydrochlorides in enzymatic separations to date has not been described in the prior art.

To prepare the ester of the compounds according to formula II in reaction alternative I, racemic compounds according to formula I



I

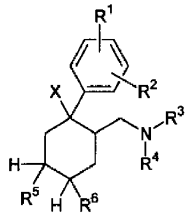
are converted with bases, preferably potassium tert-butylate or sodium hydride, in a solvent, preferably tetrahydrofuran or dimethylformamide, into the alcoholates and subsequently converted, by addition of corresponding acid halides, into the racemic esters according to formula II



II

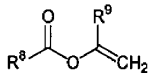
in which the substituent $OC(O)R^7$ corresponds to the position of R^5 or R^6 in formula I. Preferably esters according to formula II can be prepared in this way.

In reaction alternative II, a racemic compound according to formula I



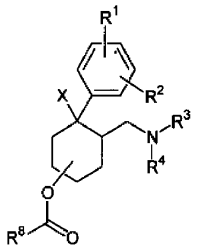
I

employed as the free base or in the form of its salt in a solvent, is converted with an ester according to formula IV

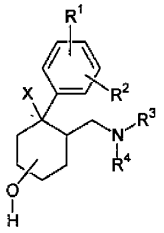


IV

wherein, independently of one another, R^8 denotes C_1-C_6-alkyl, substituted or unsubstituted; and R^9 denotes H or C_1-C_6-alkyl, substituted or unsubstituted, together with a lipase or esterase and the resulting enantiomerically pure compounds according to formulae V and Ib



V



Ib

are separated, wherein compounds according to formula Ib correspond to compounds according to formula I and the substituent OH corresponds to the position of R^5 or R^6 in formula I.

It is particularly preferable if, in reaction alternative II, R^8 in the esters according to formulae IV and V denotes methyl or ethyl and/or R^9 according to formula IV denotes H or methyl.

In particular, the ester according to formula IV is preferably vinyl propionate, vinyl acetate or isopropenyl acetate.

A lipase, in particular a lipase from *Candida rugosa*, *Candida cylindracea* or *Pseudomonas cepacia*, is preferably used as the enzyme in reaction alternative II.

Furthermore, it proved to be particularly advantageous to use an organic solvent, preferably toluene, as the solvent in reaction alternative II.

The easily achievable separation of the enantiomerically pure compounds after conclusion of the enzymatic conversion is an essential advantage of the process according to the invention in both reaction alternatives. The ester/alcohol mixtures are separated by pH-selective extraction after conclusion of the enzymatic conversion. Advantageously, a chromatographic separation can be omitted. By establishing a suitable pH, the ester and alcohol can be separated from one another by extraction, in particular by pH-selective extraction, in view of sufficiently different log P values. Scaling-up is therefore possible without problems and is particularly easy to carry out on an industrial scale.

The enzymatic processes found in the two reaction alternatives represent at the present time the only possibility of preparing aminomethyl-aryl-cyclohexanol derivatives, in particular hydroxylated tramadol derivatives, on a multigram scale with adequate purity of the enantiomers.

Overall, but in particular in the ester cleavage according to reaction alternative I, the conversion can be conducted to up to almost 50% without drastic reduction of the

selectivity, which happens in many comparable enzymatic cleavages of racemates. Over-hydrolysis was not observed under the reaction conditions used.

It is furthermore particularly preferable that the substituents R^1 and R^2 in the formulae I, Ia, Ib, II, III and V independently of one another are chosen from R^{10} or YR^{10}, where Y = C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, branched or unbranched and mono- or polysubstituted or unsubstituted, wherein R^{10} is chosen from

H, F, Cl, Br, I, CN, NO_2, C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

OR^{11}, $OC(O)R^{11}$, $OC(O)OR^{11}$, $OC(S)R^{11}$, $C(O)R^{11}$, $C(O)OR^{11}$, $C(S)R^{11}$, $C(S)OR^{11}$, SR^{11}, $S(O)R^{11}$ or $S(O_2)R^{11}$, wherein R^{11} is chosen from

H, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl or C_2-C_{18}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted; or

$NR^{12}R^{13}$, $C(O)NR^{12}R^{13}$ or $S(O_2)NR^{12}R^{13}$, wherein R^{12} and R^{13} independently of one another are chosen from

H, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl or C_2-C_{18}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

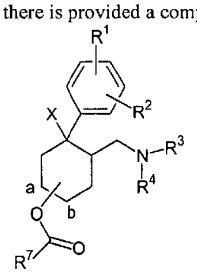
or

R^{12} and R^{13} together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N;

or

R^1 and R^2 together form -CH=CH-CH=CH-, wherein the naphthyl system formed can be mono- or polysubstituted.

In an aspect of the invention there is provided a compound according to formula II



II

wherein X is chosen from

H, F, Cl, Br, I, CF_3, $O\text{-}S(O_2)\text{-}C_6H_4\text{-}pCH_3$, OR^{14} or $OC(O)R^{14}$, wherein R^{14} is chosen from

H; C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by N, S or O; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

R^3, R^4 independently of one another are chosen from

H, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by N, S or O; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

or

R^3 and R^4 together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or NR^{15}, where R^{15} is chosen from

H, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted;

R^1 and R^2 independently of one another are either H or some substituent,

the substituent $OC(O)R^7$ at position **a** or **b** is connected to the hexane ring according to formula II

and

R^7 is selected from C_1-C_6-alkyl, unsubstituted or mono- or polysubstituted; as free base or in the form of its salt.

The following definitions apply to the full description of the entire invention described herein, and in particular also to the sections and definitions of radicals presented above, unless explicitly defined otherwise.

In connection with alkyl, alkenyl, alkinyl and cycloalkyl or the "corresponding heterocyclic radical", the term substituted in the context of this invention is understood as replacement of a hydrogen radical by F, Cl, Br, I, NH_2,

SH or OH, with polysubstituted radicals to be understood as radicals which are polysubstituted both at different and at identical atoms, for example, trisubstituted at the same C atom, as in the case of CF_3, or at different points, as in the case of $-CH(OH)-CH=CH-CHCl_2$.

Furthermore, -C(O)- denotes

which also applies to -C(S)- or -S(O)- or $-S(O_2)-$.

