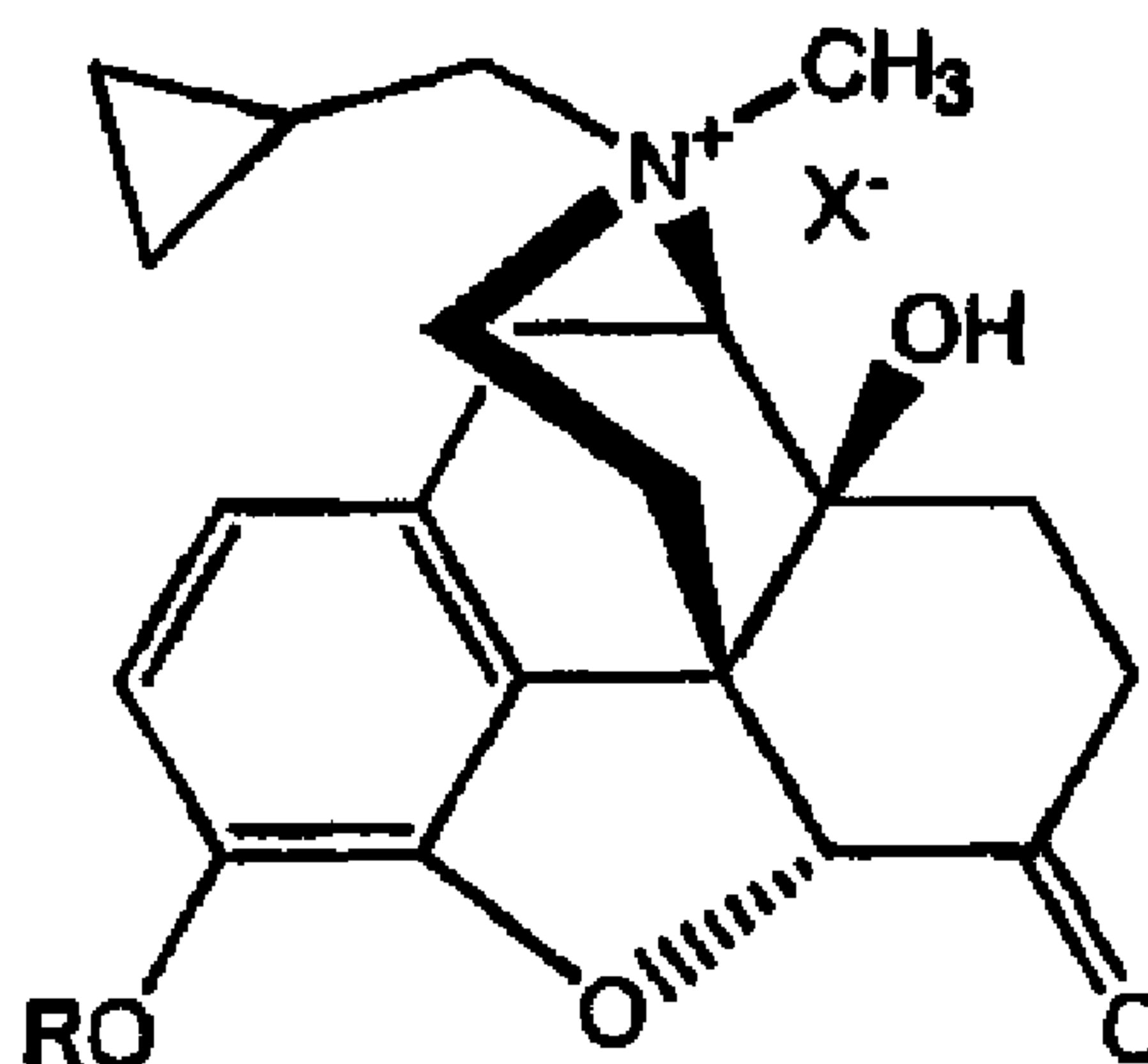




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(72) **Inventeurs/Inventors:**
DOSHAN, HAROLD D., US;
PEREZ, JULIO, US
(73) **Propriétaire/Owner:**
PROGENICS PHARMACEUTICALS, INC., US
(74) **Agent:** SMART & BIGGAR

(54) **Titre : (R)-N-METHYLNALTREXONE, PROCEDE POUR SA SYNTHESE ET SON UTILISATION PHARMACEUTIQUE**
(54) **Title: (R)-N-METHYLNALTREXONE, PROCESS FOR ITS SYNTHESIS AND ITS PHARMACEUTICAL USE**



(57) **Abrégé/Abstract:**

This invention relates to stereoselective synthesis of R-MNTX and intermediates thereof, pharmaceutical preparations comprising R-MNTX or intermediates thereof and methods for their use.



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(71) Applicant (for all designated States except US): **PRO-GENICS PHARMACEUTICALS, INC.** [US/US]; 777 Old Saw Mill River Road, Tarrytown, NY 10591 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DOSHAN, Harold, D.** [US/US]; 18 Griffith Road, Riverside, CT 06878 (US). **PEREZ, Julio** [ES/US]; 273D South Broadway, Tarrytown, NY 01591 (US).

(74) Agent: **VAN AMSTERDAM, John, R.**; WOLF, GREENFIELD & SACKS, P.C., 600 Atlantic Avenue, Boston, MA 02210 (US).

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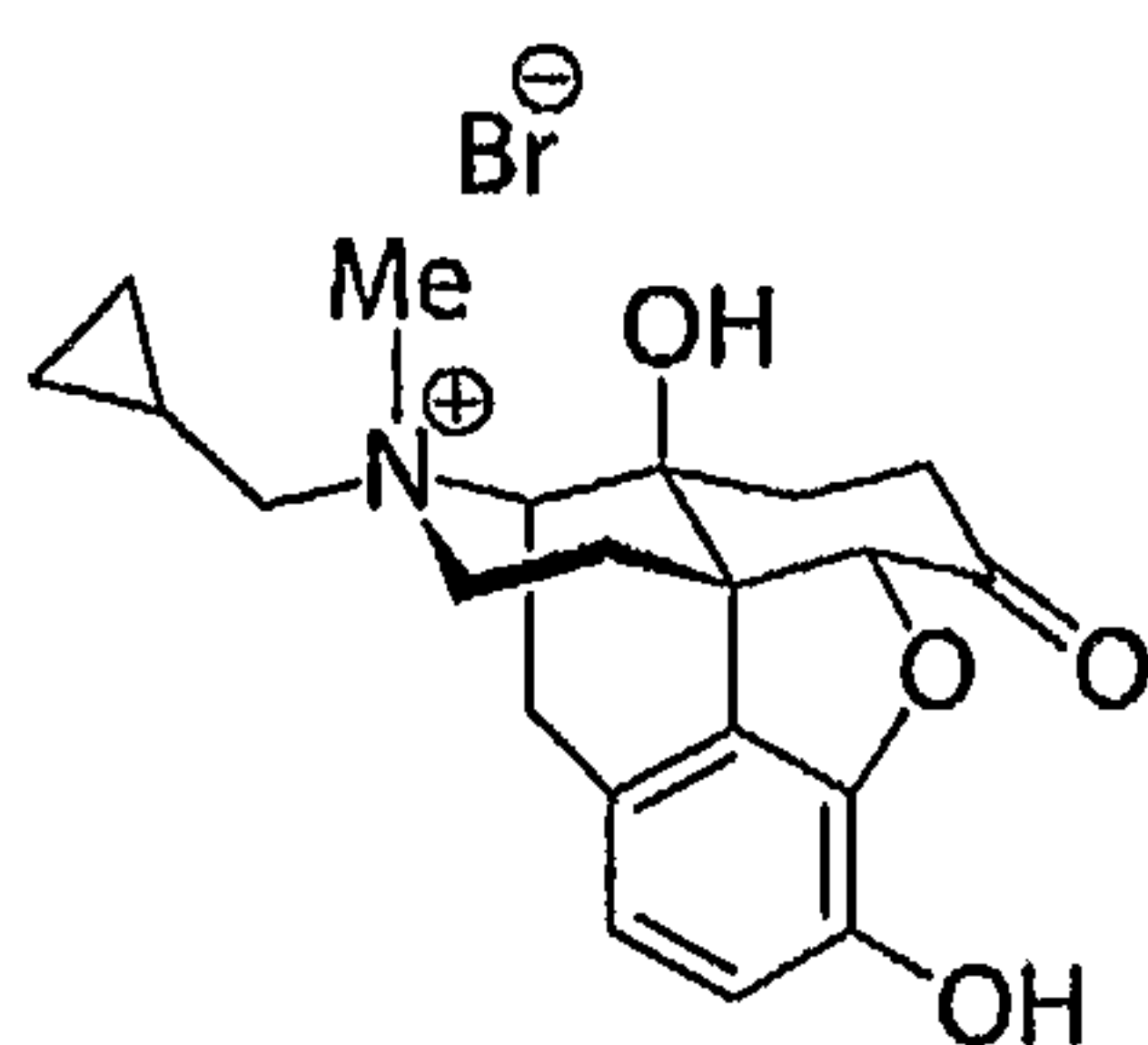
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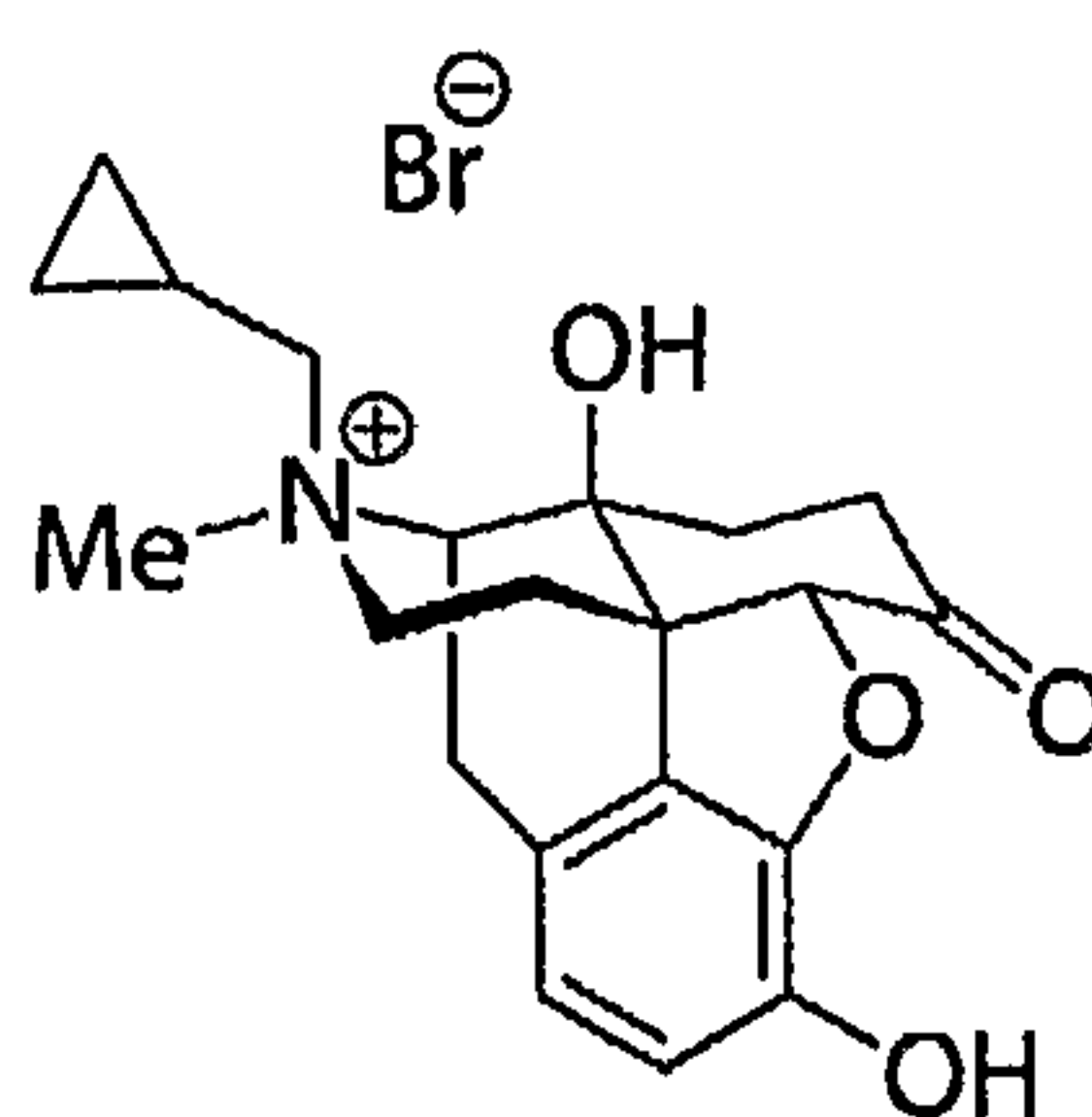
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(54) Title: (R)-N-METHYLNALTREXONE, PROCESSES FOR ITS SYNTHESIS AND ITS PHARMACEUTICAL USE



R-MNTX



S-MNTX

(57) Abstract: This invention relates to stereoselective synthesis of R-MNTX and intermediates thereof, pharmaceutical preparations comprising R-MNTX or intermediates thereof and methods for their use.

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(R)-N-METHYLNALTREXONE, PROCESS FOR ITS SYNTHESIS
AND ITS PHARMACEUTICAL USE

FIELD OF THE INVENTION

This invention relates to stereoselective synthesis of (R)-N-methylnaltrexone
5 (R-MNTX) and intermediates thereof, pharmaceutical preparations comprising R-MNTX or intermediates thereof and methods for their use.

BACKGROUND OF INVENTION

Methylnaltrexone (MNTX) is a quaternary derivative of the pure opioid
10 antagonist, naltrexone. It exists as a salt. Names used for the bromide salt of MNTX in the literature include: Methylnaltrexone bromide; N-Methylnaltrexone bromide; Naltrexone methobromide; Naltrexone methyl bromide; MRZ 2663BR. MNTX was first reported in the mid-70s by Goldberg et al as described in US Patent No.
4,176,186. It is believed that addition of the methyl group to the ring nitrogen forms a
15 charged compound with greater polarity and less liposolubility than naltrexone. This feature of MNTX prevents it from crossing the blood-brain barrier in humans. As a consequence, MNTX exerts its effects in the periphery rather than in the central nervous system with the advantage that it does not counteract the analgesic effects of opioids on the central nervous system.

20 MNTX is a chiral molecule and the quaternary nitrogen can be in R or S configuration. (See FIG. 1.) It is unknown whether the different stereoisomers of MNTX exhibit different biological and chemical properties. All of the reported functions of MNTX described in the literature indicate that MNTX is a peripheral opioid antagonist. Some of these antagonist functions are described in U.S. Patents
25 4,176,186, 4,719,215, 4,861,781, 5,102,887, 5,972,954, 6,274,591, 6,559,158, and 6,608,075, and in U.S. Patent Application Serial Nos. 10/163,482 (2003/0022909A1), 10/821,811 (20040266806), 10/821,813 (20040259899) and 10/821,809 (20050004155). These uses include reducing the side-effects of opioids without reducing the analgesic effect of opioids. Such side-effects include nausea, emesis,
30 dysphoria, pruritus, urinary retention, bowel hypomotility, constipation, gastric hypomotility, delayed gastric emptying and immune suppression. The art discloses

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that MNTX not only reduces the side-effects stemming from opioid analgesic treatment but also reduces the side-effects mediated by endogenous opioids alone or in conjunction with exogenous opioid treatment. Such side-effects include inhibition of gastrointestinal motility, post-operative gastrointestinal dysfunction, idiopathic constipation and other such conditions including, but not limited to, those mentioned above. However, it is unclear from the art whether the MNTX used in these studies was a mixture of R and S stereoisomers or a single stereoisomer.

The art suggests that isolated stereoisomers of a compound sometimes may have contrasting physical and functional properties, although it is unpredictable whether this is the case in any particular circumstance. Dextromethorphan is a cough suppressant, whereas its enantiomer, levomethorphan, is a potent narcotic. R,R-methylphenidate is a drug to treat attention deficit hyperactivity disorder (ADHD), whereas its enantiomer, S,S-methylphenidate is an antidepressant. S-fluoxetine is active against migraine, whereas its enantiomer, R-fluoxetine is used to treat depression. The S enantiomer of citalopram is therapeutically active isomer for treatment of depression. The R enantiomer is inactive. The S enantiomer of omeprazole is more potent for the treatment of heartburn than the R enantiomer.

Bianchetti et al, 1983 *Life Science* 33 (Sup I):415-418 studied three pairs of diastereoisomers of quaternary narcotic antagonist and their parent tertiary amines, levallorphan, nalorphine, and naloxone, to see how the configuration about the chiral nitrogen affected in vitro and in vivo activity. It was found that the activity varied considerably depending on how the quaternary derivatives were prepared. In each series, only the diastereomer obtained by methylation of the N-allyl-substituted tertiary amine (referred to as "N-methyl diastereomer") was potent in displacing ³H-naltrexone from rat brain membranes, and acting as a morphine antagonist in the guinea-pig ileum. Conversely, diastereoisomers obtained by reacting N-methyl-substituted tertiary amines with allyl halide (referred to as "N-allyl diastereomers") did not displace ³H-naltrexone and had negligible antagonist activity and slight agonist action in the guinea-pig ileum. In vivo findings were generally consistent with those in vitro. Thus only the "N-methyl" but not the "N-allyl diastereomers" inhibited morphine-induced constipation in rats and behaved as antagonists. The author stated

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that the prepared materials appeared to be pure by ^1H and ^{13}C nuclear magnetic resonance (NMR) analysis, but these methods are not accurate. The author cites a literature reference for the assignment of the R configuration to the "N-methyl diastereomer" of nalorphine. No assignment is proposed for the levallorphan and naloxone diastereomers. It would be adventurous to extrapolate the configuration to these diastereomers (R.J. Kobylecki et al, J. Med. Chem. 25, 1278-1280, 1982).

Goldberg et al.'s US Patent No. 4,176,186, and more recently Cantrell et al.'s WO 2004/043964 A2 describe a protocol for the synthesis of MNTX. Both describe a synthesis of MNTX by quaternizing a tertiary N-substituted morphinan alkaloid with a methylating agent. Both Goldberg et al. and Cantrell et al. are silent as to the stereoisomer(s) produced by the synthesis. The authors remained cautiously silent about the stereochemistry because the stereochemistry could not be determined based on prior art. The cyclopropylmethyl side-chain in naltrexone is different from the prior art side-chains and may have affected the stereochemical outcome in the synthesis of MNTX, as may other reaction parameters such as temperature and pressure. Based on the method of synthesis described in each, it is unknown whether the MNTX so produced was R, S or a mixture of both.

S-MNTX in pure form, and a method of making pure S-MNTX have not been described in the literature. Researchers would have been unable to definitively characterize and distinguish the stereoisomer(s) obtained by the Goldberg et al. or Cantrell et al. synthesis in the absence of pure S-MNTX as a standard.

SUMMARY OF THE INVENTION

S-MNTX has now been produced in high purity permitting the characterization of its relative retention time in chromatography versus that of R-MNTX. The pure S-MNTX has been found to have activity different from the activity of MNTX reported in the literature. This highlights the need for methods of making and purifying R-MNTX to high purity.

The present invention provides substantially pure R-MNTX and intermediates thereof, crystals of substantially pure R-MNTX and intermediates thereof, novel methods for making substantially pure R-MNTX, methods for analyzing and

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quantifying R-MNTX in a mixture of R-MNTX and S-MNTX, methods of isolating R-MNTX from a mixture of R-MNTX and S-MNTX, pharmaceutical products containing the same and related uses of these materials.

5 The invention provides synthetic routes for stereoselective synthesis of R-MNTX, substantially pure R-MNTX, crystals of substantially pure R-MNTX, pharmaceutical preparations containing substantially pure R-MNTX, and methods for their use.

According to one aspect of the invention, a composition is provided that comprises MNTX in R configuration with respect to nitrogen present at greater than
10 99.5%. In other embodiments the MNTX in R configuration with respect to nitrogen is present in the composition in greater than about 99.6 %, or about 99.7 %, or about 99.8 %, or about 99.9 %, or about 99.95 %, or even more preferably greater than 99.95%. In one embodiment, there is no detectable S-MNTX using the chromatographic procedures described herein. Preferably, the composition is free of
15 HPLC detectable S-MNTX. In one embodiment there is no HPLC detectable S-MNTX at a detection limit of 0.02% and a quantitation limit of 0.05%. In yet another embodiment the composition of the invention contains 99.85% of the MNTX is in R configuration with respect to nitrogen and it contains HPLC detectable S-MNTX at a detection limit of 0.02% and a quantitation limit of 0.05%.

20 According to one aspect of the invention a composition is provided that comprises MNTX, wherein at least 99.6%, 99.7%, 99.8%, 99.85%, 99.9% , and even 99.95% of the MNTX in the composition is in the R configuration with respect to nitrogen, and one or more of a buffering agent, a chelating agent, a preserving agent, a cryoprotecting agent, a lubricating agent, a preservative, an anti-oxidant, or a binding
25 agent.

