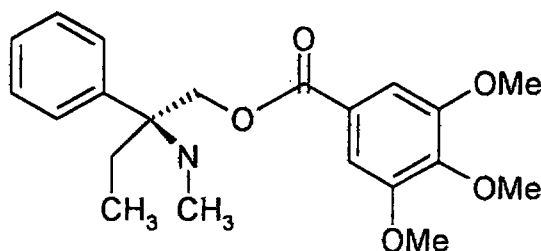


(S) 2-Methylamino-2-phenyl-n-butyl 3,4,5-trimethoxy
benzoate, its application to the treatment
of chronic pain

5 Field of the invention

The subject of the present invention is optically pure
(S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxy-
benzoate (I) of formula



10

its addition salts with pharmaceutically acceptable
acids, their preparation and their therapeutic applica-
tion in the form of medicaments to the treatment of
15 chronic pain of various etiologies.

Technological background of the invention

Pain is a complex subjective phenomenon comprising a
20 sensation reflecting a real or potential tissue lesion
and the affective response which it generates. In the
first place, pain is described as acute or chronic
according to its intensity and its duration. Thus, pain
lasting for more than 6 months is described as chronic
25 pain. In addition to this first differentiation, pain is
classified in many ways, a summary of which can be found
on p. 1422 and subsequent pages of the Merck Manual
(French ed. 1988 - Merck and Co., INC.). A particularly
major problem is that of the treatment of chronic pain.
30 Conventionally, it is treated with compounds with
so-called analgesic activity which eliminate pain while
preserving the patient's conscious state and sensitive

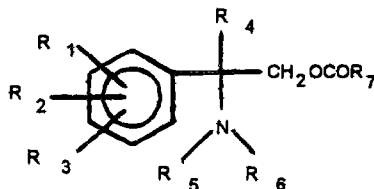
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perceptions. Essentially, these compounds belong to the nonsteroidal anti-inflammatory class (NSAID) or to the opiate analgesics and are chosen and administered to patients according to the intensity of the pain felt and the duration of the treatment envisaged. It is known that these compounds cause undesirable side effects, in particular during prolonged treatments such as precisely those necessary for chronic pain, which requires a frequent therapeutic check up, which often places excessive constrain on the patient. Thus, the NSAIDs which, in the arachidonic cascade, decrease the synthesis of prostaglandins and of algogenic thromboxanes by inhibition of cyclooxygenases, are known to be able to cause serious, in particular gastrointestinal and hematological, side effects (The Pharmacological Basis of Therapeutics - Gooddman & Gilman - 9th ed. p. 617-655). Furthermore, the opiate analgesics, in addition to central effects (respiratory depression, nausea and vomiting) or peripheral effects (gastrointestinal transit) are known to cause drug dependence phenomena (ibid. p. 521-555 and p. 557-577).

To this day, a major problem therefore exists, the resolution of which has been quite unsatisfactory, for the treatment of chronic painful conditions which, in various forms, affect a considerable number of people including for example, according to the World Health Organization, 4 million cancer sufferers who, worldwide, suffer as a result of a lack of suitable care. In addition to cancer, in the area of pain or of chronic painful syndrome with a somatic and psychological component, there are a number of conditions such as musculoskeletal or vertebral pain, neurological pain, headaches or vascular pain.

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In the context of the compounds of the prior art related to the product of the invention, British Patent GB 1,434,826 published on 5 May 1976 claims esters and carbamates of racemic amino alcohols and among them a family of esters of formula (II)



in which, more particularly:

R'₁, R'₂, R'₃ are hydrogens

R'₄ is a C₁ to C₄ alkyl

10 R'₅ and R'₆, which are similar or different, are hydrogen or a C₁ to C₄ alkyl

R'₇ is aryl optionally substituted with 1 to 3 groups chosen from a set comprising, inter alia, a C₁ to C₄ alkoxy radical.

15

These esters, in addition to motility- and gastrointestinal transit-inhibiting properties and local anesthetic properties, are said to comprise analgesic and anti-inflammatory compounds which may be useful in the treatment of pain in digestive disorders. Moreover, in the Japanese Patent Application published under the No. 16416/1980 on 1 May 1980, there is described and claimed a process for the preparation of 2-dimethylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate, whose racemate is trimebutine (INN) with spasmolytic activity (Patent 25 FR 2,369M - 1962). The Japanese application also exemplifies the synthesis of the (+) and (-) enantiomers by the claimed process without mentioning any activity of the compounds.

30

The study of the metabolism of trimebutine maleate leads to the identification, in addition to other metabolites,

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of (R,S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate (Magaribuchi, T. et al. Oyo Yakuri (1982), 24 (5), 625-9). This compound, administered by the i.v. route, is shown to inhibit gastric motility in rats and to reduce blood pressure and to lower the heart rate.

Additional studies of this racemic metabolite, called NDTMB for N-demethyltrimebutine, demonstrate:

- 10 - in vitro, an agonist affinity for the μ type opiate receptors, an affinity which is more moderate for the κ and δ type opiate receptors, which affinities confirm the activity of the studied products on gastrointestinal motility via the peripheral opiate receptors (Roman F. et al. J. Pharm. Pharmacol. (1987), 39 (5), 404-7). Without
- 15 any marked specificity for a subtype, this opiate affinity is confirmed (Pascaud, X. et al., Gastroenterol. Clin. Biol. (1987), 11 (3), 77B-81B),
- in vivo, in dogs, administered by the oral route or the
- 20 i.v. route, it is established that NDTMB participates in the effects of trimebutine on the gastrointestinal and colic motilities (Bueno, L. et al., Gastroenterol. Clin. Biol. (1987), 11 (3), 90B-93B). By the oral route in dogs, NDTMB promotes emptying of the stomach, an effect
- 25 which is inhibited by κ antagonists, which suggests the effect of the product by local stimulation of the κ receptors of the mucous membrane or submucous membrane at the antroduodenal level (Gué, M. et al., J. Pharm. Pharmacol. (1988), 40 (12), 873-5).