The term "C_1-C_8-alkyl" or "C_1-C_{10}-alkyl" in the context of this invention means hydrocarbons having 1 to 8 or 10 carbon atoms respectively. Examples which may be mentioned are methyl, ethyl, propyl, isopropyl, n-butane, sec-butyl, tert-butyl, n-pentane, neopentyl, n-hexane, n-heptane, n-octane, n-nonane or n-decane.

The term "C_1-C_{18}-alkyl" in the context of this invention means hydrocarbons having 1 to 18 carbon atoms. Examples which may be mentioned are methyl, ethyl, propyl, isopropyl, n-butane, sec-butyl, tert-butyl, n-pentane, neopentyl, n-hexane, n-heptane, n-octane, n-nonane, n-decane, n-undecane, n-dodecane, n-dodecane, n-tridecane, n-tetradecane, n-pentadecane, n-hexadecane, n-heptadecane or n-octadecane, unsubstituted or mono- or polysubstituted.

The term "C_2-C_{10}-alkenyl" or "C_2-C_{10}-alkinyl" or "C_2-C_{18}-alkenyl" or "C_2-C_{18}-alkinyl" in the context of this invention means hydrocarbons having 2 to 8 or 2 to 18 carbon atoms, respectively. Examples which may be cited are propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, unsubstituted or mono- or polysubstituted, or

propinyl, butinyl, pentinyl, hexinyl, heptinyl, octinyl, unsubstituted or mono- or polysubstituted.

The term C_3-C_7-cycloalkyl in the context of this invention means cyclic hydrocarbons having 3 to 7 carbon atoms. Examples which may be cited are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl or cycloheptenyl, saturated or unsaturated and substituted or mono- or polysubstituted. A "corresponding heterocyclic radical" in the context of the invention is understood as a C_3-C_7-cycloalkyl in which at least one C atom in the ring is replaced by S, O or N. Pyrrolidine, pyran, thiolane, piperidine or tetrahydrofuran may be cited as examples.

The term "aryl" in the context of this invention means phenyls, naphthyls or anthracenyls. The aryl radicals can also be condensed with additional rings.

The term "heteroaryl" in the context of this invention means aromatic compounds which are optionally provided with a ring system joined by condensing and contain at least one heteroatom from the group consisting of nitrogen, oxygen and/or sulfur. Thiophene, furan, pyrrole, pyridine, pyrimidine, quinoline, isoquinoline, phthalazine or quinazoline may be cited as examples of this group.

The term "alkylaryl" or "alkylheteroaryl" in the context of this invention means aryls or heteroaryls substituted at least by C_1-C_6-alkylene, wherein the terms aryl, heteroaryl and alkyl have the same meaning as above, with bonding established via the alkyl radical.

In relation to "aryl", "alkylaryl", "heteroaryl" or "alkylheteroaryl", in the context of this invention mono-

or polysubstituted is understood as substitution of the ring system by F, Cl, Br, I, NH_2, SH, OH, CF_3; =O or =S; mono- or polysubstituted or unsubstituted C_1-C_6-alkyl, C_1-C_6-alkoxy, C_2-C_8-alkenyl, C_2-C_8-alkinyl; phenyl or benzyl; on one or various atoms.

It is particularly advantageous if R^1 in formulae I, Ia, Ib, II, III and V is R^{10}, wherein R^{10} is chosen from

H, F, Cl, Br, I, CF_3, NO_2, NH_2; C_1-C_4-alkyl or C_2-C_4-alkenyl, branched or unbranched and mono- or polysubstituted or unsubstituted; OR^{11}, $C(O)OR^{11}$ or SR^{11}, wherein R^{11} is chosen from

H; C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted; preferably H, CF_3 or CH_3,

or $S(O_2)NR^{12}R^{13}$, wherein R^{12} and R^{13} independently of one another are chosen from

H; C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted;

wherein R^1 is particularly preferably chosen from H, F, Cl, OH, CH_3, C_2H_5, C_2H_3, CF_3, SCH_3, OCF_3, OCH_3, OC_2H_5, $C(O)OCH_3$, $C(O)OC_2H_5$, preferably m-OCH_3.

In particular, the substituent R^2 in formulae I, Ia, Ib, II, III and V can be R^{10}, wherein R^{10} is chosen from

H, F, Cl, Br, I, SCH_3; C_1-C_4-alkyl, C_2-C_4-alkenyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CF_3; OR^{11}, where R^{11} is chosen from C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CH_3;

wherein R^2 particularly preferably = H.

It is furthermore particularly preferable if X in the formulae I, Ia, Ib, II, III and V is selected from

H, F, Cl, OH, CF_3, $O-S(O_2)-C_6H_4-pCH_3$ or $OC(O)R^{12}$ where R^{12} = H; C_1-C_4-alkyl or C_2-C_4-alkenyl, branched or unbranched and mono- or polysubstituted or unsubstituted,

preferably H, F, Cl, OH, $O-S(O_2)-C_6H_4-pCH_3$, $OC(O)R^{12}$, where

R^{12} = C_1-C_4-alkyl, preferably CH_3;

wherein X is particularly preferably OH, F or Cl, preferably OH.

It is furthermore a preferred subject matter of the invention to select R^3 and R^4 in formulae I, II, III and V independently of one another from

C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CH_3,

or

R^3 and R^4 together to form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, wherein R^3 and R^4 particularly preferably each denote CH_3.

The invention furthermore provides intermediate products according to formula II. The definition of the cited radicals R^1-R^4 and X and R^7 has already been given above, as well as a preferred preparation process for products according to formula II in the context of reaction alternative I. The compounds according to formula II are very suitable analgesics and can be employed also for other indications. They are therefore suitable, in the form of their diastereomers or enantiomers and their free base or a salt formed with a physiologically tolerated acid, in particular the hydrochloride salt, for the preparation of a drug for treatment of pain, in particular migraine, acute pain and neuropathic or chronic pain, of inflammatory and

allergic reactions, depression, drug and/or alcohol abuse, gastritis, cardiovascular diseases, respiratory tract diseases, coughing, mental illness and/or epilepsy, and in particular of urinary incontinence, itching and/or diarrhoea.

The invention is explained below in more detail by examples, without limiting it thereto.

Examples

The following examples show processes according to the invention.