R-MNTX is a salt. Therefore there will be a counterion, which for the present application, includes the zwitterion. Typically, the counterion a halide, sulfate, phosphate, nitrate or an anionic-charged organic species. Halides include bromide, iodide, chloride, and fluoride. In certain embodiments the halide is iodide and in other
30 important embodiments the halide is bromide. In certain embodiments, the anionic-charged organic species is a sulfonate or a carboxylate. Examples of sulfonates

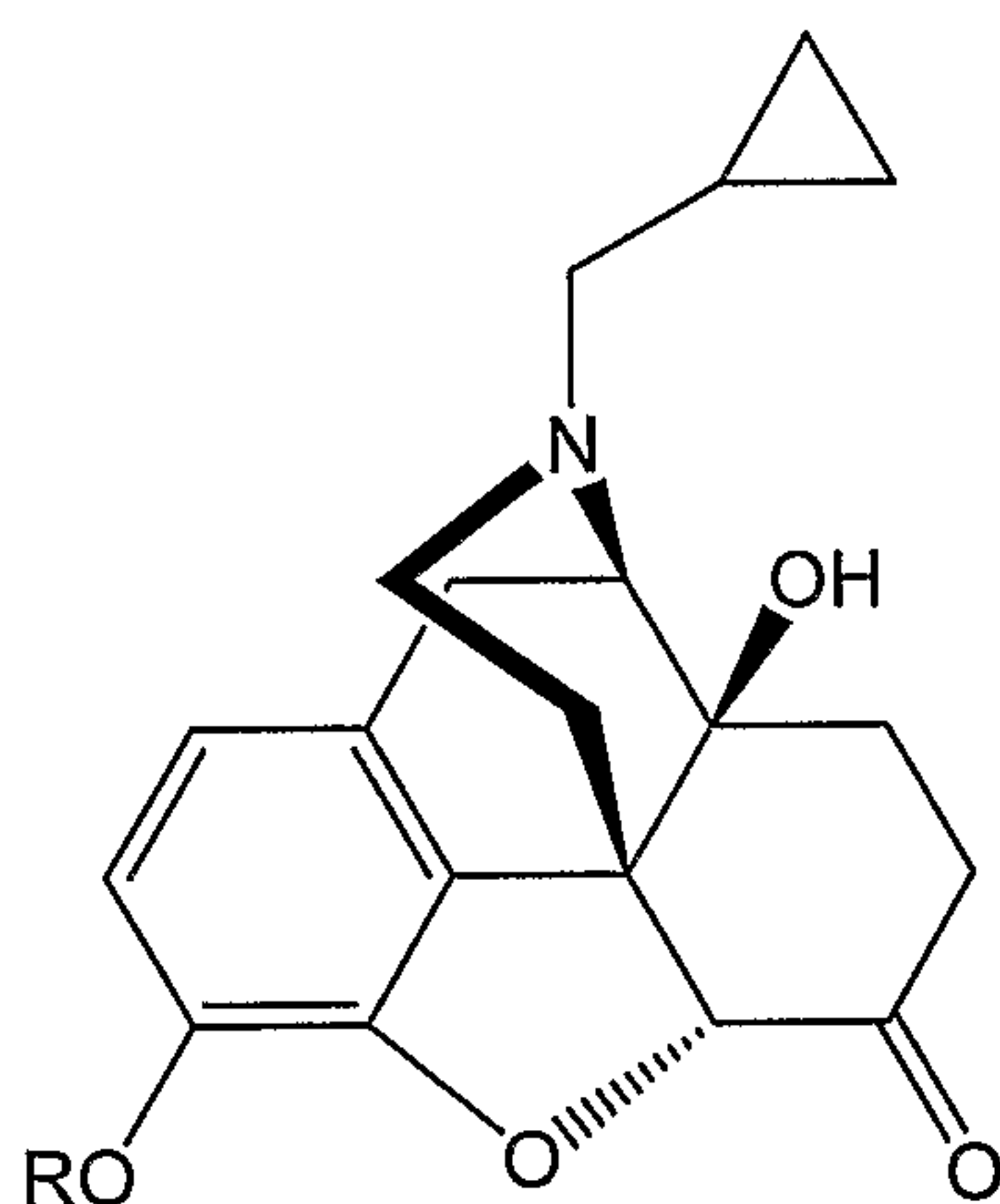
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include mesylate, besylate, tosylate, and triflate. Examples of carboxylates include formate, acetate, citrate, and fumarate.

According to another aspect of the invention, the foregoing compositions that comprise MNTX in R configuration with respect to nitrogen in some important
5 embodiments is a crystal, a solution, or a bromide salt of MNTX. In other embodiments, the foregoing compositions are pharmaceutical preparations, preferably in effective amounts and with a pharmaceutically acceptable carrier.

According to one aspect of the invention, a crystal of MNTX is provided that is at least about 99.5%, or about 99.6% or about 99.7%, or is about 99.8%, or about
10 99.9%, or most preferably greater than 99.95% of MNTX in R configuration with respect to nitrogen.

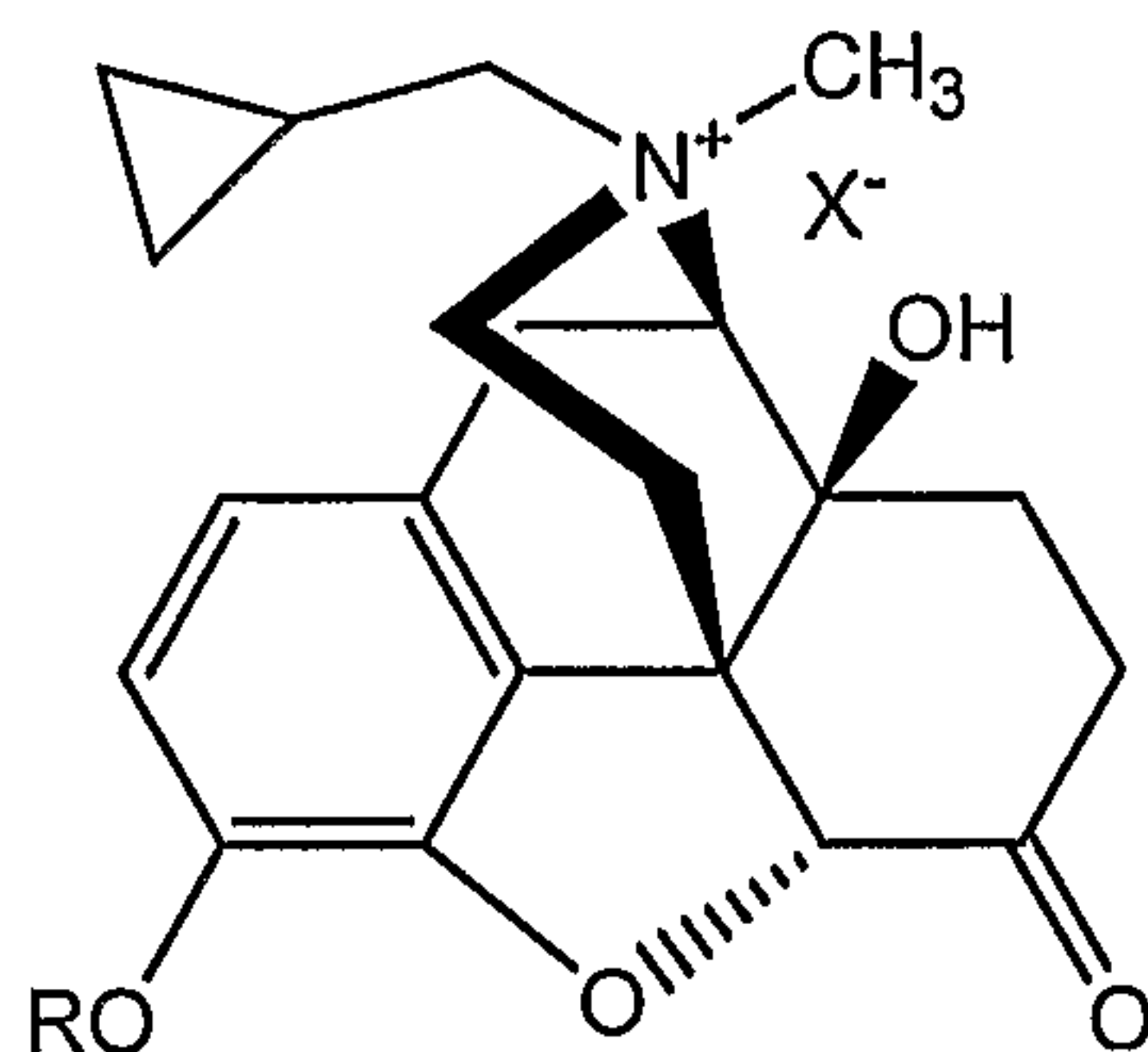
According to one aspect of the invention, there is provided a compound of the formula:



wherein R is a hydroxyl protecting group. The hydroxyl protecting group can be any of numerous such groups. In important embodiments it is selected from the group consisting of: isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, silyl ethers, 2-tetrahydropyranyl ethers, and alkyl carbonates. Most preferably the hydroxyl
20 protecting group is isobutyryl.

According to one aspect of the invention there is provided a compound of the formula:

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wherein R is a hydroxyl protecting group. The hydroxyl protecting group is selected from the group consisting of: isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, silyl ethers, 2-tetrahydropyranyl ethers, and alkyl carbonates. Most preferably the hydroxyl protecting group is isobutyryl. The compound in one embodiment is isolated. By isolated it is meant the compound is at least 50% pure. The compound can be obtained at levels of even greater purity, such as 60%, 70%, 80%, 90%, or even greater than 95% purity. In other embodiments the compound is in R configuration with respect to nitrogen, the R form being present in greater than 50%, 60%, 70%, 80%, 90%, 95% , 99%, or even 99.5%% versus the S form.

According to another aspect of the invention, a method for stereoselective synthesis of R-MNTX is provided. This method involves adding a hydroxyl protecting group to naltrexone to yield 3-O-protected-naltrexone; methylating the 3-O-protected-naltrexone to yield 3-O-protected-R-MNTX salt; and removing hydroxyl protecting group to yield R-MNTX. In some embodiments of the invention the hydroxyl protecting group can be added in the presence of each or both: an organic solvent and/or a tertiary amine that is not naltrexone. In some embodiments of the invention the naltrexone is methylated by reacting the 3-O-protected-naltrexone with methyl iodide to produce 3-O-protected-R-MNTX iodide salt. The 3-O-protected-naltrexone can be protected in important embodiments by a hydroxyl protecting group such as isobutyryl. In a preferred embodiment of the invention, the 3-O-protected-R-MNTX iodide salt is treated with hydrobromic acid to remove the protecting group and produce R-MNTX bromide/iodide salt, and the bromide/iodide salt is passed through an anion exchange resin column (bromide form) to yield R-MNTX bromide. In any of the foregoing aspects of the invention the tertiary amine that is not MNTX

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can be triethylamine. In any of the foregoing aspects of the invention the organic solvent can be tetrahydrofuran. In any of the foregoing aspects of the invention the hydroxyl protecting group can be isobutyryl.

According to another aspect of the invention a method for isolation and
5 purification of R-MNTX is provided, comprising passing the crude R-MNTX through a chromatography column and collecting the R-MNTX which elutes at the R-MNTX retention time. This process can be in addition to the method described above, after the deprotecting step and/or the anion exchange resin column step.

According to another aspect of the invention a method for analyzing R-MNTX
10 in a mixture of R-MNTX and S-MNTX is provided. The method involves conducting high performance liquid chromatography (HPLC) and applying R-MNTX to the chromatography column as a standard. The method preferably involves applying both S-MNTX and R-MNTX as standards to determine relative retention/elution times. Relative retention times of R and S are described herein.

15 Pure S-MNTX can be obtained according to the following procedure: S-MNTX salt can be synthesized by combining iodomethylcyclopropane or another cyclopropylmethyl derivative with oxymorphone in a dipolar aprotic solvent. The cyclopropylmethyl derivative contains a leaving group, preferably a halide, such as iodine or sulfonate. The dipolar aprotic solvent may be: N-methylpyrrolidone (NMP),
20 dimethyl formamide, methylphosphoramidate, acetone, 1,4-dioxane, acetonitrile, or combinations thereof. The synthesized S-MNTX can be purified by chromatography, recrystallization, multiple recrystallizations, or a combination thereof. The reaction can be carried out under atmospheric conditions across a wide temperature spectrum, for example, at 70 °C, or under a controlled reaction temperature between 65 °C to 75
25 °C. Counterions may be substituted, optionally, for iodide by transferring the S-MNTX iodo salt to a second solvent, such as isopropyl acetate or dioxane and exchanging iodide for a counterion other than iodide. Examples of counterions are bromide, chloride, fluoride, nitrate, sulfonate, or carboxylate. The sulfonate can be mesylate, besylate, tosylate or triflate. The carboxylate can be formate, acetate, citrate
30 and fumarate. The reaction in the second solvent can be conducted at room temperature.

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In one aspect of this invention, the chromatography is conducted using two solvents, solvent A and solvent B, wherein solvent A is an aqueous solvent and solvent B is a methanolic solvent and wherein both A and B contain trifluoroacetic acid (TFA). Preferably, A is 0.1% aqueous TFA and B is 0.1% methanolic TFA. In important embodiments the column comprises a bonded, end-capped silica. In important embodiments, the pore size of the column gel is 5 microns. In a most preferred embodiment, the column, flow rate and gradient program are as follows:

Column: Luna C18(2), 150 × 4.6 mm, 5 μ

Flow Rate: 1 mL/min

Gradient Program:

Time (min)	%A	%B
0:00	95	5
8:00	65	35
12:00	35	65
15:00	0	100
16:00	95	5
18:00	95	5

Detection can be carried out conveniently by ultraviolet (UV) wavelength @ 230 nm. Quantitation Limit is the lowest amount of S-MNTX that can be consistently measured and reported, regardless of variations in laboratories, analysts, instruments or reagent lots. Detection Limit is the lowest amount of S-MNTX in a sample which can be detected but not necessarily quantitated as an exact value.

The foregoing HPLC also can be used to determine the relative amount of S-MNTX and R-MNTX and the intermediates of the synthesis thereof by determining the area under the respective R and S curves in the chromatogram produced.

According to another aspect of the invention a method for isolation and purification of R-MNTX and the 3-*O*-protected-R-MNTX salt intermediate is provided, comprising recrystallizing the crude R-MNTX or intermediates thereof from a solvent or a mixture of solvents. This process can be in addition to the method described above, after the deprotection step and/or the anion exchange resin column step.

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According to another aspect of the invention, a method is provided for stereoselective synthesis of 3-*O*-protected R-MNTX salt comprising methylating a 3-*O*-protected-naltrexone with a methylating agent to yield 3-*O*-protected-R-MNTX salt. The hydroxyl protecting group of the 3-*O*-protected-naltrexone in certain
5 embodiments is isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, silyl ethers, 2-tetrahydropyranyl ethers, and alkyl carbonates. The 3-*O*-protected R-MNTX is a salt with an anion that can be, for example, a halide, sulfate, phosphate, nitrate or an organic anionic-charged species. The halide is bromide, iodide, chloride, or fluoride. The organic anionic-charged species can be, for example, a sulfonate or carboxylate.
10 Exemplary sulfonates are mesylate, besylate, tosylate, or triflate. Exemplary carboxylates are formate, acetate, citrate, or fumarate. The method can further involve exchanging the anion with a different anion. The methylating agent can be a methyl group susceptible to nucleophilic attack, and a leaving group. Exemplary methylating agents are selected from the group consisting of methyl halide, dimethyl
15 sulfate, methyl nitrate and methyl sulfonate. Methyl halides are methyl iodide, methyl bromide, methyl chloride and methyl fluoride. Methyl sulfonates include methyl mesylate, methyl besylate, methyl tosylate, and methyl triflate. In one embodiment, the methylation is conducted at a temperature range from about >70°C to about 100°C, or from 80°C to about 90°C, or preferably at about 88°C. The methylation
20 reaction is conducted for about 1 hour to 24 hours, or about 5 hour to 16 hours and in one embodiment for about 10 hours. The method can further involve purification of the 3-*O*-protected R-MNTX salt using at least one purification technique, such as chromatography or recrystallization. The chromatography can be reverse-phase chromatography or regular phase chromatography. In some embodiments, the regular
25 phase chromatography can use alumina or silica gel. The 3-*O*-protected-naltrexone can be purified prior to methylation.

According to one aspect of the invention a pharmaceutical composition is provided that comprises R-MNTX free of detectable S-MNTX by the chromatography procedures described herein or the 3-*O*-protected-R-MNTX salt intermediate and a
30 pharmaceutically acceptable carrier. In one embodiment the pharmaceutical composition is a packaged unit dosage or a multi-unit dosage. In yet another

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embodiment the packaged unit dosage is a solution. The pharmaceutical composition in one embodiment is a solution. In another embodiment it is an enteric coated solid dosage form. In still another embodiment it is a sustained release formulation.

According to yet another aspect of the invention, a pharmaceutical preparation

5 containing R-MNTX or the 3-*O*-protected-R-MNTX salt intermediate in a lyophilized formulation is prepared by combining a cryoprotective agent, such as mannitol, with the R-MNTX formulation. The lyophilized preparation may also contain any one of, any combination of, or all of a buffering agent, an antioxidant, an isotonicity agent and an opioid. In some embodiment the aforementioned pharmaceutical composition
10 can further comprise one pharmaceutical agent that is not an opioid antagonist. In one embodiment of the invention the aforementioned pharmaceutical composition can comprise a pharmaceutical agent that is an opioid. In yet another embodiment, the pharmaceutical composition can further comprise at least one opioid, and at least one pharmaceutical agent that is not an opioid or an opioid antagonist. In a preferred
15 embodiment the pharmaceutical agent that is not an opioid or an opioid antagonist is an antiviral agent, an anti-infective agent, an anticancer agent, an antispasmodic agent, an anti-muscarinic agent, a steriodal or non-steriodal anti-inflammatory agent, a pro-motility agent, a 5HT₁ agonist, a 5HT₃ antagonist, a 5HT₄ antagonist, a 5HT₄ agonist, a bile salt sequestering agent, a bulk-forming agent, an alpha2-adrenergic
20 agonist, a mineral oil, an antidepressant, a herbal medicine, an anti-diarrheal medication, a laxative, a stool softener, a fiber or a hematopoietic stimulating agent.

The pharmaceutical compositions of the invention can be provided in kits. The kits are a package containing a sealed container comprising the pharmaceutical preparations of the present invention and instructions for use. The kits contain R-
25 MNTX that is free of HPLC detectable S-MNTX. The kit in one embodiment contains 40mg/mL R-MNTX. The kit in another embodiment contains 30mg/mL of R-MNTX. The kit can further include an opioid or opioid agonist, or it can include at least one pharmaceutical agent that is not an opioid or an opioid antagonist. In one embodiment, the kit is a package containing a sealed container comprising the
30 pharmaceutical preparation that is or the 3-*O*-protected-R-MNTX salt and instructions for use. The kit in one embodiment contains 40mg/mL 3-*O*-protected-R-MNTX salt.

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The kit in another embodiment contains 30mg/mL of 3-*O*-protected-R-MNTX salt. The kit can further include an opioid or opioid agonist, or it can include at least one pharmaceutical agent that is not an opioid or an opioid antagonist.

According to another aspect of the invention, methods are provided for ensuring the manufacture of R-MNTX (which is an opioid antagonist) that is free of S-MNTX (which is an opioid agonist). The methods permit for the first time the assurance that a pharmaceutical preparation of R-MNTX which is intended for antagonist activity is not contaminated with a compound that opposes the activity of R-MNTX. This is particularly desirable when R-MNTX is administered to oppose the side effects of opioid therapy, as opioids appear to act synergistically with S-MNTX to oppose the activity of R-MNTX. In this aspect of the invention, a method is provided for manufacturing R-MNTX. The method involves:

(a) obtaining a first composition containing R-MNTX, (b) purifying the first composition by chromatography, recrystallization or a combination thereof, (c) conducting HPLC on a sample of purified first composition using S-MNTX as a standard, and (d) determining the presence or absence of S-MNTX in the sample. In an important embodiment, both R-MNTX and S-MNTX are used as standards, to determine for example relative retention time of R-MNTX and S-MNTX. In one embodiment, the purifying is multiple recrystallization steps or multiple chromatography steps. In another embodiment, the purifying is carried out until S-MNTX is absent from the sample as determined by HPLC. It should be understood, however, that the purified first composition in some aspects of the invention is not necessarily free of detectable S-MNTX. The presence of such S-MNTX, for example, might indicate that further purification steps should be conducted if purer R-MNTX is desired. The methods can further involve packaging purified first composition that is free of HPLC detectable S-MNTX. The methods further can include providing indicia on or within the packaged, purified first composition indicating that the packaged, purified first composition is free of HPLC detectable S-MNTX. The method further can involve packaging a pharmaceutically effective amount for treating anyone of the conditions described herein. The first composition containing R- and S-MNTX can be obtained by the methods described herein.