30

As reported, the prior art most closely related to the subject of the invention is (R,S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate, a known metabolite of trimebutine. Up until now, the studies carried out on

35 this metabolite demonstrate activities similar to those

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of its precursor, which leads to the metabolite being credited with participation in the overall effect of trimebutine, reported to be a musculotropic antispasmodic compound which modifies the digestive motility, involving
5 a peripheral encephalinergic agonist activity which stimulates the intestinal motility and makes it possible to inhibit it after stimulation (Vidal pharmaceutical dictionary - 1997 ed. - p. 434). Thus, the racemate, a parent compound of the (S) enantiomer which is the
10 subject of the invention, is potentially useful, like trimebutine, in the treatment of functional disorders of the gastrointestinal tract and of the bile ducts and, consequently, in relieving patients of the painful manifestations resulting from these disorders.

15

As regards the study of the compounds having affinity for the opiate receptors, when the compound has an asymmetric carbon atom, thereby generating two enantiomers with opposite absolute configuration (R or S) and their
20 equimolecular mixture called (R,S) racemate, it is known that the affinity is stereospecific, that is to say preferential for one of the enantiomers. By convention, the enantiomer with the highest affinity for the receptors is called eutomer as opposed to the less active
25 or even inactive enantiomer called distomer.

Trimebutine and its metabolite NDTMB comprise the same asymmetric carbon atom and are racemic mixtures. Potentially, in relation to the opiate receptors, they both
30 have a eutomeric form having an identical absolute configuration given the nature of the substituents of the asymmetric carbon atom which does not allow inversion of configuration and also due to the fact that the N-demethylation does not modify this configuration
35 determined according to the Cahn Ingold and Prelog rules. However, while the enantiomers of trimebutine were

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prepared as mentioned in Patent JP 16416/1980, those of its metabolite, NDTMB, are new. Given the advantageous properties of the racemates and of the likelihood of eutomeric forms for these products, the Applicant has undertaken the in vitro and in vivo study of these compounds, enantiomers and racemates.

The work reported in this report has shown particularly surprisingly that the enantiomer of (S) configuration of the metabolite NDTMB, established as a distomer in the light of its affinity for the opiate receptors, exhibits, in vivo, particularly advantageous analgesic properties for application in the treatment of chronic pain. Indeed, in spite of its low affinity for the opiate receptors compared with its (R) antipode, this enantiomer proves, in animals, to be a potent analgesic, lacking opiate side effects, in pharmacological models which are representative of chronic pain.

Summary of the invention

The invention relates to optically pure (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate, its addition salts with pharmaceutically acceptable acids, and the process for preparing them.

According to another aspect, the invention relates to medicinal compositions comprising these compounds, their preparation and their therapeutic application in the treatment of chronic pain of various etiologies.

Detailed description of the invention

In a first aspect, the invention relates to the optically pure (S) 2-methylamino-2-phenyl-n-butyl

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3,4,5-trimethoxybenzoate and its addition salts with pharmaceutically acceptable acids.

By optically pure, there is understood that, in addition
5 to the chemical purity established according to pharmaceutical industry standards, the compound is substantially purified from its (R) antipode, which means that for a minimum optical purity, the product according to the invention contains at least 90% by weight of (S)
10 enantiomer or, expressed differently, contains less than 10% of undesirable (R) enantiomer. In any case, the preferred optical purity corresponds to that of a compound according to the invention containing at least 99% by weight of (S) enantiomer or, at most, 1% by weight
15 of (R) enantiomer which is considered as an optical impurity, these levels being determined by appropriate analytical methods.

By addition salts with pharmaceutically acceptable acids,
20 an extensive list of these acids will be found in J. Pharm. Sci., 1977, 66, 1-19. These inorganic or organic acids are recognized as being nontoxic, such as for example hydrobromic, hydrochloric, sulfuric, phosphoric, nitric, acetic, succinic, tartaric, citric, maleic,
25 hydroxymaleic, benzoic, fumaric, toluenesulfonic and isethionic acids and the like. However, the hydrochloric, maleic and tartaric acids are preferred, especially the natural L(+) isomer of tartaric acid.

30 The invention also relates to a process for the preparation of the compound of the invention and of its salts. The process for the preparation of (S) 2-methyl-amino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate consists either in preparing the racemic mixture and then in
35 resolving it, or, according to the preferred process, in

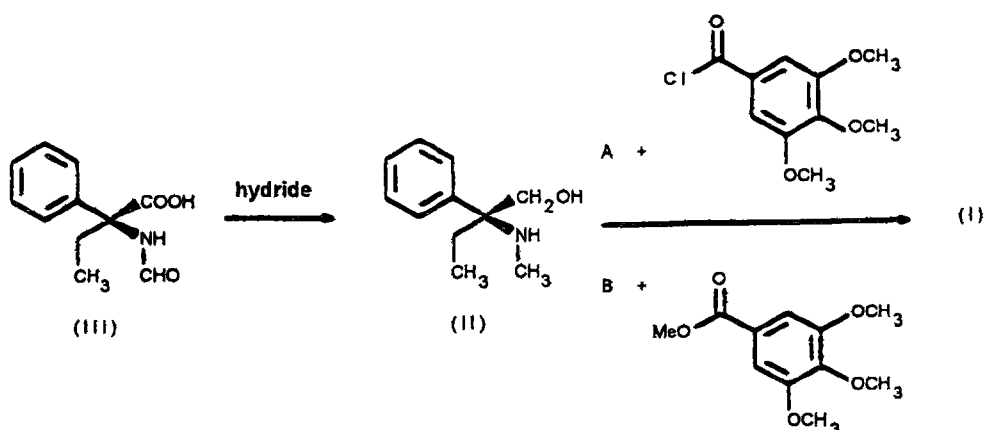
carrying out its chemical synthesis from enantiomeric precursors of (S) configuration.

5 The process involving resolution of the racemic compound consists in using an optically active acid to obtain with the racemic compound treated two diastereoisomeric addition salts which are separated and from which there is generated, by an appropriate treatment, the enantiomer of (S) configuration, eutomer for the purposes of and
10 according to the subject of the invention, and also for a comparative study of its distomeric (R) antipode. It is also possible to use a method for direct resolution of the racemic compound by liquid chromatography on a chiral column.