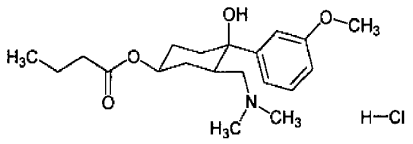
The following specifics generally apply in these:

The chemicals and solvents employed were obtained commercially from the conventional suppliers (Acros, Avocado, Aldrich, Fluka, Lancaster, Maybridge, Merck, Sigma, TCI etc.) or synthesized.

Example 1

Preparation of the carboxylic acid esters of hydroxy-tramadols

(1SR,3RS,4RS)-Butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester hydrochloride (**rac-1**)



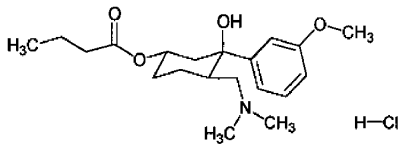
250 g (0.89 mol) (1RS,2RS,4SR)-2-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,4-diol **rac-2** were suspended in 2,500 ml dried tetrahydrofuran, and 226 g potassium *tert*-butylate (2.01 mol) were added in portions, while cooling in an ice-bath such that the internal temperature did not exceed 30°C. When the addition had ended the mixture was subsequently stirred at room temperature for one more hour. 127 ml (130.3 g, 1.22 mol) butyric acid chloride were then added, while cooling in an ice-bath, with the internal temperature between 5 and 10°C. After the addition had been completed, the mixture was stirred at room temperature for a further 15 hours. For hydrolysis, 1,187 ml of a 1 molar aqueous sodium bicarbonate solution were added dropwise, with renewed cooling in an ice-bath. After separation of the phases, the aqueous phase was extracted two more times with 500 ml ethyl acetate. The combined organic phases were dried over sodium sulfate. After removal of the solvent by distillation, the residue (277.4 g) was converted into the hydrochloride. For this, the 277.4 g of crude product were dissolved in a solvent mixture comprising 270 ml ethanol and 1,350 ml acetone.

After addition of one molar equivalent of trimethylchlorosilane and one molar equivalent of water, the hydrochloride separated by crystallization. After the mixture had been left to stand at 15°C for 15 hours, the precipitate was filtered by suction and, after drying, 273.2 g hydrochloride could be obtained with 89% yield.

Example 2

Preparation of carboxylic acid esters of hydroxy-tramadols

(1SR,3RS,4RS)-Butyric acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester hydrochloride (**rac-3**)

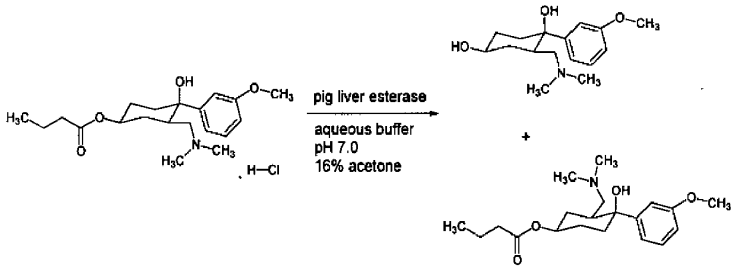


In analogy to the preparation of (1SR,3RS,4RS)-butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester hydrochloride **rac-1**, the ester **rac-3** could be obtained with a yield of 85% from (1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol **rac-4**.

Example 3:

Enzymatic ester hydrolysis

Pig liver esterase-catalysed hydrolysis of (1SR,3RS,4RS)-butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester hydrochloride (**rac-1**)



(-)-(1R,3S,4S)-Butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester (**(-)-1**)

and

(+)-(1R,2R,4S)-2-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,4-diol (**(+)-2**)

72 g (0.19 mol) (1SR,3RS,4RS)-butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester hydrochloride **rac-1** were dissolved in 620 ml aqueous phosphate buffer solution, pH 7 (Merck, art. no. 1.09439.100), and 140 ml acetone were added. After the mixture had been stirred for 10 minutes, a clear solution formed. 0.62 g pig liver esterase (Chirazyme E1 from Roche Diagnostics, lyophilisate, 40 units/mg) and 150 ml of a 1 molar aqueous sodium bicarbonate solution were then added as a single portion so that pH 7.5 developed. The reaction mixture was stirred at room temperature for 21 hours. In order to terminate the reaction, the buffer system was extracted twice with 450 ml diisopropyl ether each time and twice with a solvent mixture of diisopropyl ether and diethyl ether in the ratio 1 : 1 each time; only the ester passed into the organic phase under these conditions and

the hydrolysed alcohol remained in the aqueous phase because of the different logP value (see table 1).

In order to isolate the ester **(-)-1**, the combined organic phases were washed once with 400 ml of a 1 molar aqueous sodium carbonate solution and dried over sodium sulfate. After removal of the solvent by distillation, 30.4 g of crude product (93% of theory) comprising (-)-(1R,3S,4S)-butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester **(-)-1** were obtained. The crude base ($[\alpha]_D^{22}$= -12.0° (c = 1.02, methanol)) was taken up in 300 ml of a solvent mixture comprising ethanol and 2-butanone in the ratio 1 : 9, and 11.0 ml trimethylchlorosilane and 1.57 ml water were added. 3.6 g (10% of theoretical value) of the hydrochloride crystallized with an **ee** value of 4.8%. After separation, the mother liquor was concentrated. After liberation of the base with sodium carbonate and extraction with ethyl acetate, drying over sodium sulfate and removal of the solvent by distillation, 23.9 g (73% of theoretical value) (-)-(1R,3S,4S)-butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester **(-)-1** could be obtained with an **ee** value of 100% (determined by chiral HPLC). (-)-(1S,2S,4R)-2-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,4-diol **(-)-2** could be obtained therefrom with quantitative yield by alkaline ester hydrolysis with potassium hydroxide in ethanol (organic chemistry lab instruction).