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According to one aspect of the invention, the purifying is carried out until S-MNTX is less than 0.4%, 0.3%, 0.2%, 0.15%, 0.1%, 0.05%, even is absent from the purified first composition as determined by HPLC with a detection limit of 0.02 and a quantitation limit of 0.05%.

5 In one embodiment the method provides indicia on or with the packaged purified first composition indicating a level of S-MNTX in the packaged first purified composition.

According to one aspect of the invention a package is provided that contains a composition comprising R-MNTX and indicia on or contained within the package indicating a level of S-MNTX in the composition. In one embodiment the level of S-MNTX is less than 0.4%, 0.3%, 0.2%, 0.15%, 0.1%, 0.05%, or is absent from the sample. In yet another embodiment, the package further contains, mixed together with the R-MNTX, one or more of a buffering agent, a chelating agent, a preserving agent, a cryoprotecting agent, a lubricating agent, a preservative, an anti-oxidant, or a binding agent.

15 According to one aspect of the invention a method of preparing a pharmaceutical product is provided, by selecting a composition of R-MNTX because it contains S-MNTX at a level that is less than 0.4%, 0.3%, 0.2%, 0.15%, 0.1%, 0.05% of, or is absent from the composition, and formulating the composition into a unit or multi unit dosage for administration to a patient.

20 According to another aspect of the invention, a packaged product is provided. The package contains a composition comprising R-MNTX, wherein the composition is free of HPLC detectable S-MNTX, and indicia on or contained within the package indicating that the composition is free of detectable S-MNTX. The composition can take on a variety of forms, including, but not limited to, a standard for use in laboratory experiments, a standard for use in manufacturing protocols, or a pharmaceutical composition. If the composition is a pharmaceutical composition, then one important form of indicia is writing on a label or package insert describing the characteristics of the pharmaceutical preparation. The indicia can indicate directly that the composition is free of S-MNTX, or it can indicate the same indirectly, by stating for example that the composition is pure or 100% R-MNTX. The pharmaceutical composition can be for treating any of the conditions described herein. The

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pharmaceutical composition can contain an effective amount of the pure R-MNTX and can take any of the forms described below as if specifically recited in this summary, including, but not limited to, solutions, solids, semi-solids, enteric coated materials and the like.

5 According to one aspect of the invention, a method is provided for treating or preventing opioid-induced side effects comprising administering to a patient the R-MNTX free of detectable S-MNTX by the chromatography procedures described herein or the 3-*O*-protected-R-MNTX salt intermediate composition of any of the foregoing aspects of the invention in an amount effective to treat the opioid-induced
10 side effect. In one embodiment of the invention the patient is chronically administered opioids. In another embodiment the patient is acutely administered opioids. The opioid-induced side effect is preferably selected from a group consisting of constipation, immune suppression, inhibition of gastrointestinal motility, inhibition of gastric emptying, nausea, emesis, incomplete evacuation, bloating, abdominal
15 distension, increased gastroesophageal reflux, hypotension, bradycardia, gastrointestinal dysfunction, pruritus, dysphoria, and urinary retention. In one preferred embodiment the opioid-induced side effect is constipation. In another preferred embodiment the opioid-induced side effect is inhibition of gastrointestinal motility or inhibition of gastric emptying. In yet another preferred embodiment the
20 opioid-induced side effect is nausea or emesis. In yet another preferred embodiment the opioid-induced side effect is pruritus. In yet another preferred embodiment the opioid-induced side effect is dysphoria. In yet another preferred embodiment the opioid-induced side effect is urinary retention.

 According to one aspect of the invention, a method is provided for treating a
25 patient receiving an opioid for pain resulting from surgery comprising administering to the patient an R-MNTX composition free of detectable S-MNTX by the chromatography procedures described herein or the 3-*O*-protected-R-MNTX salt intermediate in an amount effective to promote gastrointestinal motility, gastric emptying or relief of constipation.

30 According to another aspect of the invention, a method is provided for inducing laxation in a patient in need of laxation, comprising administering to the

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patient an R-MNTX composition free of detectable S-MNTX by the chromatography procedures described herein or the 3-*O*-protected-R-MNTX salt intermediate in an effective amount.

According to yet another aspect of the invention, a method is provided for preventing and/or treating impaction in a patient in need of such prevention/treatment, comprising administering to the patient an R-MNTX composition free of detectable S-MNTX by the chromatography procedures described herein or the 3-*O*-protected-R-MNTX salt intermediate in an effective amount.

According to yet another aspect of the invention, a method is provided for preventing and/or treating post-operative bowel dysfunction following surgery, in particular abdominal surgery in a patient in need of such prevention/treatment, comprising administering to the patient an R-MNTX composition free of detectable S-MNTX by the chromatography procedures described herein or the 3-*O*-protected-R-MNTX salt intermediate in an effective amount.

According to one aspect of the invention, a method is provided for treating or preventing endogenous opioid-induced gastrointestinal dysfunction comprising administering to the patient an R-MNTX composition free of detectable S-MNTX by the chromatography procedures described herein or the 3-*O*-protected-R-MNTX salt intermediate in an amount effective to treat the endogenous opioid-induced gastrointestinal dysfunction. The gastrointestinal dysfunction can be selected from a group consisting of inhibition of gastrointestinal motility, constipation and ileus. In some embodiments of the invention the ileus is selected from the group comprising of: post-operative ileus, post-partum ileus, paralytic ileus.

According to one aspect of the invention, a method is provided for preventing or treating idiopathic constipation comprising administering to the patient an R-MNTX composition free of detectable S-MNTX by the chromatography procedures described herein or the 3-*O*-protected-R-MNTX salt intermediate in an amount effective to prevent or treat the idiopathic constipation.

According to yet another aspect of the invention, a method is provided for treating irritable bowel syndrome comprising administering to the patient an R-MNTX composition free of detectable S-MNTX by the chromatography procedures

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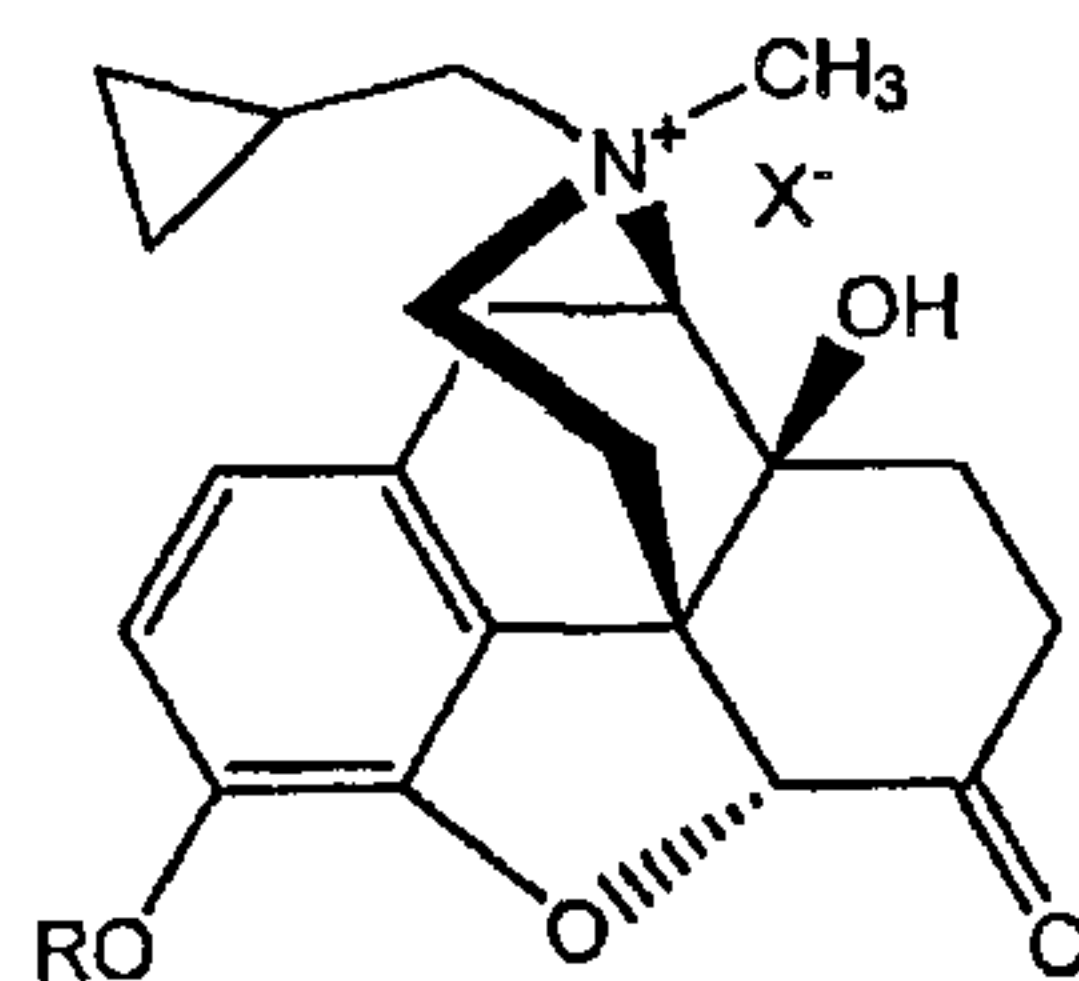
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described herein or the 3-*O*-protected-R-MNTX salt intermediate in an amount effective to ameliorate at least one symptom of the irritable bowel syndrome. In some embodiments of the invention the R-MNTX composition or the 3-*O*-protected-R-MNTX salt composition further comprises at least one irritable bowel syndrome therapeutic agent. The irritable bowel syndrome therapeutic agent can be selected from the groups consisting of antispasmodics, anti-muscarinics, anti-inflammatory agents, pro-motility agents, 5HT₁ agonists, 5HT₃ antagonists, 5HT₄ antagonists, 5HT₄ agonists, bile salt sequestering agents, bulk-forming agents, alpha2-adrenergic agonists, mineral oils, antidepressants, herbal medicines, anti-diarrheal medication and combinations thereof.

According to one aspect of the invention methods are provided for parenteral administration of the compounds and compositions of the invention including but not limited to intravenous, intramuscular and subcutaneous administration. In one embodiment of the invention the compounds of the invention are in pharmaceutical preparations suitable for use in pre-filled syringes, pre-filled pen injectors, cartridges for use in pen injectors, reusable syringes or other medical injectors, liquid dry injectors, needleless pen systems, syrettes, autoinjectors, or other patient-controlled injection devices.

Further aspects of the invention include:

- an isolated 3-*O*-protected-R-methylnaltrexone (MNTX) salt of the formula

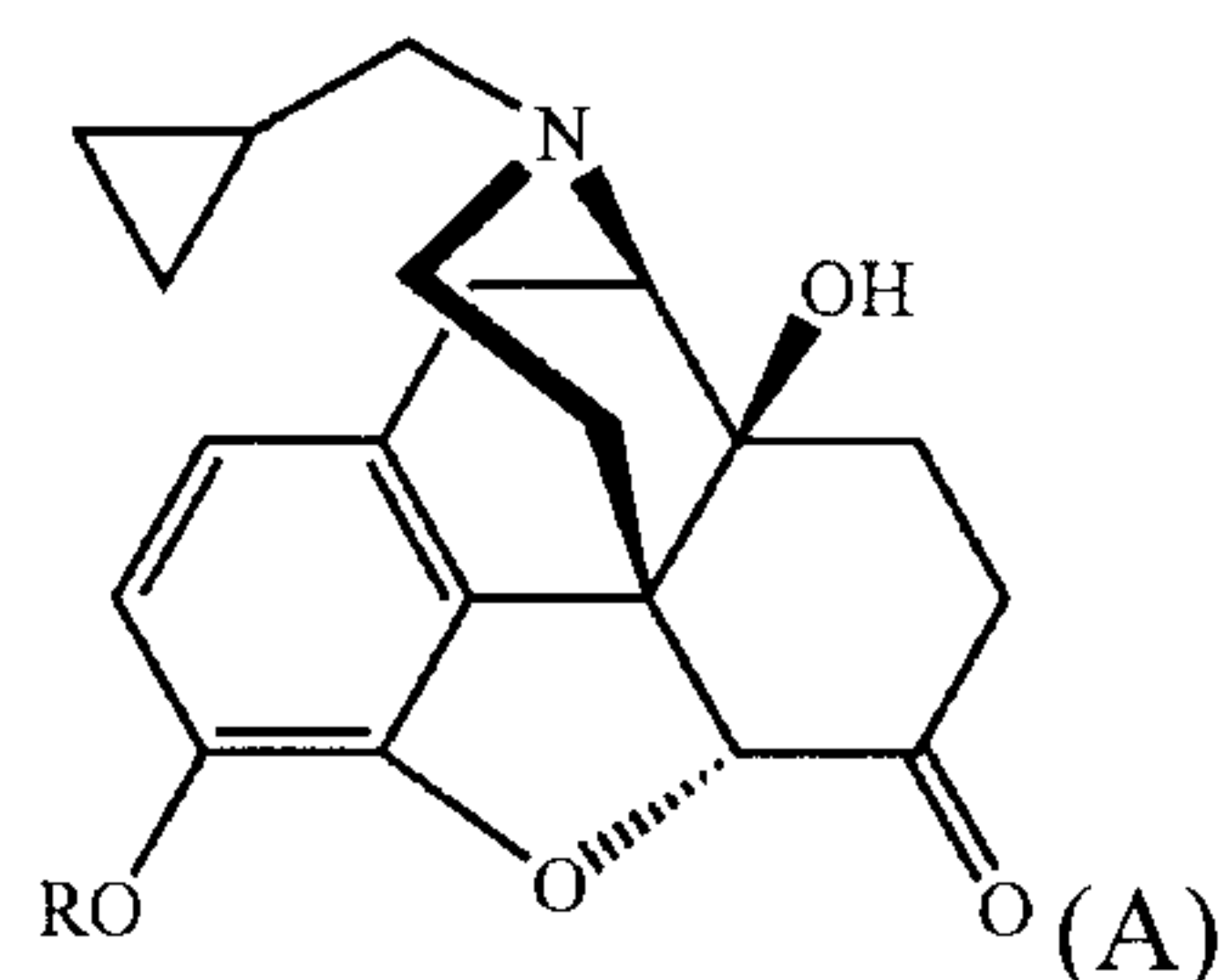


wherein R is a hydroxyl protecting group selected from the group consisting of isobutyryl, 2-methyl butyryl, and tertbutyl carbonyl, or R, taken together with the oxygen atom to which it is attached, is a silyl ether, a 2-tetrahydropyranyl ether, or an alkyl carbonate; and X⁻ is a counterion;

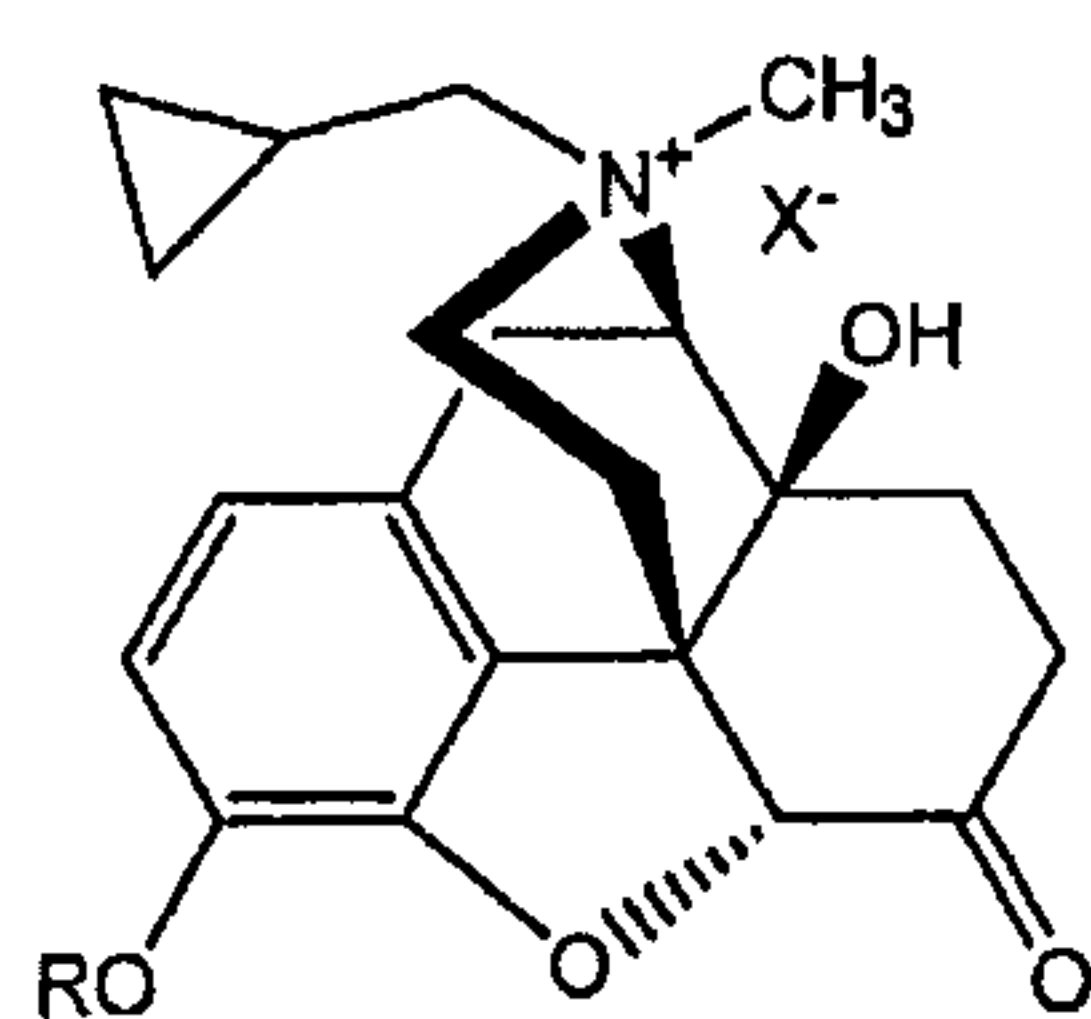
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- a method for stereoselective synthesis of R-methylnaltrexone (MNTX) comprising: (a) methylating a compound of formula A:



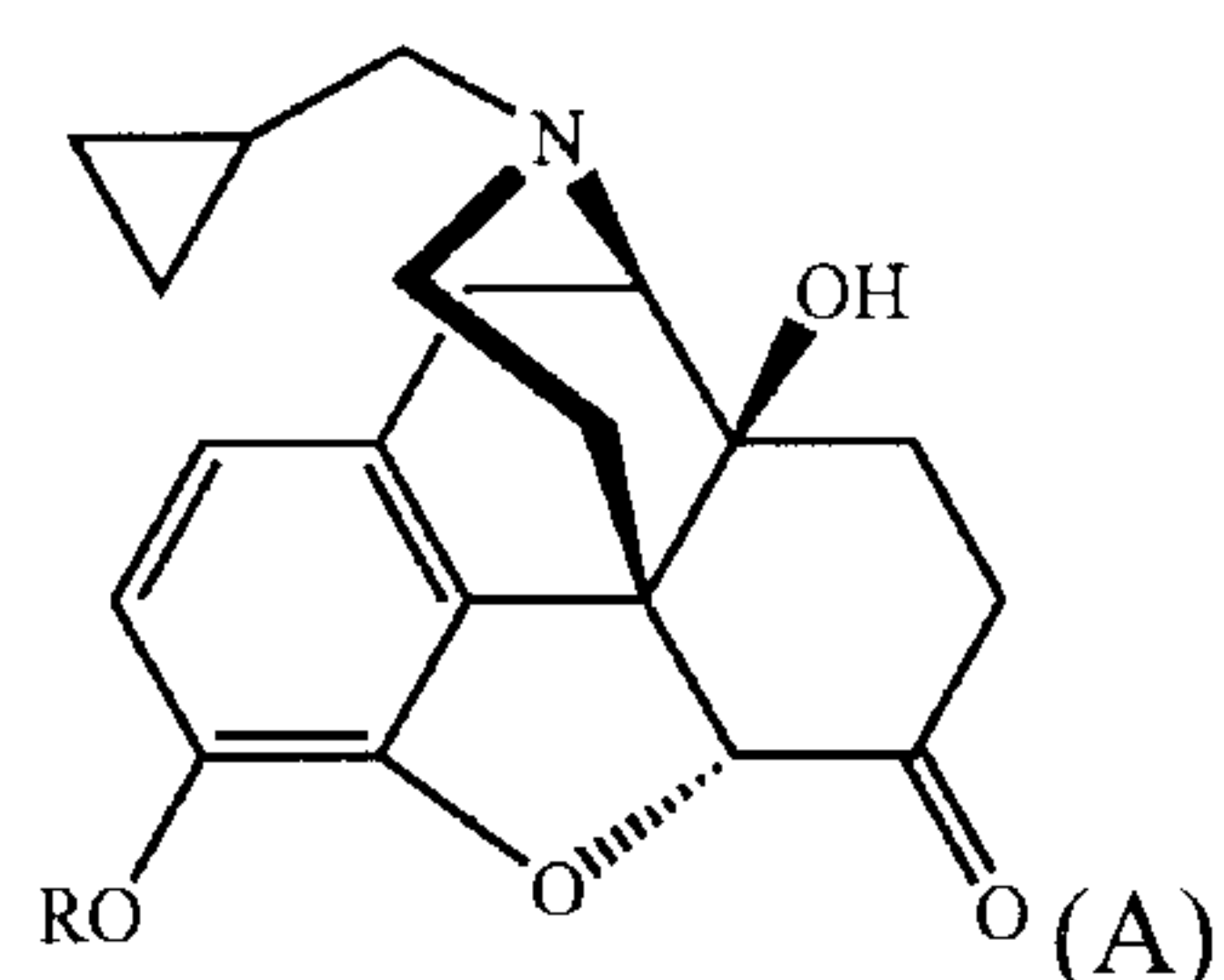
with a methylating agent to yield a compound of formula B:



(B); and

(b) removal of the 3-hydroxyl protecting group R to yield R-MNTX, wherein R is a hydroxyl protecting group selected from the group consisting of isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, or R, taken together with the oxygen atom to which it is attached, is a silyl ether, a 2-tetrahydropyranyl ether, or an alkyl carbonate; and X⁻ is a counterion;

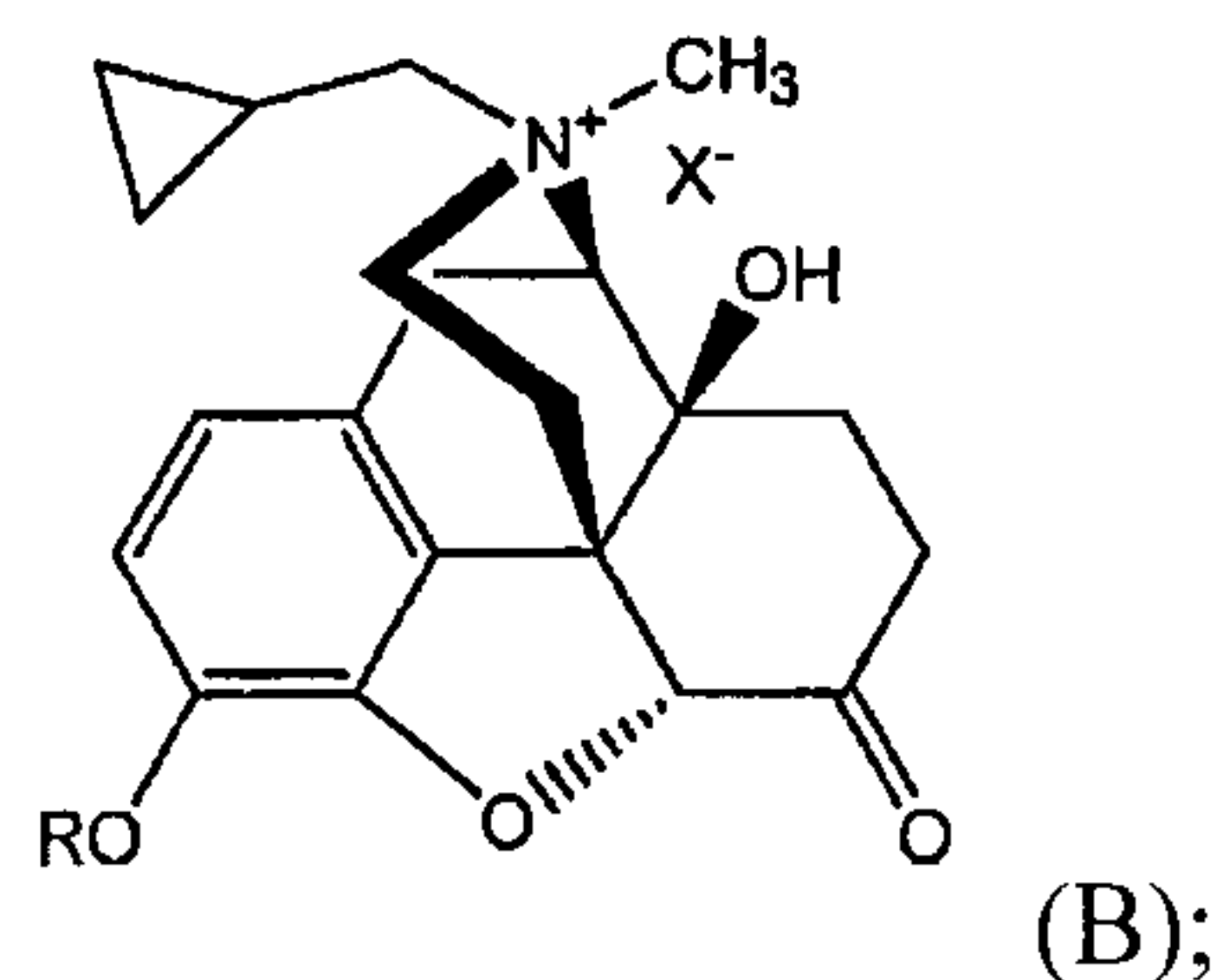
- a method for stereoselective synthesis of R-methylnaltrexone (MNTX) halide comprising: (a) methylating a compound of formula A



with a methyl halide methylating agent to yield a compound of formula B:

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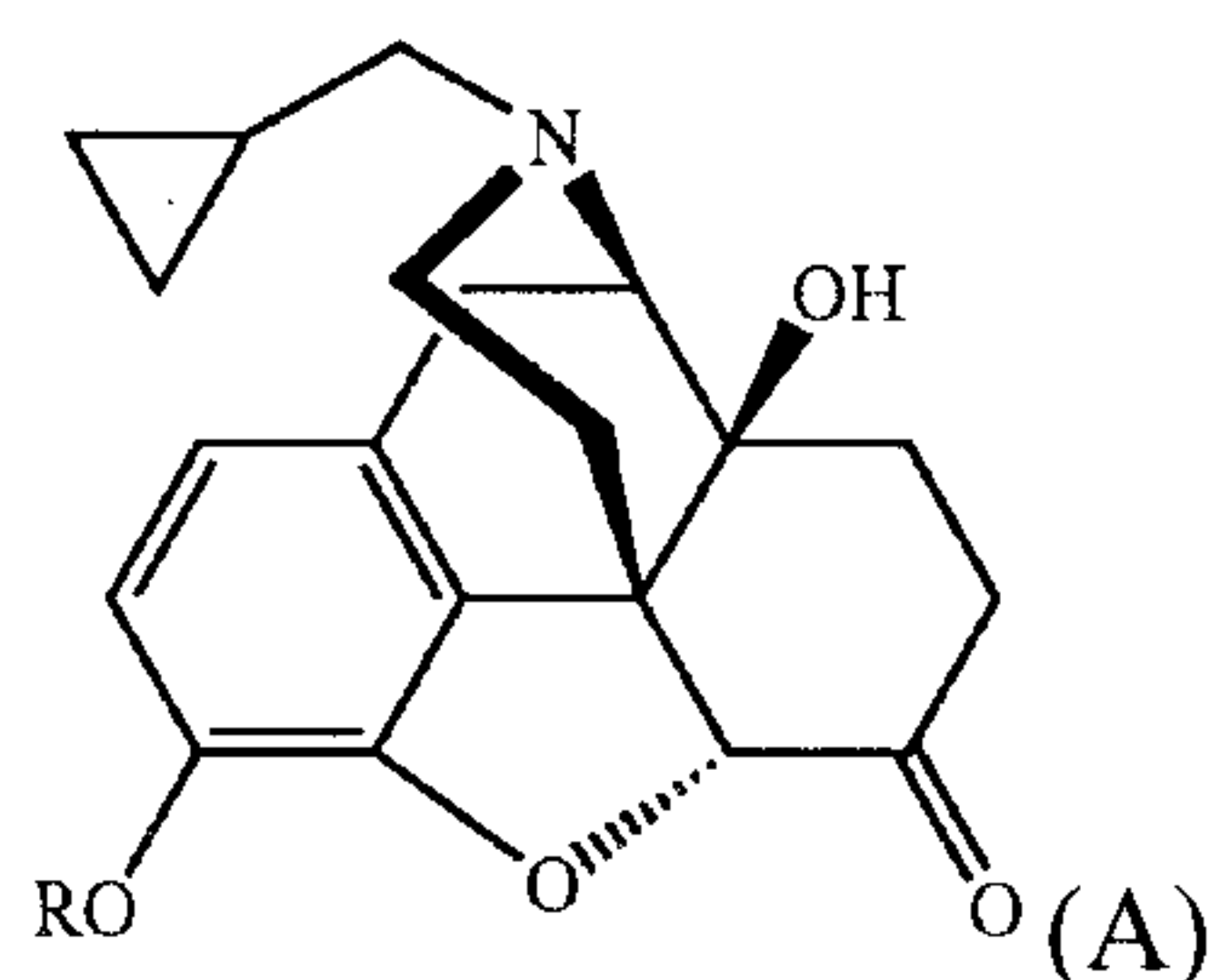
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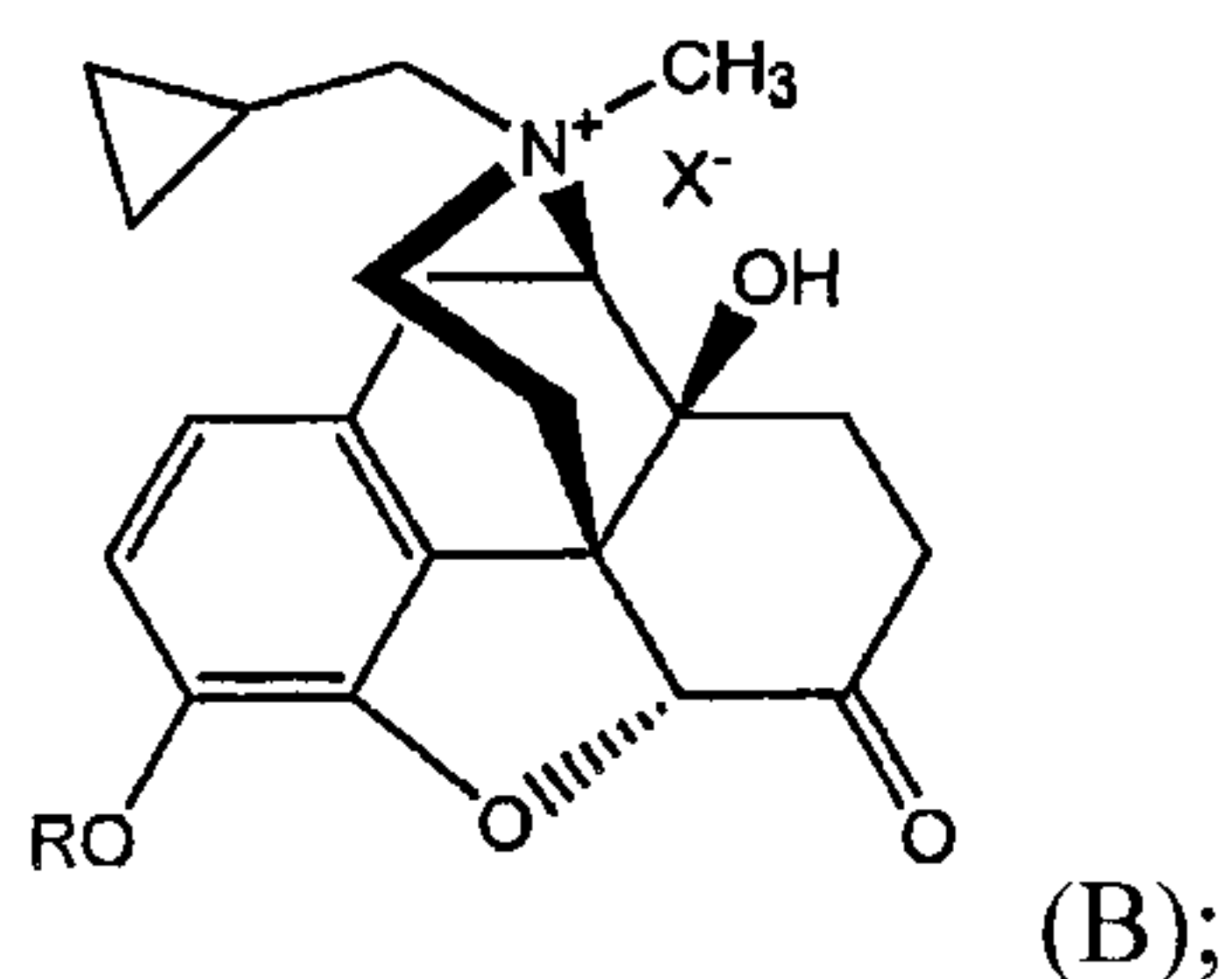
- (b) removal of the 3-hydroxyl protecting group R to yield R-MNTX halide, wherein R is a hydroxyl protecting group selected from the group consisting of isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, or R, taken together with the oxygen atom to which it is attached, is a silyl ether, a 2-tetrahydropyranyl ether, or an alkyl carbonate; and X⁻ is a halide;

- a method for stereoselective synthesis of R-methylnaltrexone (MNTX)

bromide salt comprising: (a) methylating a compound of formula A:



with methyl iodide to yield a compound of formula B:



- wherein R is a hydroxyl protecting group selected from the group consisting of isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, or R, taken together with the oxygen atom to which it is attached, is a silyl ether, a 2-tetrahydropyranyl ether, or an alkyl carbonate; and X⁻ is iodide;
- (b) hydrolysis with hydrobromic acid to remove R to yield R-MNTX bromide/iodide salt; and

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(c) passing the R-MNTX bromide/iodide salt through anion exchange (bromide form) to yield R-MNTX bromide salt;

- a composition comprising the isolated 3-O-protected-R-MNTX salt as described herein and a carrier;

5 - a pharmaceutical composition comprising the salt as described herein or the composition as described herein, and a pharmaceutically acceptable carrier;

- the use of the pharmaceutical composition as described herein in the manufacture of a medicament for the treatment or prevention of an opioid-induced side effect wherein the medicament comprises an amount effective to treat or prevent the side effect;

10 - the use of the pharmaceutical composition as described herein in the manufacture of a medicament for the treatment or prevention of a condition selected from the group consisting of idiopathic constipation, irritable bowel syndrome and post-operative bowel dysfunction, wherein the medicament comprises an amount effective to prevent or treat the condition;

15 - the use of the pharmaceutical composition as described herein in the manufacture of a medicament for inducing laxation in a patient, wherein the medicament comprises an amount effective to induce laxation;

- a patient-controlled injection device comprising the pharmaceutical composition as described herein;

20 - a kit comprising a package containing a sealed container comprising the pharmaceutical composition as described herein and instructions for use; and

- a package containing the pharmaceutical composition as described herein and indicia on or contained within the package indicating a level of S-MNTX in the composition.

These and other aspects of the invention are described in greater detail herein.

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BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 provides the chemical structure of bromide salts of R-MNTX and S-MNTX.

5 FIG. 2 is a chromatogram showing the separation of R and S forms of MNTX in a mixture of S- and R-MNTX.

FIG. 3 is a chromatogram of R-MNTX with the addition of approximately 0.1% of the S-MNTX isomer.

FIG. 4 is a chromatogram of R-MNTX with the addition of approximately 1.0% of the S-MNTX isomer.

10 FIG. 5 is a chromatogram of R-MNTX with the addition of approximately 3.0% of the S-MNTX isomer.

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FIG. 6 shows a reaction scheme for the synthesis of R-MNTX using a preferred hydroxyl protecting group.

FIG. 7 shows an alternative reaction scheme for the synthesis of R-MNTX using a preferred hydroxyl protecting group.

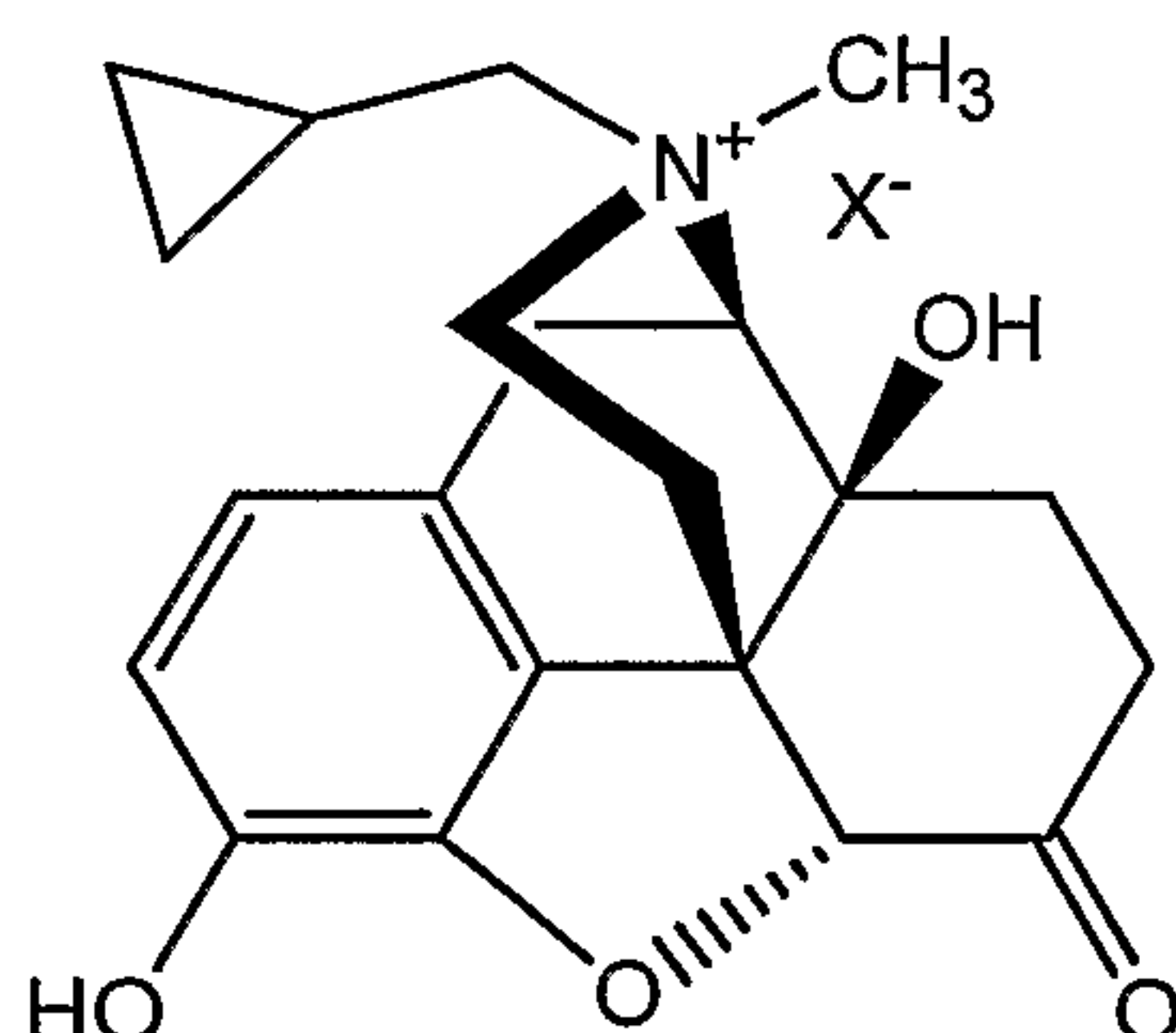
5 FIG. 8 shows a kit according to the invention.

DETAILED DESCRIPTION

The invention provides synthetic routes for stereoselective synthesis of R-MNTX, [morphinanum, 17R, 17-(cyclopropylmethyl)-4,5-epoxy-3,14-dihydroxy-17-methyl-6-oxo-, salt, (5 α)-(9Cl)], substantially pure R-MNTX, crystals of substantially pure R-MNTX, pharmaceutical preparations containing substantially pure R-MNTX, and methods for their use.