15

However, the preferred method of preparation of (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate is that by chemical synthesis from precursors of (S) configuration which essentially consists, as shown in
20 diagram 1:

- in reducing, with a complex hydride derived from boron or aluminum, (S) 2-formylamino-2-phenyl-n-butyric acid (III) in order to obtain (S) 2-methylamino-2-phenyl-n-butanol (II),
- 25 - in esterifying the amino alcohol (II) with a reagent chosen from 3,4,5-trimethoxybenzoyl chloride according to a procedure A and methyl 3,4,5-trimethoxybenzoate according to a procedure B in order to obtain (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate
30 (I).



The subject of the invention is also the use, as medicament, of the compound (I) of the invention and of its salts, as well as the compositions in which these products are used as active ingredients and which are intended for the preparation of medicinal forms useful for the treatment of chronic pain.

As previously stated, the Applicant has undertaken studies to determine the stereospecificity of the affinity for the opiate receptors of the (R) and (S) enantiomers of the metabolite NDTMB compared with the latter which is a racemate and with the precursor, namely trimebutine TMB. This in vitro study reveals a preferential affinity for the (R) configuration, eutomer in this trial with a eudismic ratio in relation to the antipode of 0.3 to 0.4 on the various μ , δ and κ subtypes, or in other words the affinity of the (R) eutomer is 2.5 to 3 times higher than the (S) antipode for these receptors. Moreover, the respective affinities of the TMB and NDTMB racemates are not very different, the affinity of NDTMB being, however, lower for the δ and κ subtypes.

Continuing the in vivo study, the Applicant used NDTMB and the (R) and (S) enantiomers in tests which are recognized as being representative of chronic pain, such as:

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- the analgesic activity on the (tardive) tonic painful phase caused by injecting a formaldehyde solution into the leg in mice,
- the analgesic activity on chronic hyperalgesia induced by PGE2 in rats.

The results of the tests show surprisingly that the (S) enantiomer, which has a lower affinity for the opiate receptors, possesses, according to the tests, an analgesic activity equal to or greater than the racemic NDTMB and its (R) antipode, which activity should be considered to be particularly advantageous since it is only very partially of an opiate nature. Indeed, in contrast to the other two compounds, the analgesic effect of the (S) enantiomer is only partially inhibited by naloxone, which is known as an antagonist of the so-called opiate analgesics, especially of those with μ affinity. Further study of the product on models representative of specific chronic pain such as neuropathic pain caused by ligation of the sciatic nerve or pain caused by experimental diabetes induced by streptozocin in rats, and also behavioral study in rats in which an inflammatory pain has been triggered by carrageenin confirm this advantage. Finally, the (S) enantiomer shows no morphine-type withdrawal effect unlike its (R) antipode, when used in a test reputed to reveal dependence phenomena following repeated administration of opiate drugs.

Considering these in vivo studies and these analgesic properties, the (S) enantiomer which is the subject of the invention is, in contrast to the in vitro receptor study presented above, the eutomer as regards the application to the treatment of chronic pain such as for example during osteoarthritis, polyarthritis, spondylarthritis, postsurgical pain, trauma, painful

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sequela of zona, polyneuropathy, amputation of a limb and also vascular conditions such as arteritis or varicose ulcer.

5 The compound of the invention and/or one of its salts is administered to the patient in a medicinal form adapted to the nature and the seriousness of the condition to be treated. The daily dosage in humans is usually between 2 mg and 1.0 g of active ingredient which may be taken in
10 single or divided doses. Compositions prepared according to techniques which are common for persons skilled in the art comprise from 0.5 to 75% by weight of active ingredients and from 99.5 to 25% of appropriate excipients which are chemically and physically compatible
15 with the active ingredient so as to obtain medicinal forms adapted to the route of administration envisaged. As nonlimiting examples, tablets, sugar-coated tablets, capsules, suppositories, gels for local application or in occlusive supports, solutions for injections or
20 administration by the oral route, are prepared.

More precisely, as regards the process for the preparation of the compound of the invention,

- by resolution of the racemate:

25 a) as regards the method of resolution via diastereoisomeric salts, it consists in reacting the racemate, in an appropriate solvent, with an optically active acid so as to form two diastereoisomers which are separated by the difference in their solubility in the solvent. The
30 diastereoisomer with the lowest solubility precipitates and it is isolated by filtration. The salts separated may be recrystallized from selective solvents to give a satisfactory optical purity or they may be treated in a basic medium in order to regenerate the respective
35 enantiomers. These may then be purified by recrystallization or used in a second purification step

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by forming new diastereoisomers, optionally with an optically active acid different from the preceding one. The enantiomers of acids commonly used for the preparation of diastereoisomeric salts are, by way of
5 nonlimiting examples, those of α -phenylglycine, α -phenylalanine and their N-carboxylated derivatives, of malic acid, of mandelic acid, of tartaric acid and their esterification derivatives with acids, or alternatively camphanic acid, 3-bromo-8-camphorsulfonic acid and its
10 position isomers, α -methoxy- α -trifluoromethylphenylacetic acid. The enantiomers of these acids are commercially available and their use has been documented; they are therefore appropriate for the resolution of the racemate or the purification of any mixture enriched with one of
15 the enantiomers.

The preparation of the diastereoisomeric salts consists in reacting, for one mol of racemate or of mixture to be separated or purified, from 0.25 to 2.00 mol of the acid enantiomer in solution in a solvent or a mixture of
20 solvents which are preferably completely or partially miscible with water, and which are usually chosen from alcohols, ketones, low-molecular-weight ethers or acetonitrile.

Preferably, the reaction is carried out in solution in
25 ethanol, methanol or acetone by reacting, for one mol of product to be treated, from 0.5 to 1.25 mol of acid enantiomer, at a temperature between 20°C and that of the boiling temperature of the solvent used, which is generally preferred. The salification is complete after a
30 period of between 5 minutes and 3 hours. After that, the reaction mixture is left, first at room temperature, and then optionally at around 0°C in order to crystallize the least soluble diastereoisomer, which crystallization is optionally facilitated by seeding with crystals of the
35 expected salt. Upon completion of the crystallization or at a time which is judged to be appropriate in order to

obtain the desired optical purity, the crystallized diastereoisomer is separated by filtration. The two phases, each containing a diastereoisomer purified to a greater or lesser degree, are treated separately, either
5 for purification of the salts, or for release of the enantiomer from its salt, which is carried out by an alkaline treatment in aqueous medium, followed by filtration or extraction of the enantiomer released.

b) As regards the resolution of the racemate or the
10 purification of any mixture of enantiomers by column liquid chromatography, various chiral or nonchiral supports can be used for this separation.