For isolation of (+)-(1R,2R,4S)-2-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,4-diol **(+)-2**, the aqueous phase of the ester hydrolysis was brought to pH 5.0 with 2 molar hydrochloric acid. The solvent was removed from the solution adjusted in this way at a bath temperature of 60°C

and under a pressure of 650 mbar to 150 mbar. The residue was then adjusted to pH 10.0 with 2 molar aqueous sodium carbonate solution and the mixture was extracted three times with 100 ml ethyl acetate each time. The combined organic phases were dried over sodium sulfate. After removal of the solvent by distillation, 26.0 g (100% of the theoretical value) crude product could be obtained. The crude base was taken up in 270 ml of a solvent mixture consisting of ethanol and 2-butanone in the ratio 1 : 9, and 12.2 ml trimethylchlorosilane and 1.73 ml water were added; the hydrochloride of (+)-(1R,2R,4S)-2-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,4-diol **(+)-2** crystalled with a yield of 78% (23.1 g) and an **ee** value of 96.3% (according to chiral HPLC) ($[\alpha]_D^{22}$ = +36.5° (c = 1.06, methanol)).

The following table 1 shows the pKa values and logP values of the compounds **1** and **2**.

Table 1: pKa values and logP values of compounds **1** and **2**.

	Compound **1** (ester)	Compound **2** (alcohol)
pKa value	8.796	9.055
logP value: water/octanol	2.898	1.101
logP value: water/cyclohexane	2.360	-0.632
logD value at pH 7.4 water/octanol	1.484	-0.564
logD value at pH 7.4 water/cyclohexane	0.946	-2.297
ΔlogP value at pH 7.4	0.538	1.733
ΔlogD value at pH 7.4	0.538	1.733

The following table 2 shows the dependence of the **ee** value of the ester and alcohol as a function of the reaction time by way of example.

Table 2: Dependency of the **ee** value of the ester and alcohol as a function of the reaction time (quanity and **ee** value of compounds **1** and **2** were determined by means of chiral HPLC):

Time in hours	Ester content in % [1]	(+)-Ester content[2] (in %)	(-)-Ester content[2] (in %)	% ee value of the (-)-ester [3]
3	91.2	40.8	50.4	10.5
19	68.6	17.7	50.9	48.4
24	64.4	14.0	50.4	56.6
28	62.2	11.4	50.9	63.4
	Alcohol content in % [1]	(-)-Alcohol content[2] (in %)	(+)-Alcohol content[2] (in %)	% ee value of the (+)-alcohol [3]
3	8.8	0.4	8.4	91.6
19	31.4	0.5	30.9	96.6
24	35.6	0.7	35.0	96.2
28	37.8	0.7	37.1	96.5

1) percentage content of ester or alcohol refers to the total content of ester and alcohol determined in the reaction mixture; 2) the percentage content of enantiomeric esters or alcohols refers to the content of ester and alcohol in the entire mixture ((+)-enantiomer (ester) + (-)-enantiomer (ester) + (+)-enantiomer (alcohol) + (-)-enantiomer (alcohol) = 100%; 3) the percentage **ee** value was determined according to the following equation: % excess enantiomer - % deficit enantiomer/% excess enantiomer + % deficit enantiomer.

The dependence of the % **ee** value of the alcohol **(+)-2** on the amount of acetone added is shown in table 3:

Table 3: Dependence of the % **ee** value of the alcohol **(+)-2** on the amount of acetone added (1.5 mmol ester **rac-1** as the hydrochloride were dissolved in 5 ml phosphate buffer pH 7.0 (Merck), and 1.2 ml of a 1 molar aqueous sodium bicarbonate solution were added; the amount of enzyme added was 5.0 mg Chirazyme E1 of the company Roche Diagnostics; the mixture was stirred in each case for 19 hours at room temperature; further processing was carried out as described in example 1)

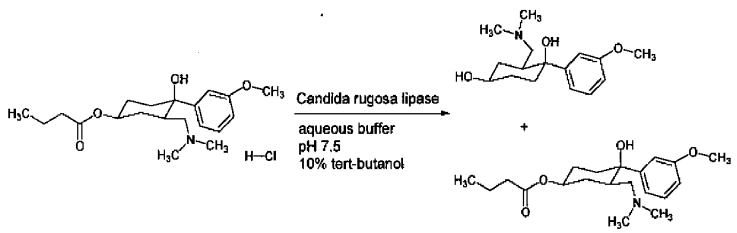
Addition of acetone (ml, %)	Total ester content[1] (in %)	% **ee** value of the (-)-ester[2]	Total alcohol content[1] (in %)	% **ee** value of the (+)-alcohol[2]
0 ml, 0%	46.1	90.7	53.9	72.5
0.6 ml, 9%	50.8	97.6	49.2	89.8
1.0 ml, 13.5%	56.8	85.7	43.3	96.9
1.2 ml, 16%	55.6	94.2	44.4	95.5

1) the percentage content of the enantiomeric esters or alcohols refers to the content of ester and alcohol in the entire mixture ((+)-enantiomer (ester) + (-)-enantiomer (ester) to (+)-enantiomer (alcohol) + (-)-enantiomer (alcohol); 2) the percentage **ee** value was determined in accordance with the following equation: % excess enantiomer - % deficit enantiomer/% excess enantiomer + % deficit enantiomer.

Example 4:

Enzymatic ester hydrolysis

Lipase-catalysed hydrolysis of (1SR,3RS,4RS)-butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester (**rac-1**)



(+)-(1S,3R,4R)-butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester (**(+)-1**)

and

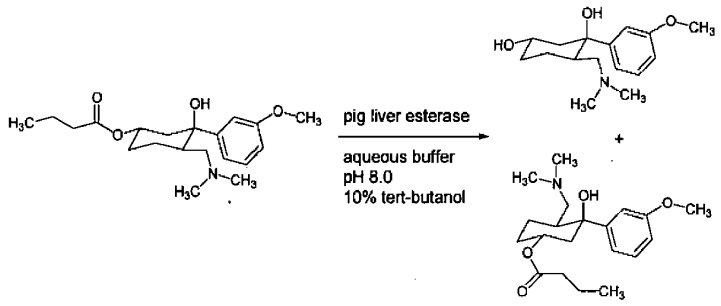
(-)-(1S,2S,4R)-2-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,4-diol (**(-)-2**)

As described in example 3, enzymatic hydrolysis of **rac-1** using the lipase *Candida rugosa* (Fluka) in an aqueous buffer system at pH 7.5 with the use of 10% tert-butanol leads to an opposite asymmetric induction after a reaction time of 24 hours at room temperature. After a conversion of 28%, the alcohol **(-)-2** could be isolated with an **ee** value of 89% and the ester **(+)-1** with an **ee** value of 37% (E = 24).