R-MNTX has the structure in the formula:

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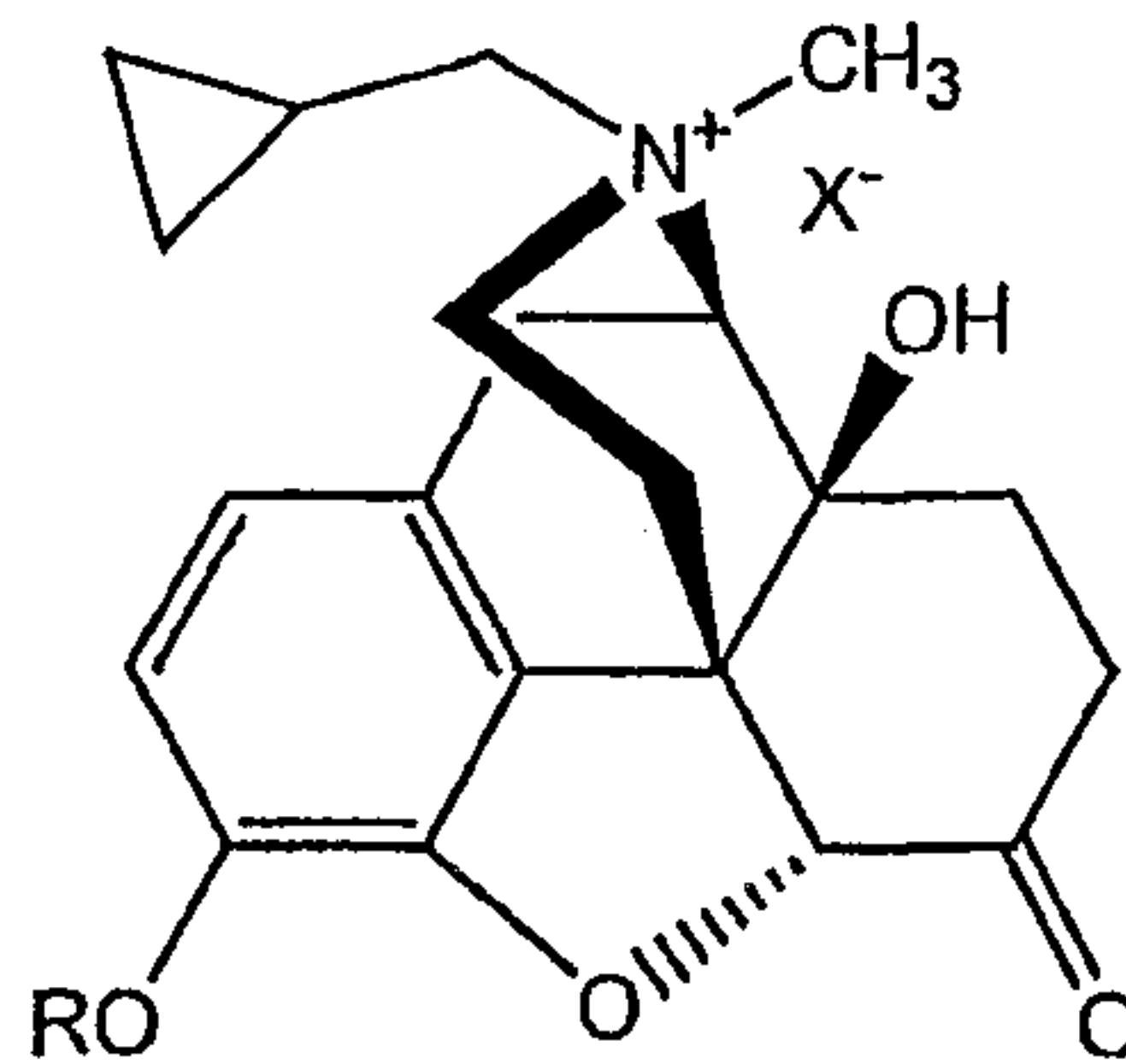


wherein X⁻ is a counterion. The counterion can be any counter ion, including a zwitterion. Preferably the counterion is pharmaceutically acceptable. Counterions include halides, sulfates, phosphates, nitrates, and anionic-charged organic species. The halide can be iodide, bromide, chloride, fluoride or a combination thereof. In one embodiment the halide is iodide. In a preferred embodiment the halide is bromide. The anionic-charged organic species may be a sulfonate or carboxylate. The sulfonate may be mesylate, besylate, tosylate, or triflate. The carboxylate may be formate, acetate, citrate, or fumarate.

The invention further provides an R-MNTX intermediate, isolated 3-O-protected-R-MNTX salt of the formula :

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wherein R is a hydroxyl protecting group, substantially pure 3-*O*-protected-R-MNTX salt, crystals of substantially pure 3-*O*-protected-R-MNTX salt, pharmaceutical preparations containing substantially pure 3-*O*-protected-R-MNTX salt, and methods for their use. The invention further provides synthetic routes for stereoselective synthesis of 3-*O*-protected-R-MNTX salt.

"Alkyl", in general, refers to an aliphatic hydrocarbon group which may be straight or branched having from 1 to about 10 carbon atoms in the chain, and all combinations and subcombinations of ranges therein. "Branched" refers to an alkyl group in which a lower alkyl group, such as methyl, ethyl or propyl, is attached to a linear alkyl chain. In certain preferred embodiments, the alkyl group is a C₁-C₅ alkyl group, i.e., a branched or linear alkyl group having from 1 to about 5 carbons. In other preferred embodiments, the alkyl group is a C₁-C₃ alkyl group, i.e., a branched or linear alkyl group having from 1 to about 3 carbons. Exemplary alkyl groups include methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl. "Lower alkyl" refers to an alkyl group having 1 to about 6 carbon atoms. Preferred alkyl groups include the lower alkyl groups of 1 to about 3 carbons.

An "alkylating agent" is a compound that can be reacted with a starting material to bind, typically covalently, an alkyl group to the starting material. The alkylating agent typically includes a leaving group that is separated from the alkyl group at the time of attachment to the starting material. Leaving groups may be, for example, halogens, halogenated sulfonates or halogenated acetates. An example of an alkylating agent is cyclopropylmethyl iodide.

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"Methylating agent" means a reactive species, having electrophilic properties, that is capable of introducing a "methyl group" at the nitrogen atom of naltrexone, so as to form a covalent bond therewith. Illustrative methylating agents can be represented by the formula CH_3Z , wherein "Z" is a leaving group which, upon its departure, enables CH_3 to form a covalent bond with the nitrogen atom of naltrexone, forming MNTX. Methylating agents in general, and leaving groups in general, are well known to those of ordinary skill in the art and are described extensively in both the patent literature and in chemistry text books. Suitable Z groups include, but are not limited to, fluoro, chloro, bromo, iodo, $-\text{OSO}_2\text{CF}_3$, $\text{CH}_3\text{OSO}_2\text{O}-$, $-\text{OSO}_2\text{CH}_3$, $-\text{OSO}_2\text{C}_6\text{H}_4\text{-p-CH}_3$, $-\text{OSO}_2\text{C}_6\text{H}_4\text{-p-Br}$.

"Alkenyl", in general, refers to an alkyl group containing at least one carbon-carbon double bond and having from 2 to about 10 carbon atoms in the chain, and all combinations and subcombinations of ranges therein. In certain preferred embodiments, the alkenyl group is a C_2 - C_{10} alkyl group, i.e., a branched or linear alkenyl group having from 2 to about 10 carbons. In other preferred embodiments, the alkenyl group is a C_2 - C_6 alkenyl group, i.e., a branched or linear alkenyl group having from 2 to about 6 carbons. In still other preferred embodiments, the alkenyl group is a C_3 - C_{10} alkenyl group, i.e., a branched or linear alkenyl group having from about 3 to about 10 carbons. In yet other preferred embodiments, the alkenyl group is a C_2 - C_5 alkenyl group, i.e., a branched or linear alkenyl group having from 2 to about 5 carbons. Exemplary alkenyl groups include, for example, vinyl, propenyl, butenyl, pentenyl, hexenyl, heptenyl, octenyl, nonenyl and decenyl groups.

"Alkylene", in general, refers to a straight or branched bivalent aliphatic hydrocarbon group having from 1 to about 6 carbon atoms, and all combinations and subcombinations of ranges therein. The alkylene group may be straight, branched or cyclic. Exemplary alkylene groups include, for example, methylene ($-\text{CH}_2-$), ethylene ($-\text{CH}_2\text{-CH}_2-$) and propylene ($-(\text{CH}_2)_3-$). There may be optionally inserted along the alkylene group one or more oxygen, sulfur or optionally substituted nitrogen atoms, wherein the nitrogen substituent is alkyl as described previously. Preferred alkylene groups have from about 1 to about 4 carbons.

"Alkenylene", in general, refers to an alkylene group containing at least one

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carbon--carbon double bond. Exemplary alkenylene groups include, for example, ethenylene (-CH=CH-) and propenylene (-CH=CHCH₂-). Preferred alkenylene groups have from 2 to about 4 carbons.

"Cycloalkyl", in general, refers to any stable monocyclic or bicyclic ring having from about 3 to about 10 carbons, and all combinations and subcombinations of ranges therein. In preferred embodiments, the cycloalkyl group is a C₃-C₈ cycloalkyl group, i.e., a cycloalkyl group having from about 3 to about 8 carbons, with C₃-C₆ cycloalkyl groups, i.e., cycloalkyl groups having from about 3 to about 6 carbons being more preferred. The cycloalkyl group may be optionally substituted with one or more cycloalkyl group substituents. Preferred cycloalkyl group substituents include alkyl, preferably C₁-C₃ alkyl, alkoxy, preferably C₁-C₃ alkoxy, or halo. Exemplary cycloalkyl groups include, for example, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl groups.

"Cycloalkyl-substituted alkyl", in general, refers to a linear alkyl group, preferably a lower alkyl group, substituted at a terminal carbon with a cycloalkyl group, preferably a C₃-C₈ cycloalkyl group. Typical cycloalkyl-substituted alkyl groups include cyclohexylmethyl, cyclohexylethyl, cyclopentylethyl, cyclopentylpropyl, cyclopropylmethyl and the like.

"Cycloalkenyl", in general, refers to an olefinically unsaturated cycloalkyl group having from about 4 to about 10 carbons, and all combinations and subcombinations of ranges therein. In preferred embodiments, the cycloalkenyl group is a C₅-C₈ cycloalkenyl group, i.e., a cycloalkenyl group having from about 5 to about 8 carbons.

"Alkoxy", in general, refers to an alkyl-O- group where alkyl is as previously described. Exemplary alkoxy groups include, for example, methoxy, ethoxy, propoxy, butoxy and heptoxy.

"Alkoxy-alkyl", in general, refers to an alkyl-O-alkyl group where alkyl is as previously described.

"Acyl", in general, means an alkyl-CO- group wherein alkyl is as previously described. Preferred acyl groups comprise lower alkyl groups, such as alkyl of about 1 to about 3 carbons. Exemplary acyl groups include acetyl, propanoyl, 2-

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methylpropanoyl, and butanoyl.

"Aryl", in general, refers to an aromatic carbocyclic radical containing 6, 10 or 14 carbons. The phenyl group may be optionally substituted with one or two or more substituents. Preferred aryl group substituents include alkyl groups, preferably C₁-C₅ alkyl groups. Exemplary aryl groups include phenyl and naphthyl.

"Aryl-substituted alkyl", in general, refers to an linear alkyl group, preferably a lower alkyl group, substituted at a carbon with an optionally substituted aryl group, preferably an optionally substituted phenyl ring. Exemplary aryl-substituted alkyl groups include, for example, phenylmethyl, phenylethyl and 3-(4-methylphenyl)propyl.

"Heterocyclic", in general, refers to a monocyclic or multicyclic ring system radical containing from about 4 to about 10 members, and all combinations and subcombinations of ranges therein, wherein one or more of the members is an element other than carbon, for example, nitrogen, oxygen or sulfur. The heterocyclic group may be aromatic or nonaromatic. Exemplary heterocyclic groups include, for example, isoxazole, pyrrole and piperidine groups.

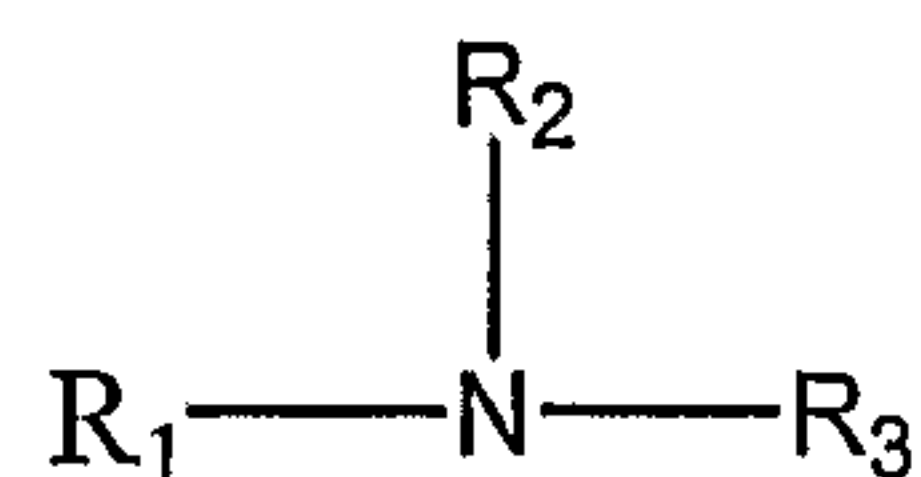
"Organic solvent" has its common ordinary meaning to those of skill in this art. Exemplary organic solvents useful in the invention include, but are not limited to tetrahydrofuran, acetone, hexane, ether, chloroform, acetic acid, acetonitrile, chloroform, cyclohexane, methanol, and toluene. Anhydrous organic solvents are included.

"Dipolar aprotic" solvents are protophilic solvents that cannot donate labile hydrogen atoms and that exhibit a permanent dipole moment. Examples include acetone, ethyl acetate, dimethyl sulfoxide (DMSO), dimethyl formamide (DMF) and N-methylpyrrolidone.

"Dipolar protic" solvents are those that can donate labile hydrogen atoms and that exhibit a permanent dipole moment. Examples include water, alcohols such as 2-propanol, ethanol, methanol, carboxylic acids such as formic acid, acetic acid, and propionic acid.

"Tertiary amines" has its common, ordinary meaning. In general, the tertiary amines useful in the invention have the general formula:

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wherein R₁, R₂, and R₃ are identical or a combination of different straight or branched
 5 chain alkyl groups, alkenyl groups, alkylene groups, alkenylene groups, cycloalkyl
 groups, cycloalkyl-substituted alkyl groups, cycloalkenyl groups, alkoxy groups,
 alkoxy-alkyl groups, acyl groups, aryl groups, aryl-substituted alkyl groups, and
 heterocyclic groups. Exemplary tertiary amines useful according to the invention are
 those where R₁₋₃ is an alkyl group of the formula (C_nH_{2n+1}, n=1-4), or aralkyl group
 10 of the formula (C₆H₅(CH₂)_n, [n=1-2]). Exemplary tertiary amines useful according to
 the invention also are cycloalkyl tertiary amines (e.g., *N*-methylmorpholine, *N*-
 methylpyrrolidine, *N*-methylpiperidine), pyridine and Proton Sponge® (*N,N,N',N'* -
 tetramethyl-1,8-naphthalene).

As will be readily understood, functional groups present may contain
 15 protecting groups during the course of synthesis. Protecting groups are known per se
 as chemical functional groups that can be selectively appended to and removed from
 functionalities, such as hydroxyl groups and carboxyl groups. These groups are
 present in a chemical compound to render such functionality inert to chemical
 reaction conditions to which the compound is exposed. Any of a variety of protecting
 20 groups may be employed with the present invention. Preferred protecting groups are
 those that are stable during formation, isolation and purification. A preferred
 protecting group is an isobutyryl groups,); silyl ethers (SiR₃, wherein each R can be
 independently C₁-C₆ alkyl, straight chain or branched); 2-tetrahydropyranyl ether,
 alkyl carbonates; a benzyloxycarbonyl group and a tert-butyloxycarbonyl group.
 25 Other preferred protecting groups that may be employed in accordance with the
 present invention are described in Greene, T. W. and Wuts, P. G. M., Protective
 Groups in Organic Synthesis 2d. Ed., Wiley & Sons, 1991. The expression "hydroxyl
 protective group" as used hereinbelow is intended to designate a group which is
 inserted in place of the hydrogen atom of an OH group.

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When the hydroxyl protective group is an aliphatic ester it preferably represents an radical selected from the group consisting of alkanoyl having 3 to 8 carbon atoms; alkenoyl having one or two double bonds and 3 to 8 carbon atoms;



wherein the cycloalkyl portion contains 3 to 7 ring atoms and r is zero, one, two or three; phenoxyacetyl; pyridinecarbonyl; and

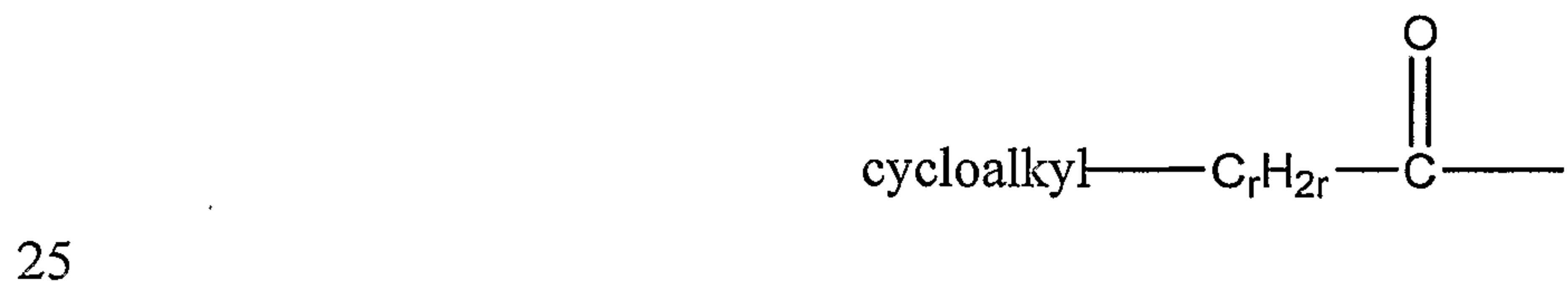


wherein r is zero, one, two or three and phenyl is unsubstituted or is substituted by 1 to 3 alkyl groups each having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, halo, trifluoromethyl, dialkylamino having 2 to 8 carbon atoms or alkanoylamino having 2 to 6 carbon atoms.

15 When the acyl group is alkanoyl, there are included both unbranched and branched alkanoyl, for example, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, 2-methylbutanoyl, pivalyl (pivaloyl), 3-methylpentanoyl, 3,3-dimethylbutanoyl, 2,2-dimethylpentanoyl and the like. Pivalyl, isobutyryl and isovaleryl are important examples.

20 When the acyl group is alkenoyl, there are included, for example, crotonyl, 2,5-hexadienoyl and 3,6-octadienoyl.

When the acyl group is



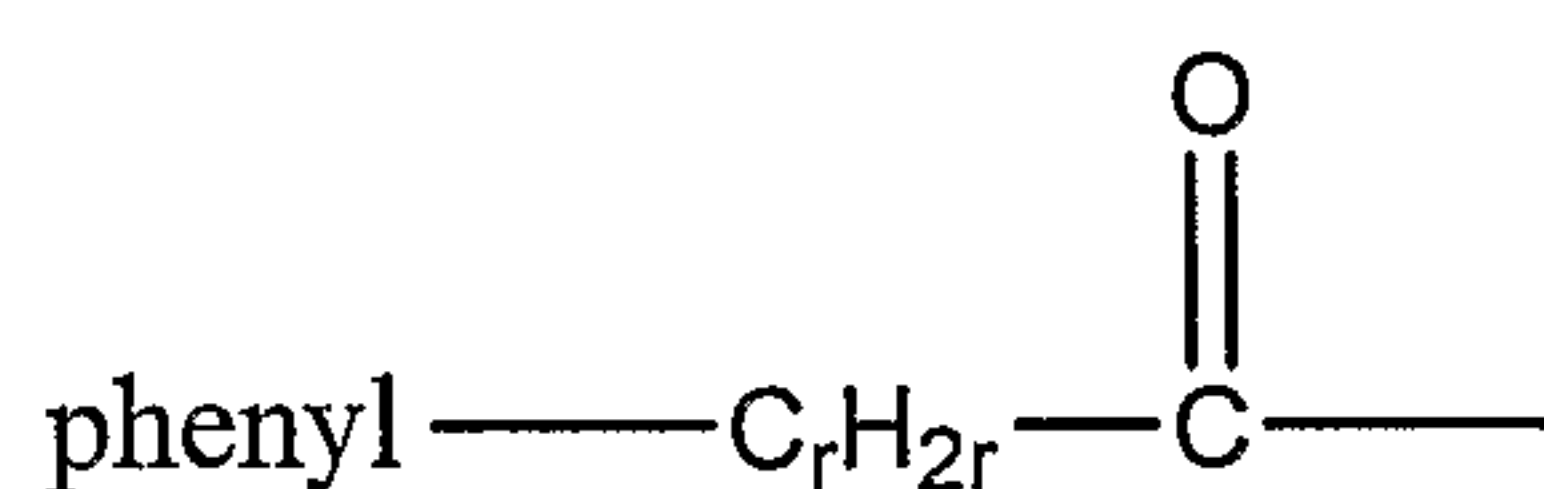
there are included cycloalkanecarbonyl and cycloalkanealkanoyl groups wherein the cycloalkane portion can optionally bear 1 or 2 alkyl groups as

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substituents, e.g. cyclopropanecarbonyl, 1-methylcyclopropanecarbonyl, cyclopropaneacetyl, α -methylcyclopropaneacetyl, 1-methylcyclopropaneacetyl, cyclopropanepropionyl, α -methylcyclopropanepropionyl, 2-isobutylcyclopropanepropionyl, cyclobutanecarbonyl, 3,3-dimethylcyclobutanecarbonyl, cyclobutaneacetyl, 2,2-dimethyl-3-ethylcyclobutaneacetyl, cyclopentanecarbonyl, cyclohexaneacetyl, cyclohexanecarbonyl, cycloheptanecarbonyl and cycloheptanepropionyl. Cyclohexanecarbonyl is especially preferred.