Thus, an appropriate method is adapted from that described in the publication JP 05215736 and consists in
15 using, as stationary phase, carboxylic esters of polysaccharide such as the phase Chiralcel OJ (supplier Diacel Chem.) and in carrying out the elution using a mixture of a buffer solution (for example HClO_4 - NaClO_4 , 0.1 M) with a water-miscible organic solvent such as
20 acetonitrile.

- by chemical synthesis from precursors of (S); the (S) enantiomer and the (R,S) racemic mixture of 2-formyl-amino-2-phenyl-n-butyric acid are known and their preparation described (H. Sobotka et al., J of Am. Chem.
25 Soc., 54, 1932, p. 4697). To prepare these compounds, an advantageous adaptation of the process consists in reacting propiophenone with potassium cyanide and ammonium carbonate, by the Bucherer-Berg reaction, in order to obtain (+/-) 5-ethyl-5-phenylhydantoin which is
30 subjected, in an alkaline aqueous-acetone medium to a stereospecific salification with (R)- α -methylbenzylamine in order to obtain the addition salt with the (S) enantiomer of hydantoin, an insoluble salt which is filtered off and from which, by treatment with an acidic
35 solution, (S) 5-ethyl-5-phenylhydantoin is obtained in a

state of optical purity greater than 98% according to the process of patent EP 0,510,168.

The (S) enantiomer of hydantoin is conventionally hydrolyzed, in an alkaline aqueous medium at 140°C, in order to obtain (S) 2-amino-2-phenyl-n-butyric acid on which N-formylation is carried out by reacting with pure formic acid and acetic anhydride in order to obtain (S) 2-formylamino-2-phenyl-n-butyric acid (III).

(R) 2-Formylamino-2-phenyl-n-butyric acid and (R,S)-2-formylamino-2-phenyl-n-butyric acid are prepared respectively from the (R) antipode or the (R,S) racemate of 5-ethyl-5-phenylhydantoin.

As regards the simultaneous reduction of the carboxylic and amide functional groups of the intermediate (III) in order to obtain respectively the primary alcohol functional group and the secondary amine functional group of the amino alcohol (II), use is made of known methods and reagents which are summarized in the summary table presented in *Advanced Organic Chemistry* p. 1095 (J. March 3rd ed. 1985 McGraw Hill). Reducing agents such as derivatives of boron hydride and of aluminum hydride are recommended as being effective for carrying out these reactions, in particular lithium aluminum hydride and the borane-dimethyl sulfide (BSM in the remainder of this text) complex which is the preferred reagent.

The reductions are carried out in aprotic media which do not dissociate in solvents such as diethyl ether, diisopropyl ether, 1,2-dimethoxyethane or tetrahydrofuran (THF) which is preferred.

The BMS complex is used in a stoichiometric excess relative to the products to be reduced in order to obtain a complete reaction. Thus, 2 to 8 mols of BMS are used per mol of product to be treated, the preferred quantities being, however, from 4 to 6 mols of BMS per mol of compound (II).

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The product is subjected to reduction at the rate of 1 to 10 parts by weight in 100 parts by volume of THF and more particularly from 3 to 7 parts in 100, protected from moisture and under a nitrogen atmosphere. The quantity of BMS is introduced and then the mixture is heated under reflux in order to have a complete reaction, a duration, which may be between 30 minutes and 10 hours; however, a duration of 3 to 5 hours is more favorable. The amino alcohol is then released from its complex with the reducing agent by adding methanol and then sodium hydroxide and finally isolated by conventional processes described in the example presented.

As regards the esterification of the (S) precursor (II), the reaction, as presented above, may be carried out according to a procedure A which consists in carrying out the alcoholysis of 3,4,5-trimethoxybenzoyl chloride with the amino alcohol (II) in order to obtain the eutomer amino esters (I) according to various widely described techniques (Sonntag, *Chem. Rev.* 52, 237-416 (1953) pages 312 to 324) which consist, for example, in reacting the reagents in an aprotic anhydrous solvent such as benzene, toluene, diethyl ether, tetrahydrofuran, dioxane, acetone, acetonitrile, pyridine, dimethylformamide, methylene chloride or chloroform which is the preferred solvent. Optionally, an acid acceptor is added to the reaction medium. This agent may be inorganic or organic. Sodium or potassium carbonates, the corresponding bicarbonates or triethylamine or pyridine are used to this effect. An alternative method, which is preferred, consists in previously preparing *in situ* a metal alcoholate of the alcohols (II) which is then subjected to the reaction with the acid chloride. The metal alcoholate is prepared by the action of alkali metals such as sodium or its hydride or alternatively its amide, or by reaction with sodium ethoxide or of

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potassium tert-butoxide in the presence of an inert compatible solvent. For example, the metallation reaction consists in reacting 1 mol of amino alcohol (II) in solution in 5 to 20 parts of THF with 0.9 to 1.1 mol of sodium hydride, the reaction of formation of the alcoholate being generally complete between 1 to 3 hours and at a temperature between 0 and 67°C.

The eutomeric amino ester (I) is obtained by reacting one mol of (II) or of its alcoholate in solution in 5 to 20 parts of solvent with 0.6 to 1.8 mol of 3,4,5-trimethoxybenzoyl chloride. However, the preferred ratios for one mol of (II) or of its alcoholate are 8 to 15 parts of solvent and 0.8 to 1.3 mol of acid chloride. The reaction is then continued at a temperature of between 10 and 110°C for a period of between 1 and 24 hours. Preferably, the reaction, carried out between 20 and 67°C for 3 to 7 hours in THF, makes it possible to obtain the ester (I) with a satisfactory yield. The compound (I) is isolated from the reaction medium and purified by conventional methods such as extractions, crystallizations and column chromatographies.