Example 5:

Enzymatic ester hydrolysis

Pig liver esterase-catalysed hydrolysis of (1SR,3RS,4RS)-butyric acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester hydrochloride (**rac-3**)



(+)-(1R,3S,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol (**(+)-4**)

and

(-)-(1R,3S,4S)-Butyric acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester (**(-)-3**)

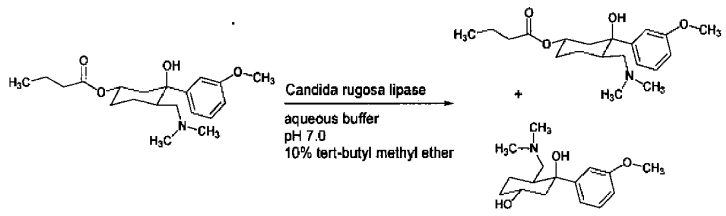
As described in example 3, enzymatic hydrolysis of **rac-3** using pig liver esterase in an aqueous buffer system at pH 8.0 and the use of 10% tert-butanol lead to a conversion of 40% after a reaction time of 6 hours at room temperature. It was possible in this manner to obtain the ester **(-)-3** with a yield of 79% and an **ee** value of 86% ($[\alpha]_D^{22}$ = -6.0° (c = 0.81, methanol)) and the alcohol **(+)-4** with a yield of

77% and an **ee** value of 94% ($[\alpha]_D^{22}$ = +21.7° (c = 0.80, methanol)) (E = 46).

Example 6:

Enzymatic ester hydrolysis

Lipase-catalysed hydrolysis of (1SR,3RS,4RS)-butyric acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester hydrochloride (**rac-3**)



(-)-(1S,3R,6S)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol (**(-)-4**)

and

(+)-(1S,3R,4R)-Butyric acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester (**(+)-3**)

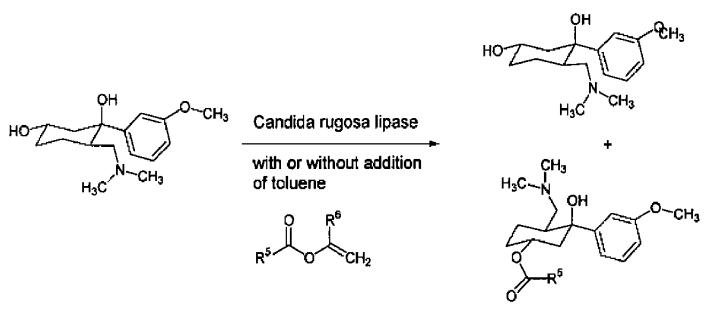
In analogy to what has been described in example 3, enzymatic hydrolysis of **rac-3** using the lipase *Candida rugosa* in an aqueous buffer system at pH 7.0 and the use of 10% tert-butyl methyl ether leads to a conversion of 45% after a reaction time of 6 hours at room temperature. It was possible in this manner to obtain the ester **(+)-3** with a yield of 80% and an **ee** value of >99% ($[\alpha]_D^{22}$ = +7.5° (c =

0.74, methanol)) and the alcohol **(-)-4** with a yield of 79% and with an **ee** value of >99% ($[\alpha]_D^{22}$ = -29.5° (c = 1.01, methanol)) (E > 200).

Example 7:

Enzymatic transacylation in organic solvents

Lipase-catalysed transacylation of (1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol **rac-4** with various acylating reagents to render esters **5** and **6**



a) $R^5 = CH_2CH_3$, $R^6 = H$

b) $R^5 = CH_3$, $R^6 = H$

C) $R^5 = CH_3$, $R^6 = CH_3$

(1R,3S,6R)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol **(+)-4**

and

$R^5 = CH_3$: (-)-(1R,3S,4S)-Acetic acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester **(-)-5**

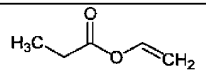
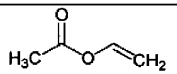
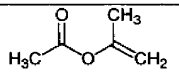
or

R^5 = CH_2CH_3: (-)-(1R,3S,4S)-Propionic acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester **(-)-6**

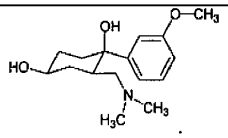
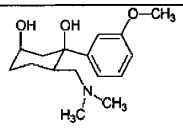
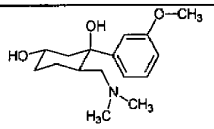
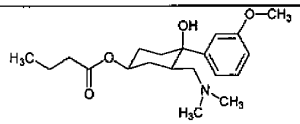
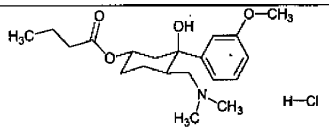
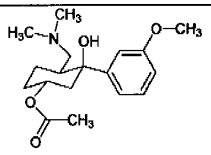
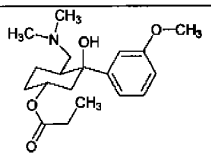
For the transacylation, 70 mg (0.25 mmol) (1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol **rac-4** were placed in a solvent mixture consisting of toluene and the transacylating reagent or the transacylating agent proper was used as the solvent, and the mixture was first stirred at room temperature for two hours. After addition of the lipase *Candida rugosa* (5 mg, 185 units), the mixture was stirred at room temperature for 5 to 9 days. In order to separate the enzyme, the mixture was filtered over silica gel. The alcohol and ester were separated from one another as described in example 1 and isolated. The results are summarized in table 4.

Instead of the lipase *Candida rugosa*, the lipases *Candida cylindracea* or *Pseudomonas cepacia* were also employed in an analogous manner.