When the acyl group is pyridinecarbonyl, there are included picolinoyl (2-pyridinecarbonyl), nicotinoyl (3-pyridinecarbonyl) and isonicotinoyl (4-pyridinecarbonyl).

When the acyl group is

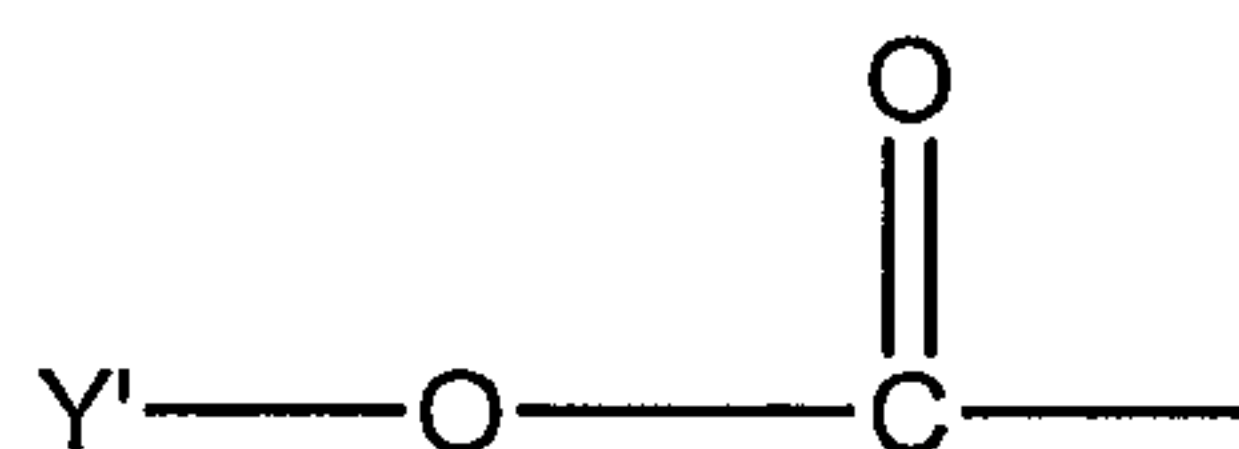


there are included, for example, benzoyl, phenylacetyl, α -phenylpropionyl, β -phenylpropionyl, p-toluyyl, m-toluyyl, o-toluyyl, o-ethylbenzoyl, p-tert-butylbenzoyl, 3,4-dimethylbenzoyl, 2-methyl-4-ethylbenzoyl, 2,4,6-trimethylbenzoyl, m-methylphenylacetyl, p-isobutylphenylacetyl, β -(p-ethylphenyl)propionyl, p-anisoyl, m-anisoyl, o-anisoyl, m-isopropoxybenzoyl, p-methoxyphenylacetyl, m-isobutoxyphenylacetyl, m-diethylaminobenzoyl, 3-methoxy-4-ethoxybenzoyl, 3,4,5-trimethoxybenzoyl, p-dibutylaminobenzoyl, 3,4-diethoxyphenylacetyl, β -(3,4,5-trimethoxyphenyl)propionyl, o-iodobenzoyl, m-bromobenzoyl, p-chlorobenzoyl, p-fluorobenzoyl, 2-bromo-4-chlorobenzoyl, 2,4,6-trichlorobenzoyl, p-chlorophenylacetyl, α -(m-bromophenyl)propionyl, p-trifluoromethylbenzoyl, 2,4-di(trifluoromethyl)benzoyl, m-trifluoromethylphenylacetyl, β -(3-methyl-4-chlorophenyl)propionyl, p-dimethylaminobenzoyl, p-(N-methyl-N-ethylamino)benzoyl, o-acetamidobenzoyl, m-propionamidobenzoyl, 3-chloro-4-acetamidophenylacetyl, p-n-butoxybenzoyl, 2,4,6-triethoxybenzoyl, β -(p-

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trifluoromethylphenyl)propionyl, 2-methyl-4-methoxybenzoyl, p-acetamidophenylpropionyl and 3-chloro-4-ethoxybenzoyl.

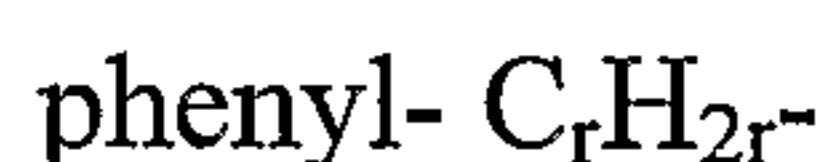
When the hydroxyl protective group is a carbonate grouping, it has the structural formula



i.e., it is an organic radical which can be considered to be derived from a carbonic acid by removal of the hydroxyl group from the COOH portion. Y' preferably represents alkyl having 1 to 7 carbon atoms; alkenyl having one or two double bonds and 2 to 7 carbon atoms;



wherein the cycloalkyl portion contains 3 to 7 ring atoms and r is zero, one, two or three; phenoxy; 2-, 3-, or 4-pyridyl; or



wherein r is zero, one, two or three and phenyl is unsubstituted or is substituted by 1 to 3 alkyl each having 1 to 4 carbon atoms, alkoxy having 1 to 4 carbon atoms, halo, trifluoromethyl, dialkylamino having 2 to 8 carbon atoms or alkanoylamino having 2 to 6 carbon atoms. Most preferably, Y' is C₁-C₇ alkyl, particularly ethyl or isopropyl.

Preferred protecting groups are those that can be selectively appended to a functionality. These groups render such functionality inert to chemical reaction conditions to which the compound may be exposed. After the protecting group has served its purpose it can be selectively removed from the functionality without altering the molecular structure. Most preferred protecting groups are those that can

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be selectively appended to and removed from the functionality under mild conditions, in high yield.

Preferred protecting groups for 3-*O*-protected-naltrexone include those that are more stable and sterically hindered compared to an acetyl protecting group, which
5 was found to be unstable during preparation and purification, thus resulting in lower yield and purity, and difficulty in handling. Examples of preferred protecting groups for use in the method of the present invention include isobutyryl, 2-methyl butyryl, tertbutyl carbonyl and the like. In a preferred embodiment, the protecting group is isobutyryl, due to its greater stability which results in higher yield and purity. Such
10 protecting groups provide yields of 3-*O*-protected-naltrexone of greater than 70, preferably greater than 75%. In one embodiment, yield of 3-*O*-protected-naltrexone is about 80% or greater.

Although some of the foregoing protecting groups and tertiary amines are not substituted, those of ordinary skill in the art will understand that substitutions can be
15 present in some circumstances.

The present invention provides a method for stereoselective synthesis of R-MNTX comprising;

- (a) methylating a 3-*O*-protected-naltrexone with a methylating agent to yield 3-*O*-protected-R-MNTX salt; and
- 20 (b) hydrolysis to remove the 3- hydroxyl protecting group to yield R-MNTX. Preferred hydroxyl protecting groups of the 3-*O*-protected-R-MNTX salt include isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, silyl ethers, 2-tetrahydropyranyl ethers, and alkyl carbonates.

Unlike the method described by Goldberg et al which teaches room
25 temperature for three weeks or 70°C for seven days for the methylation reaction to produce N-MNTX, the stereoselective methylation conditions of the present invention are conducted at a temperature above 70°C, more preferably above 80°C. In one embodiment, the reaction is carried out at about 88°C. Based on the standard principles of chemical reactions involving stereoisomers, one would expect at higher
30 temperatures the reaction would proceed with kinetic control resulting in a mixture of R-MNTX and S-MNTX with high percentages of both stereoisomers. It was

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surprising that at elevated temperatures the method of the present invention provided predominantly the R-MNTX rather than a mixture with a higher percentage of S-MNTX.

The methylation reaction of the present invention is allowed to proceed from 1 hour to about 24 hours, preferably about 5 hours to about 16 hours, more preferably about 8 to 12 hours, most preferably about 10 hours. This reaction time offers a major industrial scale advantage over the three weeks at room temperature or seven days at 70°C taught by Goldberg et al.

In a preferred embodiment, the methylation reaction is conducted at about 88°C for 10 hours. These reaction parameters are highly desirable for the development of a process amenable to scale-up in industrial scale.

The present invention further provides a method of purifying R-MNTX from a mixture of stereoisomers of R-MNTX and S-MNTX, the method comprising at least one, two or multiple recrystallizations. The recrystallized product is highly enriched in R-MNTX and substantially devoid of S-MNTX. In one embodiment the recrystallized product is greater than 98% pure R-MNTX. It is understood that an artisan skilled in the art can optimize this methodology to obtain higher purity and/or higher yield of R-MNTX in which the recrystallized product is greater than 99% pure R-MNTX and even greater than 99.9% pure R-MNTX.

The recrystallization solvent can be an organic solvent or a mixture of organic solvents or a mixture of organic solvent(s) plus water. A preferred solvent is an alcohol, more preferred a low molecular weight alcohol. In one embodiment, the low molecular weight alcohol is methanol.

Goldberg et al., and Cantrell et al., make use of organic solvent(s)/water for recrystallization. This is a standard practice to clean up a reaction mixture. It is not the Goldberg et al.'s nor Cantrell et al.'s stated goal to obtain one stereoisomer over the other, as they do not address the existence of stereoisomers, or whether a stereoisomer is obtained preferentially. Therefore, neither Goldberg et al., nor Cantrell et al., address the impact that recrystallization may have on the composition of stereoisomers. The present invention discloses the conditions under which

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recrystallization can be used advantageously to increase the purity of R-MNTX from a mixture of R-MNTX and S-MNTX.

One aspect of the invention is a method of resolving and identifying R-MNTX and S-MNTX in a solution of MNTX. The R-MNTX also is useful in HPLC assay
5 methods of quantifying an amount of R-MNTX in a composition or mixture in which the method comprises applying a sample of the composition or mixture to a chromatography column, resolving the components of the composition or mixture, and calculating the amount of R-MNTX in the sample by comparing the percentage of a resolved component in the sample with the percentage of a standard concentration of
10 R-MNTX. The method is particularly useful in reverse phase HPLC chromatography.

The pharmaceutical preparations of the invention, when used alone or in cocktails, are administered in therapeutically effective amounts. A therapeutically effective amount will be determined by the parameters discussed below; but, in any event, is that amount which establishes a level of the drug(s) effective for treating a
15 subject, such as a human subject, having one of the conditions described herein. An effective amount means that amount alone or with multiple doses, necessary to delay the onset of, lessen the severity of, or inhibit completely, lessen the progression of, or halt altogether the onset or progression of the condition being treated or a symptom associated therewith. In the case of constipation, an effective amount, for example, is
20 that amount which relieves a symptom of constipation, which induces a bowel movement, which increases the frequency of bowel movements, or which decreases oral-cecal transit time. The known and conventional definition of constipation is (i) less than one bowel movement in the previous three days or (ii) less than three bowel movements in the previous week (See e.g., U.S. Patent 6,559,158). In other words, a
25 patient is not constipated (i.e., has "regular bowel movements" as used herein) if the patient has at least one bowel movement every three days and at least three bowel movements per week. Accordingly, at least one bowel movement every two days would be considered regular bowel movements. Likewise, at least one bowel movement per day is a regular bowel movement. Effective amounts therefore can be
30 those amounts necessary to establish or maintain regular bowel movements.

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In certain instances, the amount is sufficient to induce a bowel movement within 12 hours of administration of the R-MNTX or the R-MNTX intermediate, 3-O-protected-R-MNTX salt, 10 hours, 8 hours, 6 hours, 4 hours, 2 hours, 1 hour and even immediately upon administration, depending upon the mode of administration.

5 Intravenous administration can produce an immediate effect of laxation in chronic opioid users. Subcutaneous administration can result in a bowel movement within 12 hours of administration, preferably within 4 hours of administration. When administered to a subject, effective amounts will depend, of course, on the particular condition being treated; the severity of the condition; individual patient parameters
10 including age, physical condition, size and weight; concurrent treatment and, especially, concurrent treatment with opioids where opioids are administered chronically; frequency of treatment; and the mode of administration. These factors are well known to those of ordinary skill in the art and can be addressed with no more than routine experimentation.

15 Patients amenable to the therapy of the present invention include but are not limited to terminally ill patients, patients with advanced medical illness, cancer patients, AIDS patients, post-operative patients, patients with chronic pain, patients with neuropathies, patients with rheumatoid arthritis, patients with osteoarthritis, patients with chronic back pain, patients with spinal cord injury, patients with chronic
20 abdominal pain, patients with chronic pancreatic pain, patients with pelvic/perineal pain, patients with fibromyalgia, patients with chronic fatigue syndrome, patients infected with HCV, patients with irritable bowel syndrome, patients with migraine or tension headaches, patients with sickle cell anemia, patients on hemodialysis, and the like.

25 Patients amenable to the therapy of the present invention also include but are not limited to patients suffering from dysfunctions caused by endogenous opioids, especially in post-operative settings. In certain embodiments, the R-MNTX or intermediate thereof is present in an amount sufficient to accelerate discharge from hospital post-surgery, including abdominal surgeries such as rectal resection,
30 colectomy, stomach, esophageal, duodenal, appendectomy, hysterectomy, or non-abdominal surgeries such as orthopedic, trauma injuries, thoracic or transplantation

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surgery. This treatment can be effective to shorten the length of the time in the hospital, or to shorten the time to a hospital discharge order written post-operatively by shortening the time to bowel sounds after surgery, or first flatus, to first laxation or to solid diet intake following surgery. The R-MNTX or intermediate thereof may
5 continue to be provided after the patient has ceased to receive opioid pain medications post-operatively.

Certain patients particularly amenable to treatment are patients having the symptoms of constipation and/or gastrointestinal immotility and who have failed to obtain relief or ceased to obtain relief or a consistent degree of relief of their
10 symptoms using a laxative or a stool softener, either alone or in combination, or who are otherwise resistant to laxatives and/or stool softeners. Such patients are said to be refractory to the conventional laxatives and/or stool softeners. The constipation and/or gastrointestinal immotility may be induced or a consequence of one or more diverse conditions including, but not limited to, a disease condition, a physical
15 condition, a drug-induced condition, a physiological imbalance, stress, anxiety, and the like. The conditions inducing constipation and/or gastrointestinal immotility may be acute conditions or chronic conditions.

The subjects can be treated with a combination of R-MNTX, or the 3-O-protected-R-MNTX intermediate thereof, and a laxative and/or a stool softener (and
20 optionally, an opioid). In these circumstances the R-MNTX or the intermediate thereof and the other therapeutic agent(s) are administered close enough in time such that the subject experiences the effects of the various agents as desired, which typically is at the same time. In some embodiments the R-MNTX or the intermediate thereof will be delivered first in time, in some embodiments second in time, and still
25 in some embodiments at the same time. As discussed in greater detail herein, the invention contemplates pharmaceutical preparations where the R-MNTX or intermediate thereof is administered in a formulation including the R-MNTX or the intermediate thereof and one or both of a laxative and a stool softener (and, optionally, an opioid). These formulations may be parenteral or oral, such as the ones
30 described in U.S. Serial No. 10/821,809. Included are solid, semisolid, liquid, controlled release, lyophilized and other such formulations.

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In an important embodiment, the administered amount of R-MNTX is sufficient to induce laxation. This has particular application where the subject is a chronic opioid user. Chronic opioid use as used herein includes daily opioid treatment for a week or more or intermittent opioid use for at least two weeks. It previously was determined that patients receiving opioids chronically become tolerant to opioids and need increasing doses. Thus, a patient receiving oral doses of opioids chronically would be receiving typically between 40 and 100 mg per day of a morphine-equivalent dose of opioid. It likewise was determined surprisingly that such subjects become more responsive to the effects of MNTX and that surprisingly lower doses induced side effects. Thus, to induce immediate laxation, it requires on the order of only about 0.15 mg/kg MNTX intravenously. For oral administration, a sufficient dose is believed to be less than 3 mg/kg uncoated and even less when the R-MNTX is enterically coated.

Patients using opioids chronically include late stage cancer patients, elderly patients with osteoarthritic changes, methadone maintenance patients, neuropathic pain and chronic back pain patients. Treatment of these patients is important from a quality of life standpoint, as well as to reduce complications arising from chronic constipation, such as hemorrhoids, appetite suppression, mucosal breakdown, sepsis, colon cancer risk, and myocardial infarction.

The opioid can be any pharmaceutically acceptable opioid. Common opioids are those selected from the group consisting of alfentanil, anileridine, asimadoline, bremazocine, buprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenoxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone, hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, and tramadol. The opioid also may be mixed together with the R-MNTX or intermediate thereof and provided in any of the forms described above in connection with R-MNTX or intermediate thereof.

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Generally, oral doses of R-MNTX and intermediates thereof will be from about 0.25 to about 19.0 mg/kg body weight per day. Generally, parenteral administration, including intravenous and subcutaneous administration, will be from about 0.01 to 1.0 mg/kg body weight depending on whether administration is as a bolus or is spread out over time such as with an I.V. drip. Generally, the I.V. dose for post-operative bowel dysfunction (POBD) is 0.3mg/kg. It is expected that doses ranging from 0.01 to 0.45 mg/kg body weight will yield the desired results. Dosage may be adjusted appropriately to achieve desired drug levels, local or systemic, depending on the mode of administration. For example, it is expected that the dosage for oral administration of the opioid antagonists in an enterically-coated formulation would be lower than in an immediate release oral formulation. In the event that the response in a patient is insufficient at such doses, even higher doses (or effectively higher dosage by a different, more localized delivery route) may be employed to the extent that the patient tolerance permits. Multiple doses per day are contemplated to achieve appropriate systemic levels of compounds. Appropriate systemic levels can be determined by, for example, measurement of the patient's peak or sustained plasma level of the drug. Peak plasma levels below 100 ng/ml are preferred in some instances. "Dose" and "dosage" are used interchangeably herein.

A variety of administration routes are available. The particular mode selected will depend, of course, upon the particular combination of drugs selected, the severity of the condition being treated, or prevented, the condition of the patient, and the dosage required for therapeutic efficacy. The methods of this invention, generally speaking, may be practiced using any mode of administration that is medically acceptable, meaning any mode that produces effective levels of the active compounds without causing clinically unacceptable adverse effects. Such modes of administration include oral, rectal, topical, transdermal, sublingual, intravenous infusion, pulmonary, intra-arterial, intra-adipose tissue, intra-lymphatic, intramuscular, intracavity, aerosol, aural (e.g., via eardrops), intranasal, inhalation, intra-articular, needleless injection, subcutaneous or intradermal (e.g., transdermal) delivery. For continuous infusion, a patient-controlled analgesia (PCA) device or an implantable drug delivery device may be employed. Oral, rectal, or topical

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administration may be important for prophylactic or long-term treatment. Preferred rectal modes of delivery include administration as a suppository or enema wash.

The pharmaceutical preparations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy.

5 All methods include the step of bringing the compounds of the invention into association with a carrier which constitutes one or more accessory ingredients. In general, the compositions are prepared by uniformly and intimately bringing the compounds of the invention into association with a liquid carrier, a finely divided solid carrier, or both, and then, if necessary, shaping the product.

10 When administered, the pharmaceutical preparations of the invention are applied in pharmaceutically acceptable compositions. Such preparations may routinely contain salts, buffering agents, preservatives, compatible carriers, lubricants, and optionally other therapeutic ingredients. When used in medicine the salts should be pharmaceutically acceptable, but non-pharmaceutically acceptable salts may
15 conveniently be used to prepare pharmaceutically acceptable salts thereof and are not excluded from the scope of the invention. Such pharmacologically and pharmaceutically acceptable salts include, but are not limited to, those prepared from the following acids: hydrochloric, hydrobromic, sulfuric, nitric, phosphoric, maleic, acetic, salicylic, p-toluenesulfonic, tartaric, citric, methanesulfonic, formic, succinic,
20 naphthalene-2-sulfonic, pamoic, 3-hydroxy-2-naphthalenecarboxylic, and benzene sulfonic.

It should be understood that when referring to MNTX, R- and S-MNTX, and therapeutic agent(s) of the invention, it is meant to encompass salts of the same. Such salts are of a variety well known to those of ordinary skill in the art. When used in
25 pharmaceutical preparations, the salts preferably are pharmaceutically-acceptable for use in humans. Bromide is an example of one such salt.