According to procedure B which is particularly preferred, the alcoholysis of methyl 3,4,5-trimethoxybenzoate with the amino alcohols (II) leads to the product of the invention (I) by transesterification which is carried out in solution in anhydrous aprotic solvents in the presence of catalysts of an acidic or basic nature. The latter method is preferred and leads, on the one hand, by extension, to the choice of 3,4,5-trimethoxybenzoic acid esters in which the alkyl radical comprises from 1 to 3 carbon atoms in order to obtain, by transesterification, low-boiling point alcohols such as methyl, ethyl, propyl or isopropyl alcohols and, on the other hand, the use, as reaction solvents, of benzene, toluene or xylenes which form azeotropes with these alcohols. The removal, during the reaction, of the alcohol formed is favorable, which

is carried out by adding to the medium agents for sequestering this alcohol, such as molecular sieves of appropriate porosity or by removal by distillation as it is formed. Particular preference is given to the use of
5 methyl 3,4,5-trimethoxybenzoate which, under these transesterification conditions, generates methanol which, itself, with toluene which is the preferred reaction solvent, gives an advantageous azeotropic mixture by virtue of its composition and its relatively high boiling
10 point which allows rapid progress of the reaction. The acid or basic catalysts may be of an inorganic and/or organic nature. The basic catalysts are however preferred, such as alkali or nonalkali metals and their derivatives such as, for example, potassium tert-
15 butoxide, aluminum triisopropylate, magnesium methoxide, sodium, sodium hydride, sodium ethoxide and methoxide, the latter alcoholate being particularly preferred.

In practice, the reaction consists in dissolving one mol of amino alcohol (II) in 10 to 50 parts by weight of the
20 appropriate solvent, and then in adding to the solution from 1.1 to 2.0 mol of benzoic ester. After addition of 0.025 to 0.05 mol of catalyst, the mixture is heated at a sufficient temperature to remove, by distillation, the alcohol formed or its azeotrope with the solvent. This
25 temperature may be between 50 and 130°C and may be maintained for between 1 to 6 hours in order to obtain a satisfactory result. A particularly valuable technique consists in the addition of the catalyst in fractions or continuously during the reaction, and also in the case of
30 an azeotropic distillation, to add solvent during the reaction in order to make up for the loss caused by the distillation.

The preferred conditions consist in dissolving one mol of amino alcohol (II), 1.25 to 1.75 mol of methyl 3,4,5-
35 trimethoxybenzoate in 25 to 35 parts by weight of toluene relative to the quantity of (II) used. The solution is

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heated to 65-75°C, 0.025 to 0.05 mol of sodium methoxide is added and the toluene-methanol azeotrope formed is slowly distilled for 1 to 2 hours. 0.0125 to 0.025 mol of sodium methoxide is again added and distillation is carried out for 30 min to 1 h and this last operation is again repeated once. The products of the reaction are then isolated and purified according to the techniques mentioned above.

The invention is illustrated in a nonlimiting manner by the following examples which refer to procedures A and B described above.

The purity, identity and physicochemical characteristics of the products of the invention are determined, thus:

- the purity is checked by thin-layer chromatographies on silica gel. The R_f observed in the elution solvent used is reported in the examples.

- the identity of the products obtained with the proposed structures is checked by their proton nuclear magnetic resonance spectrum at 400 MHz, the products being dissolved in deuteriochloroform with tetramethylsilane as internal standard. The nature of the signals, their chemical shifts in ppm as well as the number of protons which they represent are noted.

- for the products obtained in solid form, the value of the melting point obtained by differential thermal analysis is indicated.

The technical description of the following examples illustrates the scope of the invention without, however, limiting it.

Experimental section

a) - Chemistry

Example 1 (S) 2-Methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate (I)

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- Stage 1: (S) 2-Methylamino-2-phenyl-n-butanol (II)
55.0 g (0.27 mol) of (S) 2-formylamino-2-phenyl-n-butyric
acid ($\alpha_D^{20} = +123^\circ$, $c = 1$ NaOH N) in 1375 ml of anhydrous
tetrahydrofuran (THF) are introduced into a reactor
5 protected from moisture and under a nitrogen atmosphere.
125.9 ml, that is to say 100.8 g (1.33 mol) of borane-
dimethyl sulfide complex are added, with stirring, at
20°C, to the suspension over one hour. After introduc-
tion, the solution which is obtained is heated and
10 maintained under reflux for 4 h.

The suspension is cooled to 0-5°C and 200 ml of methanol
are added without exceeding 10°C, followed under the same
conditions with 220 ml of a 10% NaOH solution.

The mixture is stirred for one hour at 20-25°C and then
15 the solvents are removed by vacuum distillation and on a
water bath. The residue is taken up in 1250 ml of water
and, after cooling to 0°C, acidified, with stirring, to
pH 1 with about 40 ml of concentrated HCl.

The acidic phase is extracted with 5 times 220 ml of
20 methyl-t-butyl ether and then alkalized at $t < 10^\circ\text{C}$,
with stirring, by addition of 26.5 g of NaOH pellets.

The mixture is extracted 3 times with 170 ml of
dichloromethane. The combined organic phases are washed
with water, dehydrated over Na_2SO_4 , and the solvent
25 removed by vacuum distillation. The crude product is
obtained in a satisfactory state of chromatographic
purity to be used as such in the next stage.

Weight = 35.3 g Y = 74.2%

TLC: Rf 0.50-0.60 (butanol-acetic ac. - water 8-2-2 v/v/v)

30 $[\alpha]_D^{20} = +13.6^\circ$ ($c = 2$, HCl N)

- ^1H - NMR δ (ppm): 0.70 (t, 3H); 1.55-1.65 (m, 1H); 1.75-
1.85 (m, 1H); 2.15 (s, 3H); 2.20-2.40 (m, 2H); 3.70-3.85
(m, 2H); 7.20-7.30 (m, 3H); 7.35-7.50 (m, 2H)

IR (film - NaCl pellets): 3300, 2900, 1600, 1490, 1440,
35 1380, 1330, 1130, 1040, 1010, 840, 760, 700 cm^{-1} .