Table 4: Results of the enzymatic transacylation of (1RS,3SR,6RS)-6-dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol **rac-4**

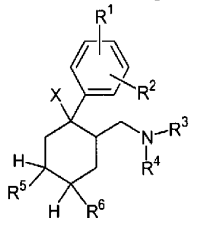
Example no.	Transacylating reagent, solvent	Reaction time (days)	Conversion (%)	Ester	% **ee** value of the ester	Alcohol	% **ee** value of the alcohol	E value
5a	 1.25 mmol propionic acid vinyl ester in 5 ml toluene	9	48	**(-)-6**	87	**(+)-4**	68	30
5b	 53.75 mmol acetic acid vinyl ester without addition of toluene	7	56	**(-)-5**	91	**(+)-4**	97	89
5c	 1.5 mmol acetic acid isopropenyl ester in 5 ml toluene	5	34	**(-)-5**	99	**(+)-4**	60	>200

Nomenclature - Table

Formula	Nomenclature
	(1RS,2RS,4SR)-2-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,4-diol
	(1RS,3RS,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol
	(1RS,3SR,6RS)-6-Dimethylaminomethyl-1-(3-methoxy-phenyl)-cyclohexane-1,3-diol
	(1SR,3RS,4RS)-Butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester
	(1SR,3RS,4RS)-Butyric acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester
	(-)-(1R,3S,4S)-Acetic acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester
	(-)-(1R,3S,4S)-Propionic acid 4-dimethylaminomethyl-3-hydroxy-3-(3-methoxy-phenyl)-cyclohexyl ester

The claims defining the invention are as follows:

1. A process for the stereoselective enzymatic cleavage of racemates of aminomethyl-aryl-cyclohexanol derivatives of the general formula I



I

wherein X is chosen from

H, F, Cl, Br, I, CF_3, O-S(O_2)-C_6H_4-pCH_3, OR^{14} or $OC(O)R^{14}$, wherein R^{14} is chosen from

H; C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by N, S or O; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

R^3, R^4 independently of one another are chosen from

H, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by N, S or O; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

or

R^3 and R^4 together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or NR^{15}, where R^{15} is chosen from

H, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted;

R^1 and R^2 independently of one another are chosen from R^{10} or YR^{10}, where Y = C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl,

branched or unbranched and mono- or polysubstituted or unsubstituted, wherein R^{10} is chosen from

H, F, Cl, Br, I, CN, NO_2, C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

OR^{11}, $OC(O)R^{11}$, $OC(O)OR^{11}$, $OC(S)R^{11}$, $C(O)R^{11}$, $C(O)OR^{11}$, $C(S)R^{11}$, $C(S)OR^{11}$, SR^{11}, $S(O)R^{11}$ or $S(O_2)R^{11}$, wherein R^{11} is chosen from

H, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl or C_2-C_{18}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted; or

$NR^{12}R^{13}$, $C(O)NR^{12}R^{13}$ or $S(O_2)NR^{12}R^{13}$, wherein R^{12} and R^{13} independently of one another are chosen from

H, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl or C_2-C_{18}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

or

R^{12} and R^{13} together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N;

or

R^1 and R^2 together form -CH=CH-CH=CH-, wherein the naphthyl system formed can be mono- or polysubstituted

and

in each case one of the substituents R^5 and R^6 corresponds to H and the other corresponds to OH, characterized in that, depending on the desired enantiomer of the aminomethyl-aryl-cyclohexanol derivatives of the general formula I

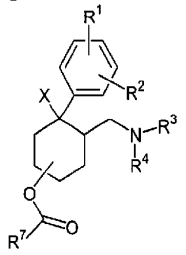
either in reaction alternative 1

the racemate of compounds according to formula I is first esterified and then converted enzymatically and the resulting enantiomerically pure hydroxy compound and alkanoyl derivative are separated,

or in reaction alternative II

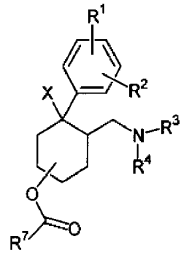
the racemate of compounds according to formula I is converted enzymatically in the presence of an ester and the resulting enantiomerically pure hydroxy compound and alkanoyl derivative are separated.

2. The process according to claim 1, characterized in that, in reaction alternative 1, a racemic compound according to formula II

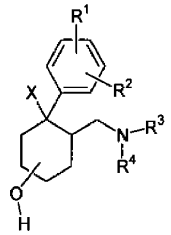


II

in which the substituent $OC(O)R^7$ corresponds to the position of R^5 or R^6 in formula I and R^7 is chosen from C_1-C_6-alkyl, unsubstituted or mono- or polysubstituted; as the free base or in the form of its salt is converted enzymatically in a solvent with a lipase or esterase and the resulting enantiomerically pure compounds, according to formulae III and Ia



III



Ia

where compounds according to formula Ia correspond to compounds according to formula I and the substituent OH corresponds to the position of R^5 or R^6 in formula I, are separated.

3. The process according to claim 2, characterized in that R^7 is chloroacetyl, butyl or pentyl.

4. The process according to any one of claims 2 or 3, characterized in that the enzyme used is an esterase, preferably a pig liver esterase.

5. The process according to any one of claims 2 to 4, characterized in that an aqueous buffer system, preferably with a pH between 6.0 and 8.0 - preferably a pH between 7.0 and 7.5 - is used as the solvent.

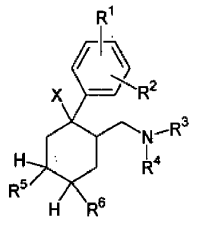
6. The process according to any one of claims 2 to 5, characterized in that an aqueous buffer system, preferably with a pH which is physiological for the enzyme used, is used as the solvent.

7. The process according to any one of claims 5 or 6, characterized in that one or more organic solvents, preferably acetone or butanol, are added to the

aqueous buffer system up to a volume percentage of 1 to 50%, preferably 5 to 20%.

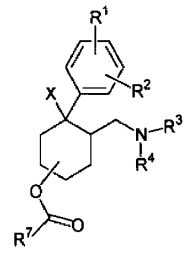
8. The process according to any one of claims 2 to 7, characterized in that the compound according to formula II is employed as hydrochloride salt.

9. The process according to any one of claims 2 to 8, characterized in that the compounds according to formula II employed are prepared by a process in which racemic compounds according to formula I



I

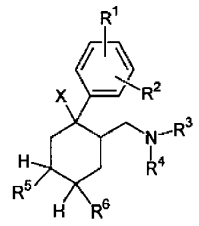
are converted with bases, preferably potassium tert-butylate or sodium hydride, in a solvent, preferably tetrahydrofuran or dimethylformamide, into the alcoholates and, subsequently, upon addition of the corresponding acid halides, converted into the racemic esters according to formula II



II

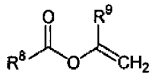
in which the substituent $OC(O)R^7$ corresponds to the position of R^5 or R^6 in formula I.