The pharmaceutical preparations of the present invention may include or be diluted into a pharmaceutically-acceptable carrier. The term "pharmaceutically-acceptable carrier" as used herein means one or more compatible solid or liquid
30 fillers, diluents or encapsulating substances which are suitable for administration to a human or other mammal such as non-human primate, a dog, cat, horse, cow, sheep,

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pig, or goat. The term "carrier" denotes an organic or inorganic ingredient, natural or synthetic, with which the active ingredient is combined to facilitate the application. The carriers are capable of being commingled with the preparations of the present invention, and with each other, in a manner such that there is no interaction which would substantially impair the desired pharmaceutical efficacy or stability. Carrier formulations suitable for oral administration, for suppositories, and for parenteral administration, etc., can be found in Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, Pa.

Aqueous formulations may include a chelating agent, a buffering agent, an anti-oxidant and, optionally, an isotonicity agent, preferably pH adjusted to between 3.0 and 3.5. Examples of such formulations that are stable to autoclaving and long term storage are described in co-pending U.S. Application Serial No. 10/821,811, entitled "Pharmaceutical Formulation."

Chelating agents include, for example, ethylenediaminetetraacetic acid (EDTA) and derivatives thereof, citric acid and derivatives thereof, niacinamide and derivatives thereof, sodium desoxycholate and derivatives thereof, and L-glutamic acid, N, N-diacetic acid and derivatives thereof.

Buffering agents include those selected from the group consisting of citric acid, sodium citrate, sodium acetate, acetic acid, sodium phosphate and phosphoric acid, sodium ascorbate, tartaric acid, maleic acid, glycine, sodium lactate, lactic acid, ascorbic acid, imidazole, sodium bicarbonate and carbonic acid, sodium succinate and succinic acid, histidine, and sodium benzoate and benzoic acid, or combinations thereof.

Antioxidants include those selected from the group consisting of an ascorbic acid derivative, butylated hydroxy anisole, butylated hydroxy toluene, alkyl gallate, sodium meta-bisulfite, sodium bisulfite, sodium dithionite, sodium thioglycollate acid, sodium formaldehyde sulfoxylate, tocopheral and derivatives thereof, monothioglycerol, and sodium sulfite. The preferred antioxidant is monothioglycerol.

Isotonicity agents include those selected from the group consisting of sodium chloride, mannitol, lactose, dextrose, glycerol, and sorbitol.

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Preservatives that can be used with the present compositions include benzyl alcohol, parabens, thimerosal, chlorobutanol and preferably benzalkonium chloride. Typically, the preservative will be present in a composition in a concentration of up to about 2% by weight. The exact concentration of the preservative, however, will vary depending upon the intended use and can be easily ascertained by one skilled in the art.

The compounds of the invention can be prepared in lyophilized compositions, preferably in the presence of a cryoprotecting agent such as mannitol, or lactose, sucrose, polyethylene glycol, and polyvinyl pyrrolidines. Cryoprotecting agents which result in a reconstitution pH of 6.0 or less are preferred. The invention therefore provides a lyophilized preparation of therapeutic agent(s) of the invention. The preparation can contain a cryoprotecting agent, such as mannitol or lactose, which is preferably neutral or acidic in water.

Oral, parenteral and suppository formulations of agents are well known and commercially available. The therapeutic agent(s) of the invention can be added to such well known formulations. It can be mixed together in solution or semi-solid solution in such formulations, can be provided in a suspension within such formulations or could be contained in particles within such formulations.

A product containing therapeutic agent(s) of the invention and, optionally, one or more other active agents can be configured as an oral dosage. The oral dosage may be a liquid, a semisolid or a solid. An opioid may optionally be included in the oral dosage. The oral dosage may be configured to release the therapeutic agent(s) of the invention before, after or simultaneously with the other agent (and/or the opioid). The oral dosage may be configured to have the therapeutic agent(s) of the invention and the other agents release completely in the stomach, release partially in the stomach and partially in the intestine, in the intestine, in the colon, partially in the stomach, or wholly in the colon. The oral dosage also may be configured whereby the release of the therapeutic agent(s) of the invention is confined to the stomach or intestine while the release of the other active agent is not so confined or is confined differently from the therapeutic agent(s) of the invention. For example, the therapeutic agent(s) of the invention may be an enterically coated core or pellets contained within a pill or

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capsule that releases the other agent first and releases the therapeutic agent(s) of the invention only after the therapeutic agent(s) of the invention passes through the stomach and into the intestine. The therapeutic agent(s) of the invention also can be in a sustained release material, whereby the therapeutic agent(s) of the invention is released throughout the gastrointestinal tract and the other agent is released on the same or a different schedule. The same objective for therapeutic agent(s) of the invention release can be achieved with immediate release of therapeutic agent(s) of the invention combined with enteric coated therapeutic agent(s) of the invention. In these instances, the other agent could be released immediately in the stomach, throughout the gastrointestinal tract or only in the intestine.

The materials useful for achieving these different release profiles are well known to those of ordinary skill in the art. Immediate release is obtainable by conventional tablets with binders which dissolve in the stomach. Coatings which dissolve at the pH of the stomach or which dissolve at elevated temperatures will achieve the same purpose. Release only in the intestine is achieved using conventional enteric coatings such as pH sensitive coatings which dissolve in the pH environment of the intestine (but not the stomach) or coatings which dissolve over time. Release throughout the gastrointestinal tract is achieved by using sustained-release materials and/or combinations of the immediate release systems and sustained and/or delayed intentional release systems (e.g., pellets which dissolve at different pHs).

In the event that it is desirable to release the therapeutic agent(s) of the invention first, the therapeutic agent(s) of the invention could be coated on the surface of the controlled release formulation in any pharmaceutically acceptable carrier suitable for such coatings and for permitting the release of the therapeutic agent(s) of the invention, such as in a temperature sensitive pharmaceutically acceptable carrier used for controlled release routinely. Other coatings which dissolve when placed in the body are well known to those of ordinary skill in the art.

The therapeutic agent(s) of the invention also may be mixed throughout a controlled release formulation, whereby it is released before, after or simultaneously with another agent. The therapeutic agent(s) of the invention may be free, that is,

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solubilized within the material of the formulation. The therapeutic agent(s) of the invention also may be in the form of vesicles, such as wax coated micropellets dispersed throughout the material of the formulation. The coated pellets can be fashioned to immediately release the therapeutic agent(s) of the invention based on temperature, pH or the like. The pellets also can be configured so as to delay the release of the therapeutic agent(s) of the invention, allowing the other agent a period of time to act before the therapeutic agent(s) of the invention exerts its effects. The therapeutic agent(s) of the invention pellets also can be configured to release the therapeutic agent(s) of the invention in virtually any sustained release pattern, including patterns exhibiting first order release kinetics or sigmoidal order release kinetics using materials of the prior art and well known to those of ordinary skill in the art.

The therapeutic agent(s) of the invention also can be contained within a core within the controlled release formulation. The core may have any one or any combination of the properties described above in connection with the pellets. The therapeutic agent(s) of the invention may be, for example, in a core coated with a material, dispersed throughout a material, coated onto a material or adsorbed into or throughout a material.

It should be understood that the pellets or core may be of virtually any type. They may be drug coated with a release material, drug interspersed throughout material, drug adsorbed into a material, and so on. The material may be erodible or nonerodible.

The therapeutic agent(s) of the invention, may be provided in particles. Particles as used herein means nano or microparticles (or in some instances larger) which can consist in whole or in part of the therapeutic agent(s) of the inventions or the other agents as described herein. The particles may contain the therapeutic agent(s) in a core surrounded by a coating, including, but not limited to, an enteric coating. The therapeutic agent(s) also may be dispersed throughout the particles. The therapeutic agent(s) also may be adsorbed into the particles. The particles may be of any order release kinetics, including zero order release, first order release, second order release, delayed release, sustained release, immediate release, and any

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combination thereof, etc. The particle may include, in addition to the therapeutic agent(s), any of those materials routinely used in the art of pharmacy and medicine, including, but not limited to, erodible, nonerodible, biodegradable, or nonbiodegradable material or combinations thereof. The particles may be

5 microcapsules which contain the antagonist in a solution or in a semi-solid state. The particles may be of virtually any shape.

Both non-biodegradable and biodegradable polymeric materials can be used in the manufacture of particles for delivering the therapeutic agent(s). Such polymers may be natural or synthetic polymers. The polymer is selected based on the period of

10 time over which release is desired. Bioadhesive polymers of particular interest include bioerodible hydrogels described by H.S. Sawhney, C.P. Pathak and J.A. Hubell in *Macromolecules*, (1993) 26:581-587.

These include polyhyaluronic acids, casein, gelatin, glutin, polyanhydrides, polyacrylic acid, alginate, chitosan, poly(methyl methacrylates),

15 poly(ethyl methacrylates), poly(butylmethacrylate), poly(isobutyl methacrylate), poly(hexylmethacrylate), poly(isodecyl methacrylate), poly(lauryl methacrylate), poly(phenyl methacrylate), poly(methyl acrylate), poly(isopropyl acrylate), poly(isobutyl acrylate), and poly(octadecyl acrylate).

The therapeutic agent(s) may be contained in controlled release systems. The

20 term "controlled release" is intended to refer to any drug-containing formulation in which the manner and profile of drug release from the formulation are controlled. This refers to immediate as well as nonimmediate release formulations, with nonimmediate release formulations including but not limited to sustained release and delayed release formulations. The term "sustained release" (also referred to as

25 "extended release") is used in its conventional sense to refer to a drug formulation that provides for gradual release of a drug over an extended period of time, and that preferably, although not necessarily, results in substantially constant blood levels of a drug over an extended time period. The term "delayed release" is used in its conventional sense to refer to a drug formulation in which there is a time delay

30 between administration of the formulation and the release of the drug therefrom. "Delayed release" may or may not involve gradual release of drug over an extended

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period of time, and thus may or may not be "sustained release." These formulations may be for any mode of administration.

Delivery systems specific for the gastrointestinal tract are roughly divided into three types: the first is a delayed release system designed to release a drug in response to, for example, a change in pH; the second is a timed-release system designed to release a drug after a predetermined time; and the third is a microflora enzyme system making use of the abundant enterobacteria in the lower part of the gastrointestinal tract (e.g., in a colonic site-directed release formulation).

An example of a delayed release system is one that uses, for example, an acrylic or cellulosic coating material and dissolves on pH change. Because of ease of preparation, many reports on such "enteric coatings" have been made. In general, an enteric coating is one which passes through the stomach without releasing substantial amounts of drug in the stomach (i.e., less than 10% release, 5% release and even 1% release in the stomach) and sufficiently disintegrating in the intestinal tract (by contact with approximately neutral or alkaline intestine juices) to allow the transport (active or passive) of the active agent through the walls of the intestinal tract.

Various *in vitro* tests for determining whether or not a coating is classified as an enteric coating have been published in the pharmacopoeia of various countries. A coating which remains intact for at least 2 hours, in contact with artificial gastric juices such as HCl of pH 1 at 36 to 38 °C and thereafter disintegrates within 30 minutes in artificial intestinal juices such as a KH₂PO₄ buffered solution of pH 6.8 is one example. One such well known system is EUDRAGIT material, commercially available and reported on by Behringer, Manchester University, Saale Co., and the like. Enteric coatings are discussed further, below.

A timed release system is represented by Time Erosion System (TES) by Fujisawa Pharmaceutical Co., Ltd. and Pulsincap by R. P. Scherer. According to these systems, the site of drug release is decided by the time of transit of a preparation in the gastrointestinal tract. Since the transit of a preparation in the gastrointestinal tract is largely influenced by the gastric emptying time, some time release systems are also enterically coated.

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Systems making use of the enterobacteria can be classified into those utilizing degradation of azoaromatic polymers by an azo reductase produced from enterobacteria as reported by the group of Ohio University (M. Saffran, et al., Science, Vol. 233: 1081 (1986)) and the group of Utah University (J. Kopecek, et al., Pharmaceutical Research, 9(12), 1540-1545 (1992)); and those utilizing degradation of polysaccharides by beta-galactosidase of enterobacteria as reported by the group of Hebrew University (unexamined published Japanese patent application No. 5-50863 based on a PCT application) and the group of Freiberg University (K. H. Bauer et al., Pharmaceutical Research, 10(10), S218 (1993)). In addition, the system using chitosan degradable by chitosanase by Teikoku Seiyaku K. K. (unexamined published Japanese patent application No. 4-217924 and unexamined published Japanese patent application No. 4-225922) is also included.

The enteric coating is typically, although not necessarily, a polymeric material. Preferred enteric coating materials comprise bioerodible, gradually hydrolyzable and/or gradually water-soluble polymers. The "coating weight," or relative amount of coating material per capsule, generally dictates the time interval between ingestion and drug release. Any coating should be applied to a sufficient thickness such that the entire coating does not dissolve in the gastrointestinal fluids at pH below about 5, but does dissolve at pH about 5 and above. It is expected that any anionic polymer exhibiting a pH-dependent solubility profile can be used as an enteric coating in the practice of the present invention. The selection of the specific enteric coating material will depend on the following properties: resistance to dissolution and disintegration in the stomach; impermeability to gastric fluids and drug/carrier/enzyme while in the stomach; ability to dissolve or disintegrate rapidly at the target intestine site; physical and chemical stability during storage; non-toxicity; ease of application as a coating (substrate friendly); and economical practicality.

Suitable enteric coating materials include, but are not limited to: cellulosic polymers such as cellulose acetate phthalate, cellulose acetate trimellitate, hydroxypropylmethyl cellulose phthalate, hydroxypropylmethyl cellulose succinate and carboxymethylcellulose sodium; acrylic acid polymers and copolymers, preferably formed from acrylic acid, methacrylic acid, methyl acrylate, ammonium

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methylacrylate, ethyl acrylate, methyl methacrylate and/or ethyl methacrylate (e.g., those copolymers sold under the trade name EUDRAGIT); vinyl polymers and copolymers such as polyvinyl acetate, polyvinylacetate phthalate, vinylacetate crotonic acid copolymer, and ethylene-vinyl acetate copolymers; and shellac (purified lac). Combinations of different coating materials may also be used. Well known enteric coating material for use herein are those acrylic acid polymers and copolymers available under the trade name EUDRAGIT from Rohm Pharma (Germany). The EUDRAGIT series E, L, S, RL, RS and NE copolymers are available as solubilized in organic solvent, as an aqueous dispersion, or as a dry powder. The EUDRAGIT series RL, NE, and RS copolymers are insoluble in the gastrointestinal tract but are permeable and are used primarily for extended release. The EUDRAGIT series E copolymers dissolve in the stomach. The EUDRAGIT series L, L-30D and S copolymers are insoluble in stomach and dissolve in the intestine, and are thus most preferred herein.

A particular methacrylic copolymer is EUDRAGIT L, particularly L-30D and EUDRAGIT L 100-55. In EUDRAGIT L-30D, the ratio of free carboxyl groups to ester groups is approximately 1:1. Further, the copolymer is known to be insoluble in gastrointestinal fluids having pH below 5.5, generally 1.5-5.5, i.e., the pH generally present in the fluid of the upper gastrointestinal tract, but readily soluble or partially soluble at pH above 5.5, i.e., the pH generally present in the fluid of lower gastrointestinal tract. Another particular methacrylic acid polymer is EUDRAGIT S, which differs from EUDRAGIT L-30D in that the ratio of free carboxyl groups to ester groups is approximately 1:2. EUDRAGIT S is insoluble at pH below 5.5, but unlike EUDRAGIT L-30D, is poorly soluble in gastrointestinal fluids having a pH in the range of 5.5 to 7.0, such as in the small intestine. This copolymer is soluble at pH 7.0 and above, i.e., the pH generally found in the colon. EUDRAGIT S can be used alone as a coating to provide drug delivery in the large intestine. Alternatively, EUDRAGIT S, being poorly soluble in intestinal fluids below pH 7, can be used in combination with EUDRAGIT L-30D, soluble in intestinal fluids above pH 5.5, in order to provide a delayed release composition which can be formulated to deliver the active agent to various segments of the intestinal tract. The more EUDRAGIT L-30D

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used, the more proximal release and delivery begins, and the more EUDRAGIT S used, the more distal release and delivery begins. It will be appreciated by those skilled in the art that both EUDRAGIT L-30D and EUDRAGIT S can be replaced with other pharmaceutically acceptable polymers having similar pH solubility characteristics. In certain embodiments of the invention, the preferred enteric coating is ACRYL-EZE™ (methacrylic acid co-polymer type C; Colorcon, West Point, PA).

The enteric coating provides for controlled release of the active agent, such that drug release can be accomplished at some generally predictable location. The enteric coating also prevents exposure of the therapeutic agent and carrier to the epithelial and mucosal tissue of the buccal cavity, pharynx, esophagus, and stomach, and to the enzymes associated with these tissues. The enteric coating therefore helps to protect the active agent, carrier and a patient's internal tissue from any adverse event prior to drug release at the desired site of delivery. Furthermore, the coated material of the present invention allows optimization of drug absorption, active agent protection, and safety. Multiple enteric coatings targeted to release the active agent at various regions in the gastrointestinal tract would enable even more effective and sustained improved delivery throughout the gastrointestinal tract.

The coating can, and usually does, contain a plasticizer to prevent the formation of pores and cracks that would permit the penetration of the gastric fluids. Suitable plasticizers include, but are not limited to, triethyl citrate (Citroflex 2), triacetin (glyceryl triacetate), acetyl triethyl citrate (Citroflex A2), Carbowax 400 (polyethylene glycol 400), diethyl phthalate, tributyl citrate, acetylated monoglycerides, glycerol, fatty acid esters, propylene glycol, and dibutyl phthalate. In particular, a coating comprised of an anionic carboxylic acrylic polymer will usually contain approximately 10% to 25% by weight of a plasticizer, particularly dibutyl phthalate, polyethylene glycol, triethyl citrate and triacetin. The coating can also contain other coating excipients such as detackifiers, antifoaming agents, lubricants (e.g., magnesium stearate), and stabilizers (e.g., hydroxypropylcellulose, acids and bases) to solubilize or disperse the coating material, and to improve coating performance and the coated product.

The coating can be applied to particles of the therapeutic agent(s), tablets of

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the therapeutic agent(s), capsules containing the therapeutic agent(s) and the like, using conventional coating methods and equipment. For example, an enteric coating can be applied to a capsule using a coating pan, an airless spray technique, fluidized bed coating equipment, or the like. Detailed information concerning materials,
5 equipment and processes for preparing coated dosage forms may be found in Pharmaceutical Dosage Forms: Tablets, eds. Lieberman et al. (New York: Marcel Dekker, Inc., 1989), and in Ansel et al., Pharmaceutical Dosage Forms and Drug Delivery Systems, 6th Ed. (Media, PA: Williams & Wilkins, 1995). The coating thickness, as noted above, must be sufficient to ensure that the oral dosage form
10 remains intact until the desired site of topical delivery in the lower intestinal tract is reached.

In another embodiment, drug dosage forms are provided that comprise an enterically coated, osmotically activated device housing a formulation of the invention. In this embodiment, the drug-containing formulation is encapsulated in a
15 semipermeable membrane or barrier containing a small orifice. As known in the art with respect to so-called "osmotic pump" drug delivery devices, the semipermeable membrane allows passage of water in either direction, but not drug. Therefore, when the device is exposed to aqueous fluids, water will flow into the device due to the osmotic pressure differential between the interior and exterior of the device. As water
20 flows into the device, the drug-containing formulation in the interior will be "pumped" out through the orifice. The rate of drug release will be equivalent to the inflow rate of water times the drug concentration. The rate of water influx and drug efflux can be controlled by the composition and size of the orifice of the device. Suitable materials for the semipermeable membrane include, but are not limited to,
25 polyvinyl alcohol, polyvinyl chloride, semipermeable polyethylene glycols, semipermeable polyurethanes, semipermeable polyamides, semipermeable sulfonated polystyrenes and polystyrene derivatives; semipermeable poly(sodium styrenesulfonate), semipermeable poly(vinylbenzyltrimethylammonium chloride), and cellulosic polymers such as cellulose acetate, cellulose diacetate, cellulose triacetate,
30 cellulose propionate, cellulose acetate propionate, cellulose acetate butyrate, cellulose trivalerate, cellulose trilmate, cellulose tripalmitate, cellulose trioctanoate, cellulose

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tripropionate, cellulose disuccinate, cellulose dipalmitate, cellulose dicylate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate heptanate, cellulose acetaldehyde dimethyl acetal, cellulose acetate ethylcarbamate, cellulose acetate methylcarbamate, cellulose
5 dimethylaminoacetate and ethylcellulose.

In another embodiment, drug dosage forms are provided that comprise a sustained release coated device housing a formulation of the invention. In this embodiment, the drug-containing formulation is encapsulated in a sustained release membrane or film. The membrane may be semipermeable, as described above. A
10 semipermeable membrane allows for the passage of water inside the coated device to dissolve the drug. The dissolved drug solution diffuses out through the semipermeable membrane. The rate of drug release depends upon the thickness of the coated film and the release of drug can begin in any part of the GI tract. Suitable membrane materials for such a membrane include ethylcellulose.