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- Stage 2: (S) 2-Methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate (I).

Procedure A

7.03 g of a 60% (w/w) suspension of sodium hydride in a mineral oil (that is to say 4.22 g - 0.176 mol of pure product) are introduced into 42 ml of anhydrous THF in a reactor protected from moisture and under a nitrogen atmosphere. The suspension is heated under reflux, with stirring, and a solution of 30.0 g (0.167 mol) of (S) 2-methylamino-2-phenyl-n-butanol (II) in 21 ml of THF is added dropwise over about 30 min.

The mixture is kept for 1 h under reflux and then a solution of 43.3 g (0.184 mol) of 3,4,5-trimethoxybenzoyl chloride at 98% in 89 ml of THF is added at 50-60°C over about 1 h. After addition, the mixture is kept for 2 h under reflux and then 110 ml of THF are distilled off at ordinary pressure, 105 ml of toluene are added to the concentrated medium and, after having cooled to 20°C, 60 ml of water are added. After stirring for 15 min, the organic phase is acidified with a solution of 9.0 ml of 93% H₂SO₄ in 225 ml of water, the acidic phase is separated, alkalized in the cold state with 33 ml of 30% NaOH solution and then extracted with 3 times 100 ml of dichloromethane. The combined organic phases are washed with water, dehydrated over Na₂SO₄ and then the solvent is removed by vacuum distillation. The residue is taken up in 250 ml of hexane at 50°C. Upon cooling, the expected compound crystallizes. After stirring for 2 h at 10°C, the product is filtered off and then dried.

Weight = 37.2 g Y = 59.5% m.p. = 46°C

TLC: R_f 0.10-0.20 (toluene-acetone 9-1 - v/v)

$[\alpha]_{20}^D$ = not significant in a 10 cm polarimetric tube for a 4% ethanolic solution

- optical purity determined by HPLC > 99%

- ¹H - NMR δ (ppm): 0.80 (t, 3H); 1.50-1.70 (m, 1H); 1.80-1.95 (m, 2H); 2.25 (s, 3H); 3.80 (s, 6H); 3.90 (s, 3H);

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4.50-4.65 (m, 2H); 7.15 (s, 2H); 7.20-7.25 (m, 1H); 7.30-7.40 (m, 2H); 7.50-7.55 (m, 2H)

- IR (KBr pellet): 2800, 1710, 1590, 1500, 1460, 1410, 1360, 1330, 1220, 1180, 1120, 1000, 760, 700 cm^{-1}

5

Example 2 (S) 2-methylamino-2-phenyl-*n*-butyl 3,4,5-trimethoxybenzoate (I)

Procedure B (preferred)

In a reactor protected from moisture and under a nitrogen atmosphere, there are introduced in a mixture composed of
10 440 ml of anhydrous toluene and 22 ml of absolute ethanol:

- 10.0 g (0.056 mol) of (S) 2-methylamino-2-phenyl-*n*-butanol as prepared in stage 1 of Example 1,

15 - 19.0 g (0.084 mol) of methyl 3,4,5-trimethoxybenzoate.

The solution is heated with stirring and, at ordinary pressure, 110 ml of a mixture of solvents are distilled off. After cooling to 100°C, 180 ml of anhydrous toluene and 2.7 ml of a methanolic solution of 4 N sodium
20 methoxide are added. The mixture is heated and 150 ml of solvent are distilled off over one hour, following which the mixture is cooled to 100°C, 150 ml of anhydrous toluene and 0.9 ml of 4 N sodium methoxide solution are added, the mixture heated so as to distill off over 1 h
25 140 ml of solvent, cooled to 100°C and the addition of toluene and methoxide repeated so as to finally distill off 120 ml of solvent over one hour.

The reaction mixture is concentrated under vacuum, the residue is taken up in 120 ml of 1N HCl and the mixture
30 extracted with 3 times 70 ml of dichloromethane. The combined organic phases are washed and dried and then the solvents are evaporated under vacuum. The oily residue (17.6 g) is purified by rapid chromatography on a silica column. Elution with a dichloromethane-acetone 95-5 (v/v)
35 mixture makes it possible to obtain the product in the pure state.

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Weight = 15.6 g Y = 74.6%

Analyses in accordance with and identical to that for the product obtained in Example 1 - stage 2.

5 Example 3 (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate L(+)-tartrate (I)

15.0 g (0.040 mol) of (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate and 6.03 g (0.040 mol) of L(+)-tartaric acid are added to 150 ml of absolute ethanol in
10 a reactor.

The mixture is heated and kept under reflux for 5 min, with stirring. 50 ml of ethanol are then distilled off at ordinary pressure, and then 1 ml of water is added dropwise.

15 The salt crystallizes upon cooling. The mixture is left for 4 h at 15-20°C and then the L(+)-tartrate monohydrate crystals are filtered off and dried.

Weight = 16.0 g Y = 73.9%

m.p. = 94 - 97°C

20 Analysis in conformity for $C_{21}H_{27}NO_5$, $C_4H_6O_6 \cdot H_2O$.

According to the procedures of these examples, starting with (R,S) or (R) 2-formylamino-2-phenyl-n-butyric acids, there are respectively prepared:

25 a) (R,S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate and its hemimaleate (m.p. = 138°C)

b) (R) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate and its anhydrous salt with D(-)-tartaric acid (m.p. = 132°C)

30 **b) - Receptor study in vitro**

The study consisting in evaluating the respective affinity of the (S), (R) enantiomers and of NDTMB which is their racemic mixture in solution in their salified forms on the μ , δ and κ opiate receptors was carried out
35 in comparison to their racemic precursor trimebutine TMB.

The tests consist, on preparations appropriate for each receptor, in putting the affinities of the compounds in competition with those of radioactive ligands specific for each of the subtypes according to a technique adapted from that described by F. Roman et. al. in *J. Pharm. Pharmacol.* (1987), 39, p. 404-407, which consists in incubating solutions of appropriate concentration of test compounds with preparations loaded with the radioactive ligand, and then, after competition and displacement of the latter, in filtering and then in determining the radioactivity.