10. The process according to claim 1, characterized in that, in reaction alternative II, a racemic compound according to formula I



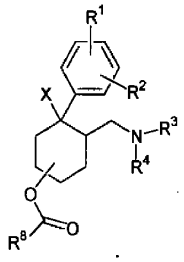
I

is employed as free base or in the form of its salt in a solvent with an ester according to formula IV

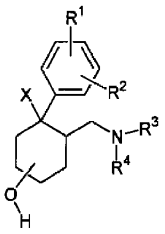


IV

wherein, independently of one another, R^8 denotes C_1-C_6-alkyl, substituted or unsubstituted; and R^9 denotes H or C_1-C_6-alkyl, substituted or unsubstituted, is converted enzymatically with a lipase or esterase, and the resulting enantiomerically pure compounds according to formulae V and Ib



V



Ib

wherein compounds according to formula Ib correspond to compounds according to formula I and the substituent OH corresponds to the position of R^5 or R^6 in formula I, are separated.

11. The process according to claim 10, characterized in that in the esters according to formulae IV and V, R^8 denotes methyl or ethyl and/or R^9 of formula IV denotes H or methyl.

12. The process according to any one of claims 10 or 11, characterized in that the ester according to formula IV is vinyl propionate, vinyl acetate or isopropenyl acetate.

13. The process according to any one of claims 10 to 12, characterized in that the enzyme used is a lipase, preferably a lipase from *Candida rugosa*, *Candida cylindracea* or *Pseudomonas cepacia*.

14. The process according to any one of claims 10 to 13, characterized in that an organic solvent, preferably toluene, is used as the solvent.

15. The process according to any one of claims 1 to 14, characterized in that the ester/alcohol mixtures are

separated by pH-selective extraction after conclusion of the enzymatic conversion.

16. The process according to any one of claims 1 to 15, characterized in that R^1 and R^2 of formulae I, Ia, Ib, II, III and V independently of one another are chosen from R^{10} or YR^{10}, where Y = C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, branched or unbranched and mono- or polysubstituted or unsubstituted, wherein R^{10} is chosen from

H, F, Cl, Br, I, CN, NO_2, C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

OR^{11}, $OC(O)R^{11}$, $OC(O)OR^{11}$, $OC(S)R^{11}$, $C(O)R^{11}$, $C(O)OR^{11}$, $C(S)R^{11}$, $C(S)OR^{11}$, SR^{11}, $S(O)R^{11}$ or $S(O_2)R^{11}$, wherein R^{11} is chosen from

H, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl or C_2-C_{18}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each

case mono- or polysubstituted or unsubstituted; or

$NR^{12}R^{13}$, $C(O)NR^{12}R^{13}$ or $S(O_2)NR^{12}R^{13}$, wherein R^{12} and R^{13} independently of one another are chosen from

H, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl or C_2-C_{18}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

or

R^{12} and R^{13} together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N;

or

R^1 and R^2 together form -CH=CH-CH=CH-, wherein the resulting naphthyl system can be mono- or polysubstituted.

17. The process according to any one of claims 1 to 16, characterized in that $R^1 = R^{10}$, wherein R^{10} is chosen from

H, F, Cl, Br, I, CF_3, NO_2, NH_2; C_1-C_4-alkyl or C_2-C_4-alkenyl, branched or unbranched and mono- or

polysubstituted or unsubstituted; OR^{11}, $C(O)OR^{11}$ or SR^{11}, wherein R^{11} is chosen from

H; C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted; preferably H, CF_3 or CH_3,

or $S(O_2)NR^{12}R^{13}$, wherein R^{12} and R^{13} independently of one another are chosen from

H; C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted;

wherein R^1 is particularly preferably chosen from H, F, Cl, OH, CH_3, C_2H_5, C_2H_3, CF_3, SCH_3, OCF_3, OCH_3, OC_2H_5, $C(O)OCH_3$, $C(O)OC_2H_5$, preferably m-OCH_3.

18. The process according to any one of claims 1 to 17, characterized in that $R^2 = R^{10}$, wherein R^{10} is chosen from

H, F, Cl, Br, I, SCH_3; C_1-C_4-alkyl, C_2-C_4-alkenyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CF_3; OR^{11}, where R^{11} is chosen from C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CH_3;

wherein R^2 = H is particularly preferred.

19. The process according to any one of claims 1 to 18, characterized in that X is chosen from

H, F, Cl, OH, CF_3, $O-S(O_2)-C_6H_4-pCH_3$ or $OC(O)R^{12}$ where R^{12} = H; C_1-C_4-alkyl or C_2-C_4-alkenyl, branched or unbranched and mono- or polysubstituted or unsubstituted,

preferably H, F, Cl, OH, $O-S(O_2)-C_6H_4-pCH_3$, $OC(O)R^{12}$ where R^{12} = C_1-C_4-alkyl, preferably CH_3;

wherein X = OH, F or Cl is particularly preferred.

20. The process according to any one of claims 1 to 19, characterized in that R^3 and R^4 independently of one another are chosen from

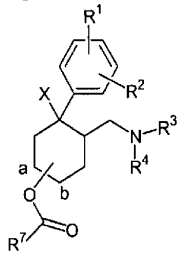
C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CH_3,

or

R^3 and R^4 together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted,

wherein R^3 and R^4 particularly preferably in each case denote CH_3.

21. A compound according to formula II



II

wherein X is chosen from

H, F, Cl, Br, I, CF_3, O-S(O_2)-C_6H_4-pCH_3, OR^{14} or $OC(O)R^{14}$, wherein R^{14} is chosen from

H; C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by N, S or O; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

R^3, R^4 independently of one another are chosen from

H, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by N, S or O; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

or

R^3 and R^4 together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or NR^{15}, where R^{15} is chosen from

H, C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted;

R^1 and R^2 independently of one another are either H or some substituent,

the substituent $OC(O)R^7$ at position **a** or **b** is connected to the hexane ring according to formula II

and

R^7 is selected from C_1-C_6-alkyl, unsubstituted or mono- or polysubstituted; as free base or in the form of its salt.