Thus, for the determination of the affinity for the μ receptors, a suspension of rat brain membranes previously incubated with [3 H]-DAGO is used, for the determination of the affinity for the δ receptors, a suspension of guinea pig brain membranes previously incubated with [3 H]-DADLE and for the determination of the affinity for the κ receptors rKOR-CHO cells previously incubated with [3 H]-U69,593. For each experiment, the radioactivity filtered is determined, and then, by computer processing of the results, the inhibition constant for 50% of the radioactive ligand is calculated and expressed by a K_i value in nM. The results of the study are reported in the table below:

Compound	K_i nM μ	K_i nM δ	K_i nM κ
(S) enantiomer	221	2456	1053
(R) enantiomer	82	735	405
(R,S) NDTMB	152	943	491
(R,S) TMB	123	302	145

The affinities are evidence of the stereospecificity for the (R) enantiomer which, in these tests, is the eutomer

regardless of the opiate subtype considered, the reciprocal of the eudismic ratio ($K_i(S)/K_i(R)$) being respectively 2.7 for the μ subtype, 3.3 for the δ subtype and 2.6 for the κ subtype. Moreover, a decrease in
5 affinity is observed overall in particular for the δ and κ subtypes of NDTMB and its enantiomers compared with the affinities of the racemic TMB which is their biological precursor.

c) - Analgesic activity: studies in vivo

10 In these tests, the products were used in salified form, namely in tartrate form for the (S) and (R) enantiomers and in maleate form for the racemic NDTMB.

15 c.1) - Comparative activity of the (R), (S) enantiomers and of their racemic mixture NDTMB

This activity was evaluated in tests recognized to be representative of chronic pain namely:

- the analgesic activity on the (tardive) tonic painful phase caused by an injection of a formaldehyde solution
20 into the leg in mice,
- the analgesic activity on chronic hyperalgesia induced by PGE2 in rats,

c.1.1) - Formaldehyde test in mice

25 The technique is adapted from that described by S. Hunsbarr (*J. of Neurosciences Methods*, 1985, 14, p. 69-76) and consists in causing, in one leg of the animal, a painful inflammation by intraplantar injection of 20 μ l of a 5% (v/v) sterile saline solution of
30 formaldehyde. The duration of the reactions of licking the treated leg by the animal are compatible in the period between the twentieth and twenty-fifth minute after the injection of formalin considered as t_0 of the test.

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For the evaluation of the activity of the products, they are administered by the s.c. route in an amount of 1 ml/100 g as a pretreatment 10 min before the intraplantar injection of formalin. In tests where the opiate component of the test is sought, 1 mg/kg of naloxone in solution is also administered by the s.c. route 5 min after the injection of formalin, that is to say 15 min after the s.c. administration of the test product. Comparison of the times for the batches of treated animals compared with the time for the batch having received the vehicle makes it possible to determine a result expressed in % analgesic activity.

s.c. dose mg/kg	(S) enantiomer		(R,S) NDTMB		(R) enantiomer	
	pdt alone	+ nalox.	pdt alone	+ nalox.	Pdt alone	+ nalox.
10	16	13	22	2	14	2
15	33	44	36	11	26	6
20	65	64	65	46	37	28

These results are evidence of the particularly advantageous activity of the (S) enantiomer which is the subject of the invention and this in two respects in the light of the preceding in vitro study:

- the (S) enantiomer shows an activity which is practically equal to that of the racemate but in any case greater than that of the (R) antipode,
- whereas the analgesic activity is notably inhibited by naloxone both for the (R,S) racemate and for the (R) antipode, it is unchanged as regards the (S) enantiomer, which suggests that, under test conditions related to a chronic pain, the compound acts by a non-opiate mechanism different from the products to which it is compared.

c.1.2) - Analgesic activity on chronic hyperalgesia induced by PGE₂ in rats

The test consists in determining the analgesic effect of the test compounds by the Randall and Selitto test in rats in which chronic hyperalgesia has been triggered by intraplantar injection of PGE₂ over four days into a leg according to a protocol adapted from that described by M. Nakamura-Craig et al. (Pain, 63, (1995) 33-37).

Practically, the study is carried out on batches of 120-140 g Sprague-Dawley rats to which 100 ng of PGE₂ is administered in a volume of 100 µl by the intraplantar route for four consecutive days at a rate of twice a day, which causes chronic hyperalgesia in the leg from the fifth day, and this for at least one week. On the day of the test, in the morning, the threshold of reaction to pain is checked by the Randall and Selitto test and animals whose threshold is ≤ 110 arbitrarily defined units are selected and then, in the afternoon, the measurement is repeated after prior administration by the s.c. route of a solution of the test product. This administration is carried out 30 min before the determination of the pain threshold. The mean of the thresholds determined before and after treatment is calculated for each batch and makes it possible, compared with the animals receiving only the vehicle for the test product to determine a result in % analgesic activity.

In a first test series, the administration of increasing doses made it possible to determine the comparative activity of the (R), (S) enantiomers and of their racemic mixture NDTMB. A second test series, in which the products are administered in a single dose with and without naloxone, made it possible to determine the opiate participation in the observed effect. The results of these tests are reported in % analgesic activity in the tables below.

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- Comparative activity of the products:

Comp. mg/kg s.c.	(S) enantiomer	(R,S) NDTMB	(R) enantiomer
6	8%	18%	NT
8	42%	NT	NT
10	48%	35%	11%
16	59%	NT	NT
20	67%	NT	NT

NT : not tested

5

- Evaluation of the opiate participation in the analgesic effect for an s.c. administration of 10 mg/kg with and without naloxone in an amount of 0.3 mg/kg

(S) enantiomer		(R,S) NDTMB		(R) enantiomer	
pdt alone	+ naloxone	pdt alone	+ naloxone	pdt alone	+ naloxone
55%	37%	33%	3%	20%	3%

10

These tests are evidence of the analgesic activity of the (S) eutomer of the invention compared to its antipode and the racemic mixture but, in particular, that the activity is only slightly due to an opiate effect since, in the presence of naloxone, 67% of the activity is maintained whereas for the other two compounds, naloxone inhibits practically the entire activity which is therefore attributable to an opiate mechanism.

15

c.2) - Activity of the (S) enantiomer on various representative models of chronic pain

- Activity on a hyperalgesia model in diabetic rats

The test is carried out in rats according to a technique
5 described by Burchiel et al. (*Diabetes*, 34. (1985) 1210-
1213) which consists in causing, in the animal, an
experimental diabetes by injecting streptozotocin, and,
after verifying the diabetic condition and the
hyperalgesia, in carrying out the test for determining
10 the analgesic effect of the test compounds. This
determination is carried out by immersing the tail of the
animals in a water bath whose temperature is kept at
44°C, the nociceptive reaction being determined by the
time in seconds before the tail is removed from the hot
15 water bath. In this test, the (S) enantiomer of the present
invention exhibits, administered by the s.c. route, an
analgesic activity at the dose of 30 mg/kg.

- Activity on neuropathic pain

20 The mononeuropathy model in rats is produced by loose
ligations of the sciatic nerve according to the Bennett
and Xie technique, the effect of the test compounds is
determined according to a modification of the Randall and
Sellitto method with the aid of a U. Basile analgesimeter
25 according to the technique described by G. Catheline et
al. (*European Journal of Pharmacology*, 318 (1996) 273-
281). In this test, the (S) enantiomer which is the subject
of the invention shows analgesic activity from the dose
of 1 mg/kg by the s.c. route, an effect which is not
30 modified by naloxone.

- Activity on behavioral pain

The test is carried out with rats in which a lasting pain
has been triggered by injecting carrageenin into the hind
35 legs and which are placed in an area whose exploration is
made painful. Different behavioral variables in the

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animal are observed which make it possible to qualitatively and quantitatively assess a possible analgesic effect of a test product. In this test, the (S) eutomer shows an analgesic effect from the dose of 3 mg/kg by the s.c. route.

c.3) - Evaluation of an opiate dependence effect:

Saelens test

The test according to J.K. Saelens et al. (*Arch. Int. Pharmacodyn.* (1971), 213-218) consists in causing addiction in mice by repeated administrations of a putative opiate product, followed by administration of naloxone, in bringing about a sudden withdrawal which causes characteristic reactions in the animal, in particular jumps of which the number, over a given lapse of time, reflects the morphine-type state of dependence in the animal under the action of the test product.

The (S) eutomer which is the subject of the invention, its (R) antipode and, as reference, morphine were used in the test. In male mice, repeated quantities, in increasing doses, of the products are administered by the s.c. route in an amount of 0.20 ml/20 g of weight of animal over two days: at 10, 11, 12, 14 and 16 hours on the first day and at 10 and 12 hours on the second day and then at 14 hours a solution of naloxone is injected by the intraperitoneal route in an amount of 100 mg/kg and, immediately, the number of jumps per mouse is counted over 15 minutes. The mean number of jumps per batch of mice and the percentage per batch of dependent animals are then calculated. The results are presented in the table below:

Total d.	(S) enantiomer		(R) enantiomer		Morphine	
mg/kg	Jumps	%/batch	Jumps	%/batch	Jumps	%/batch
8.56	0	0	NT	-	5.8	10
17.13	0	0	NT	-	3.1	40
34.25	0	0	0.3	10	4.6	70
68.50	0	0	0.3	20	17.0	80
137.0	0	0	3.2	40	31.5	100
275.0	0	0	12.2	90	41.1	100

NT : not tested

The results clearly show that the (S) enantiomer causes
 5 no addiction after administration by the s.c. route
 whereas its (R) antipode causes this condition without,
 however, reaching the degree observed with the morphine
 used as positive reference in the test.

d) - Galenic section

10 By way of illustration of the pharmaceutical dosage forms
 according to the invention, the composition and the
 preparation of tablets comprising, as active ingredient,
 (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate
 L(+) tartrate (product of Example 3) is described.

15	Product of Example 3	1 to 75 mg
	Lactose	124 to 74 mg
	Microcrystalline cellulose	36 to 60 mg
	Polyvinylpyrrolidone	6 mg
	Sodium carboxymethylstarch	8 mg
20	Magnesium stearate	1 mg

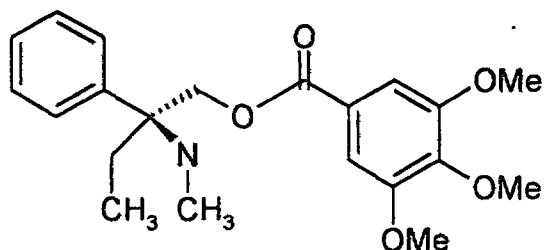
Mix the active ingredient, the lactose, the microcrystal-
 line cellulose and the carboxymethylstarch. Wet with the

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aid of an alcoholic solution of polyvinylpyrrolidone of appropriate concentration and granulate. Dry and size the granule. Mix homogeneously the magnesium stearate and then tablet at the rate of 200 mg per tablet.

Claims

1. (S) 2-Methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate (I) of formula



5

and its addition salts with pharmaceutically acceptable acids.

2. (S) 2-Methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate L(+)-tartrate and its hydrates,

- 10 3. Process for preparation of (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate or of one of its pharmaceutically acceptable salts which consists:

- in reducing, with a hydride derived from boron, (S) 2-formylamino-2-phenyl-n-butyric acid in order to obtain

- 15 (S) 2-methylamino-2-phenyl-n-butanol, and then

- in esterifying the (S) 2-methylamino-2-phenyl-n-butanol with a reagent chosen from 3,4,5-trimethoxybenzoyl chloride or methyl 3,4,5-trimethoxybenzoate in order to obtain (S) 2-methylamino-2-phenyl-n-butyl

- 20 3,4,5-trimethoxybenzoate (I).

4. Pharmaceutical composition characterized in that it comprises a therapeutically effective quantity of (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate or of one of its pharmaceutically acceptable salts combined with pharmaceutically compatible excipients.

25

5. Use of (S) 2-methylamino-2-phenyl-n-butyl 3,4,5-trimethoxybenzoate or of one of its pharmaceutically acceptable salts for the preparation of medicaments for the treatment of chronic pain.