22. The compound according to Claim 21, characterised in that R^1 and R^2 in formula II independently of one another are chosen from R^{10} or YR^{10}, where Y = C_1-C_{10}-alkyl, C_2-C_{10}-alkenyl or C_2-C_{10}-alkinyl, branched or unbranched and mono- or polysubstituted or unsubstituted, wherein R^{10} is chosen from

H, F, Cl, Br, I, CN, NO_2, C_1-C_8-alkyl, C_2-C_8-alkenyl or C_2-C_8-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

OR^{11}, $OC(O)R^{11}$, $OC(O)OR^{11}$, $OC(S)R^{11}$, $C(O)R^{11}$, $C(O)OR^{11}$, $C(S)R^{11}$, $C(S)OR^{11}$, SR^{11}, $S(O)R^{11}$ or $S(O_2)R^{11}$, wherein R^{11} is chosen from

H, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl or C_2-C_{18}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted; or

$NR^{12}R^{13}$, $C(O)NR^{12}R^{13}$ or $S(O_2)NR^{12}R^{13}$, wherein R^{12} and R^{13} independently of one another are chosen from

H, C_1-C_{18}-alkyl, C_2-C_{18}-alkenyl or C_2-C_{18}-alkinyl, in each case branched or unbranched and mono- or polysubstituted or unsubstituted; C_3-C_7-cycloalkyl,

saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N; alkylaryl or alkylheteroaryl, saturated or unsaturated and mono- or polysubstituted or unsubstituted; aryl or heteroaryl, in each case mono- or polysubstituted or unsubstituted;

or

R^{12} and R^{13} together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted, or a corresponding heterocyclic radical in which a C atom in the ring is replaced by S, O or N;

or

R^1 and R^2 together form -CH=CH-CH=CH-, wherein the naphthyl system formed can be mono- or polysubstituted.

23. The compound according to any one of Claims 21 or 22, characterised in that $R^1 = R^{10}$, wherein R^{10} is chosen from

H, F, Cl, Br, I, CF_3, NO_2, NH_2; C_1-C_4-alkyl or C_2-C_4-alkenyl, branched or unbranched and mono- or polysubstituted or unsubstituted; OR^{11}, $C(O)OR^{11}$ or SR^{11}, wherein R^{11} is chosen from

H; C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted; preferably H, CF_3 or CH_3,

or $S(O_2)NR^{12}R^{13}$, wherein R^{12} and R^{13} independently of one another are chosen from

H; C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted;

wherein R^1 is particularly preferably chosen from

H, F, Cl, OH, CH_3, C_2H_5, C_2H_3, CF_3, SCH_3, OCF_3, OCH_3, OC_2H_5, $C(O)OCH_3$, $C(O)OC_2H_5$, preferably m-OCH_3.

24. The compound according to any one of Claims 21 to 23, characterised in that $R^2 = R^{10}$, wherein R^{10} is chosen from

H, F, Cl, Br, I, SCH_3; C_1-C_4-alkyl, C_2-C_4-alkenyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CF_3; OR^{11}, where R^{11} is

chosen from C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CH_3;

wherein R^2 = H is particularly preferred.

25. The compound according to any one of Claims 21 to 24, characterised in that X is chosen from

H, F, Cl, OH, CF_3, O-S(O_2)-C_6H_4-pCH_3 or OC(O)R^{12} where R^{12} = H; C_1-C_4-alkyl or C_2-C_4-alkenyl, branched or unbranched and mono- or polysubstituted or unsubstituted,

preferably H, F, Cl, OH, O-S(O_2)-C_6H_4-pCH_3, OC(O)R^{12} where R^{12} = C_1-C_4-alkyl, preferably CH_3;

wherein X = OH, F or Cl is particularly preferred.

26. The compound according to any one of Claims 21 to 25, characterised in that R^3 and R^4 independently of one another are chosen from

C_1-C_4-alkyl, branched or unbranched and mono- or polysubstituted or unsubstituted, preferably CH_3,

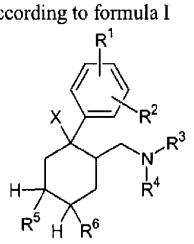
or

R^3 and R^4 together form a C_3-C_7-cycloalkyl, saturated or unsaturated and mono- or polysubstituted or unsubstituted,

wherein it is particularly preferred that R^3 and R^4 each stand for CH_3.

27. The compound according to any one of Claims 21 to 26, characterised in that it is (1SR,3RS,4RS)-butyric acid 3-dimethylaminomethyl-4-hydroxy-4-(3-methoxy-phenyl)-cyclohexyl ester, particularly the hydrochloride.

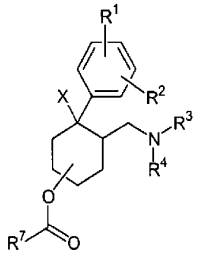
28. A process for preparing a compound according to any one of claims 21 to 27, in which racemic compounds according to formula I



I

converted with bases, preferably potassium tert-butylate or sodium hydride, in a solvent, preferably tetrahydrofuran or dimethylformamide, into the alcoholates and

subsequently converted, by addition of the corresponding acid halides, into the racemic esters according to formula II



II

in which the substituent $OC(O)R^7$ corresponds to the position of R^5 or R^6 in formula I.

29. Drugs containing a compound according to any one of Claims 21 to 27 in the form of their diastereomers or enantiomers, as well as their free base or salt formed with a physiologically tolerated acid, particularly the hydrochloride salt.

30. Use of a compound according to any one of claims 21 to 27, in the form of their diastereomers or enantiomers, as well as their free base or one of their salts formed with a physiologically tolerated acid, particularly the hydrochloride salt, for preparing a drug for the treatment of pain, particularly migraine, acute pain as well as neuropathic or chronic pain, of inflammatory and allergic reactions, depression, drug and/or alcohol abuse, gastritis, cardiovascular disease and/or epilepsy, as well as, in particular, urin incontinence, itching and/or diarrhoea.

31. A process according to claim 1 substantially as hereinbefore described with reference to any one of examples 3 to 7.

32. A hydroxyl compound when prepared by the process of any one of claims 1 to 20 or 31.

33. An alkanoyl derivative when prepared by the process of any one of claims 1 to 20 or 31.

34. A compound according to claim 21 substantially as hereinbefore described with reference to any one of examples 1 to 7.

35. A process according to claim 28 substantially as hereinbefore described with reference to example 1 or example 2.

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36. A compound according to claim 21 when made by the process of claim 28 or claim 35.

Dated 8 May, 2006
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