15 In another embodiment, drug dosage forms are provided that comprise a sustained release device housing a formulation of the invention. In this embodiment, the drug-containing formulation is uniformly mixed with a sustained release polymer. These sustained release polymers are high molecular weight water-soluble polymers, which when in contact with water, swell and create channels for water to diffuse
20 inside and dissolve the drug. As the polymers swell and dissolve in water, more of drug is exposed to water for dissolution. Such a system is generally referred to as sustained release matrix. Suitable materials for such a device include hydropropyl methylcellulose, hydroxypropyl cellulose, hydroxyethyl cellulose and methyl cellulose.

25 In another embodiment, drug dosage forms are provided that comprise an enteric coated device housing a sustained release formulation of the invention. In this embodiment, the drug containing product described above is coated with an enteric polymer. Such a device would not release any drug in the stomach and when the device reaches the intestine, the enteric polymer is first dissolved and only then would
30 the drug release begin. The drug release would take place in a sustained release fashion.

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Enterically coated, osmotically activated devices can be manufactured using conventional materials, methods and equipment. For example, osmotically activated devices may be made by first encapsulating, in a pharmaceutically acceptable soft capsule, a liquid or semi-solid formulation of the compounds of the invention as described previously. This interior capsule is then coated with a semipermeable membrane composition (comprising, for example, cellulose acetate and polyethylene glycol 4000 in a suitable solvent such as a methylene chloride-methanol admixture), for example using an air suspension machine, until a sufficiently thick laminate is formed, e.g., around 0.05 mm. The semipermeable laminated capsule is then dried using conventional techniques. Then, an orifice having a desired diameter (e.g., about 0.99 mm) is provided through the semipermeable laminated capsule wall, using, for example, mechanical drilling, laser drilling, mechanical rupturing, or erosion of an erodible element such as a gelatin plug. The osmotically activated device may then be enterically coated as previously described. For osmotically activated devices containing a solid carrier rather than a liquid or semi-solid carrier, the interior capsule is optional; that is, the semipermeable membrane may be formed directly around the carrier-drug composition. However, preferred carriers for use in the drug-containing formulation of the osmotically activated device are solutions, suspensions, liquids, immiscible liquids, emulsions, sols, colloids, and oils. Particularly preferred carriers include, but are not limited to, those used for enterically coated capsules containing liquid or semisolid drug formulations.

Cellulose coatings include those of cellulose acetate phthalate and trimellitate; methacrylic acid copolymers, e.g. copolymers derived from methylacrylic acid and esters thereof, containing at least 40% methylacrylic acid; and especially hydroxypropyl methylcellulose phthalate. Methacrylates include those of molecular weight above 100,000 daltons based on, e.g. methylacrylate and methyl or ethyl methylacrylate in a ratio of about 1:1. Typical products include Endragit L, e.g. L 100-55, marketed by Rohm GmbH, Darmstadt, Germany. Typical cellulose acetate phthalates have an acetyl content of 17-26% and a phthalate content of from 30-40% with a viscosity of ca. 45-90 cP. Typical cellulose acetate trimellitates have an acetyl content of 17-26%, a trimellityl content from 25-35% with a viscosity of ca. 15-20 cS.

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An example of a cellulose acetate trimellitate is the marketed product CAT (Eastman Kodak Company, USA). Hydroxypropyl methylcellulose phthalates typically have a molecular weight of from 20,000 to 130,000 daltons, a hydroxypropyl content of from 5 to 10%, a methoxy content of from 18 to 24% and a phthalyl content from 21 to 35%. An example of a cellulose acetate phthalate is the marketed product CAP (Eastman Kodak, Rochester N.Y., USA). Examples of hydroxypropyl methylcellulose phthalates are the marketed products having a hydroxypropyl content of from 6-10%, a methoxy content of from 20-24%, a phthalyl content of from 21-27%, a molecular weight of about 84,000 daltons, sold under the trademark HP50 and available from Shin-Etsu Chemical Co. Ltd., Tokyo, Japan, and having a hydroxypropyl content, a methoxyl content, and a phthalyl content of 5-9%, 18-22% and 27-35%, respectively, and a molecular weight of 78,000 daltons, known under the trademark HP55 and available from the same supplier.

The therapeutic agents may be provided in capsules, coated or not. The capsule material may be either hard or soft, and as will be appreciated by those skilled in the art, typically comprises a tasteless, easily administered and water soluble compound such as gelatin, starch or a cellulosic material. The capsules are preferably sealed, such as with gelatin bands or the like. See, for example, Remington: The Science and Practice of Pharmacy, Nineteenth Edition (Easton, Pa.: Mack Publishing Co., 1995), which describes materials and methods for preparing encapsulated pharmaceuticals.

A product containing therapeutic agent(s) of the invention can be configured as a suppository. The therapeutic agent(s) of the invention can be placed anywhere within or on the suppository to favorably affect the relative release of the therapeutic agent(s). The nature of the release can be zero order, first order, or sigmoidal, as desired.

Suppositories are solid dosage forms of medicine intended for administration via the rectum. Suppositories are compounded so as to melt, soften, or dissolve in the body cavity (around 98.6 °F) thereby releasing the medication contained therein.

Suppository bases should be stable, nonirritating, chemically inert, and physiologically inert. Many commercially available suppositories contain oily or

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fatty base materials, such as cocoa butter, coconut oil, palm kernel oil, and palm oil, which often melt or deform at room temperature necessitating cool storage or other storage limitations. U.S. Patent No. 4,837,214 to Tanaka et al. describes a suppository base comprised of 80 to 99 percent by weight of a lauric-type fat having a hydroxyl value of 20 or smaller and containing glycerides of fatty acids having 8 to 18 carbon atoms combined with 1 to 20 percent by weight diglycerides of fatty acids (which erucic acid is an example of). The shelf life of these type of suppositories is limited due to degradation. Other suppository bases contain alcohols, surfactants, and the like which raise the melting temperature but also can lead to poor absorption of the medicine and side effects due to irritation of the local mucous membranes (see for example, U.S. Patent No. 6,099,853 to Hartelendy et al., U.S. Patent No. 4,999,342 to Ahmad et al., and U.S. Patent No. 4,765,978 to Abidi et al.).

The base used in the pharmaceutical suppository composition of this invention includes, in general, oils and fats comprising triglycerides as main components such as cacao butter, palm fat, palm kernel oil, coconut oil, fractionated coconut oil, lard and WITEPSOL®, waxes such as lanolin and reduced lanolin; hydrocarbons such as VASELINE®, squalene, squalane and liquid paraffin; long to medium chain fatty acids such as caprylic acid, lauric acid, stearic acid and oleic acid; higher alcohols such as lauryl alcohol, cetanol and stearyl alcohol; fatty acid esters such as butyl stearate and dilauryl malonate; medium to long chain carboxylic acid esters of glycerin such as triolein and tristearin; glycerin-substituted carboxylic acid esters such as glycerin acetoacetate; and polyethylene glycols and its derivatives such as macrogols and cetomacrogol. They may be used either singly or in combination of two or more. If desired, the composition of this invention may further include a surface-active agent, a coloring agent, etc., which are ordinarily used in suppositories.

The pharmaceutical composition of this invention may be prepared by uniformly mixing predetermined amounts of the active ingredient, the absorption aid and optionally the base, etc. in a stirrer or a grinding mill, if required at an elevated temperature. The resulting composition, may be formed into a suppository in unit dosage form by, for example, casting the mixture in a mold, or by forming it into a gelatin capsule using a capsule filling machine.

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The compositions according to the present invention also can be administered as a nasal spray, nasal drop, suspension, gel, ointment, cream or powder. The administration of a composition can also include using a nasal tampon or a nasal sponge containing a composition of the present invention.

5 The nasal delivery systems that can be used with the present invention can take various forms including aqueous preparations, non-aqueous preparations and combinations thereof. Aqueous preparations include, for example, aqueous gels, aqueous suspensions, aqueous liposomal dispersions, aqueous emulsions, aqueous microemulsions and combinations thereof. Non-aqueous preparations include, for
10 example, non-aqueous gels, non-aqueous suspensions, non-aqueous liposomal dispersions, non-aqueous emulsions, non-aqueous microemulsions and combinations thereof. The various forms of the nasal delivery systems can include a buffer to maintain pH, a pharmaceutically acceptable thickening agent and a humectant. The pH of the buffer can be selected to optimize the absorption of the therapeutic agent(s)
15 across the nasal mucosa.

 With respect to the non-aqueous nasal formulations, suitable forms of buffering agents can be selected such that when the formulation is delivered into the nasal cavity of a mammal, selected pH ranges are achieved therein upon contact with, e.g., a nasal mucosa. In the present invention, the pH of the compositions should be
20 maintained from about 2.0 to about 6.0. It is desirable that the pH of the compositions is one which does not cause significant irritation to the nasal mucosa of a recipient upon administration.

 The viscosity of the compositions of the present invention can be maintained at a desired level using a pharmaceutically acceptable thickening agent. Thickening
25 agents that can be used in accordance with the present invention include methyl cellulose, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, polyvinyl alcohol, alginates, acacia, chitosans and combinations thereof. The concentration of the thickening agent will depend upon the agent selected and the viscosity desired. Such agents can also be used in a powder formulation discussed
30 above.

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The compositions of the present invention can also include a humectant to reduce or prevent drying of the mucus membrane and to prevent irritation thereof. Suitable humectants that can be used in the present invention include sorbitol, mineral oil, vegetable oil and glycerol; soothing agents; membrane conditioners; sweeteners; and combinations thereof. The concentration of the humectant in the present compositions will vary depending upon the agent selected.

One or more therapeutic agents may be incorporated into the nasal delivery system or any other delivery system described herein.

A composition formulated for topical administration may be liquid or semi-solid (including, for example, a gel, lotion, emulsion, cream, ointment, spray or aerosol) or may be provided in combination with a "finite" carrier, for example, a non-spreading material that retains its form, including, for example, a patch, bioadhesive, dressing or bandage. It may be aqueous or non-aqueous; it may be formulated as a solution, emulsion, dispersion, a suspension or any other mixture.

Important modes of administration include topical application to the skin, eyes or mucosa. Thus, typical vehicles are those suitable for pharmaceutical or cosmetic application to body surfaces. The compositions provided herein may be applied topically or locally to various areas in the body of a patient. As noted above, topical application is intended to refer to application to the tissue of an accessible body surface, such as, for example, the skin (the outer integument or covering) and the mucosa (the mucous-producing, secreting and/or containing surfaces). Exemplary mucosal surfaces include the mucosal surfaces of the eyes, mouth (such as the lips, tongue, gums, cheeks, sublingual and roof of the mouth), larynx, esophagus, bronchial, nasal passages, vagina and rectum/anus; in some embodiments, preferably the mouth, larynx, esophagus, vagina and rectum/anus; in other embodiments, preferably the eyes, larynx, esophagus, bronchial, nasal passages, and vagina and rectum/anus. As noted above, local application herein refers to application to a discrete internal area of the body, such as, for example, a joint, soft tissue area (such as muscle, tendon, ligaments, intraocular or other fleshy internal areas), or other internal area of the body. Thus, as used herein, local application refers to applications to discrete areas of the body.

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With respect to topical and/or local administration of the present compositions, desirable efficacy may involve, for example, penetration of therapeutic agent(s) of the invention into the skin and/or tissue to substantially reach a hyperalgesic site to provide desirable anti-hyperalgesic pain relief. The efficacy of the present compositions may be about the same as that achieved, for example, with central opiate analgesics. But, as discussed in detail herein, the efficacy achieved with therapeutic agent(s) of the invention is preferably obtained without the undesirable effects that are typically associated with central opiates including, for example, respiratory depression, sedation, and addiction, as it is believed that therapeutic agent(s) of the invention does not cross the blood brain barrier.

Also in certain preferred embodiments, including embodiments that involve aqueous vehicles, the compositions may also contain a glycol, that is, a compound containing two or more hydroxy groups. A glycol which is particularly preferred for use in the compositions is propylene glycol. In these preferred embodiments, the glycol is preferably included in the compositions in a concentration of from greater than 0 to about 5 wt. %, based on the total weight of the composition. More preferably, the compositions contain from about 0.1 to less than about 5 wt. % of a glycol, with from about 0.5 to about 2 wt. % being even more preferred. Still more preferably, the compositions contain about 1 wt. % of a glycol.

For local internal administration, such as intra-articular administration, the compositions are preferably formulated as a solution or a suspension in an aqueous-based medium, such as isotonic buffered saline or are combined with a biocompatible support or bioadhesive intended for internal administration.

Lotions, which, for example, may be in the form of a suspension, dispersion or emulsion, contain an effective concentration of one or more of the compounds. The effective concentration is preferably to deliver an effective amount, typically at a concentration of between about 0.1-50% [by weight] or more of one or more of the compounds provided herein. The lotions also contain [by weight] from 1% to 50% of an emollient and the balance water, a suitable buffer, and other agents as described above. Any emollients known to those of skill in the art as suitable for application to human skin may be used. These include, but are not limited to, the following: (a)

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Hydrocarbon oils and waxes, including mineral oil, petrolatum, paraffin, ceresin, ozokerite, microcrystalline wax, polyethylene, and perhydrosqualene. b) Silicone oils, including dimethylpolysiloxanes, methylphenylpolysiloxanes, water-soluble and alcohol-soluble silicone-glycol copolymers. (c) Triglyceride fats and oils, including
5 those derived from vegetable, animal and marine sources. Examples include, but are not limited to, castor oil, safflower oil, cotton seed oil, corn oil, olive oil, cod liver oil, almond oil, avocado oil, palm oil, sesame oil, and soybean oil. (d) Acetoglyceride esters, such as acetylated monoglycerides. (e) Ethoxylated glycerides, such as ethoxylated glyceryl monstearate. (f) Alkyl esters of fatty acids having 10 to 20
10 carbon atoms. Methyl, isopropyl and butyl esters of fatty acids are useful herein. Examples include, but are not limited to, hexyl laurate, isohexyl laurate, isohexyl palmitate, isopropyl palmitate, isopropyl myristate, decyl oleate, isodecyl oleate, hexadecyl stearate, decyl stearate, isopropyl isostearate, diisopropyl adipate, diisohexyl adipate, dihexyldecyl adipate, diisopropyl sebacate, lauryl lactate, myristyl
15 lactate, and cetyl lactate. (g) Alkenyl esters of fatty acids having 10 to 20 carbon atoms. Examples thereof include, but are not limited to, oleyl myristate, oleyl stearate, and oleyl oleate. (h) Fatty acids having 9 to 22 carbon atoms. Suitable examples include, but are not limited to, pelargonic, lauric, myristic, palmitic, stearic, isostearic, hydroxystearic, oleic, linoleic, ricinoleic, arachidonic, behenic, and erucic
20 acids. (i) Fatty alcohols having 10 to 22 carbon atoms, such as, but not limited to, lauryl, myristyl, cetyl, hexadecyl, stearyl, isostearyl, hydroxystearyl, oleyl, ricinoleyl, behenyl, erucyl, and 2-octyl dodecyl alcohols. (j) Fatty alcohol ethers, including, but not limited to ethoxylated fatty alcohols of 10 to 20 carbon atoms, such as, but are not limited to, the lauryl, cetyl, stearyl, isostearyl, oleyl, and cholesterol alcohols having
25 attached thereto from 1 to 50 ethylene oxide groups or 1 to 50 propylene oxide groups or mixtures thereof. (k) Ether-esters, such as fatty acid esters of ethoxylated fatty alcohols. (l) Lanolin and derivatives, including, but not limited to, lanolin, lanolin oil, lanolin wax, lanolin alcohols, lanolin fatty acids, isopropyl lanolate, ethoxylated lanolin, ethoxylated lanolin alcohols, ethoxylated cholesterol, propoxylated lanolin
30 alcohols, acetylated lanolin, acetylated lanolin alcohols, lanolin alcohols linoleate, lanolin alcohols ricinoleate, acetate of lanolin alcohols ricinoleate, acetate of

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ethoxylated alcohols-esters, hydrogenolysis of lanolin, ethoxylated hydrogenated lanolin, ethoxylated sorbitol lanolin, and liquid and semisolid lanolin absorption bases. (m) polyhydric alcohols and polyether derivatives, including, but not limited to, propylene glycol, dipropylene glycol, polypropylene glycol [M.W. 2000-4000], polyoxyethylene polyoxypropylene glycols, polyoxypropylene polyoxyethylene glycols, glycerol, ethoxylated glycerol, propoxylated glycerol, sorbitol, ethoxylated sorbitol, hydroxypropyl sorbitol, polyethylene glycol [M.W. 200-6000], methoxy polyethylene glycols 350, 550, 750, 2000, 5000, poly(ethylene oxide) homopolymers [M.W. 100,000-5,000,000], polyalkylene glycols and derivatives, hexylene glycol (2-methyl-2,4-pentanediol), 1,3-butylene glycol, 1,2,6,-hexanetriol, ethohexadiol USP (2-ethyl-1,3-hexanediol), C.sub.15 -C.sub.18 vicinal glycol and polyoxypropylene derivatives of trimethylolpropane. (n) polyhydric alcohol esters, including, but not limited to, ethylene glycol mono- and di-fatty acid esters, diethylene glycol mono- and di-fatty acid esters, polyethylene glycol [M.W. 200-6000], mono- and di-fatty esters, propylene glycol mono- and di-fatty acid esters, polypropylene glycol 2000 monooleate, polypropylene glycol 2000 monostearate, ethoxylated propylene glycol monostearate, glyceryl mono- and di-fatty acid esters, polyglycerol poly-fatty acid esters, ethoxylated glyceryl monostearate, 1,3-butylene glycol monostearate, 1,3-butylene glycol distearate, polyoxyethylene polyol fatty acid ester, sorbitan fatty acid esters, and polyoxyethylene sorbitan fatty acid esters. (o) Wax esters, including, but not limited to, beeswax, spermaceti, myristyl myristate, and stearyl stearate and beeswax derivatives, including, but not limited to, polyoxyethylene sorbitol beeswax, which are reaction products of beeswax with ethoxylated sorbitol of varying ethylene oxide content that form a mixture of ether-esters. (p) Vegetable waxes, including, but not limited to, carnauba and candelilla waxes. (q) phospholipids, such as lecithin and derivatives. (r) Sterols, including, but not limited to, cholesterol and cholesterol fatty acid esters. (s) Amides, such as fatty acid amides, ethoxylated fatty acid amides, and solid fatty acid alkanolamides.

The lotions further preferably contain [by weight] from 1% to 10%, more preferably from 2% to 5%, of an emulsifier. The emulsifiers can be nonionic, anionic or cationic. Examples of satisfactory nonionic emulsifiers include, but are not limited

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to, fatty alcohols having 10 to 20 carbon atoms, fatty alcohols having 10 to 20 carbon atoms condensed with 2 to 20 moles of ethylene oxide or propylene oxide, alkyl phenols with 6 to 12 carbon atoms in the alkyl chain condensed with 2 to 20 moles of ethylene oxide, mono- and di-fatty acid esters of ethylene oxide, mono- and di-fatty acid esters of ethylene glycol where the fatty acid moiety contains from 10 to 20 carbon atoms, diethylene glycol, polyethylene glycols of molecular weight 200 to 6000, propylene glycols of molecular weight 200 to 3000, glycerol, sorbitol, sorbitan, polyoxyethylene sorbitol, polyoxyethylene sorbitan and hydrophilic wax esters. Suitable anionic emulsifiers include, but are not limited to, the fatty acid soaps, e.g., sodium, potassium and triethanolamine soaps, where the fatty acid moiety contains from 10 to 20 carbon atoms. Other suitable anionic emulsifiers include, but are not limited to, the alkali metal, ammonium or substituted ammonium alkyl sulfates, alkyl arylsulfonates, and alkyl ethoxy ether sulfonates having 10 to 30 carbon atoms in the alkyl moiety. The alkyl ethoxy ether sulfonates contain from 1 to 50 ethylene oxide units. Among satisfactory cationic emulsifiers are quaternary ammonium, morpholinium and pyridinium compounds. Certain of the emollients described in preceding paragraphs also have emulsifying properties. When a lotion is formulated containing such an emollient, an additional emulsifier is not needed, though it can be included in the composition.

The balance of the lotion is water or a C₂ or C₃ alcohol, or a mixture of water and the alcohol. The lotions are formulated by simply admixing all of the components together. Preferably the compound, such as loperamide, is dissolved, suspended or otherwise uniformly dispersed in the mixture.

Other conventional components of such lotions may be included. One such additive is a thickening agent at a level from 1% to 10% by weight of the composition. Examples of suitable thickening agents include, but are not limited to: cross-linked carboxypolymethylene polymers, ethyl cellulose, polyethylene glycols, gum tragacanth, gum kharaya, xanthan gums and bentonite, hydroxyethyl cellulose, and hydroxypropyl cellulose.

Creams can be formulated to contain a concentration effective to deliver an effective amount of therapeutic agent(s) of the invention to the treated tissue, typically

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at between about 0.1%, preferably at greater than 1% up to and greater than 50%, preferably between about 3% and 50%, more preferably between about 5% and 15% therapeutic agent(s) of the invention. The creams also contain from 5% to 50%, preferably from 10% to 25%, of an emollient and the remainder is water or other
5 suitable non-toxic carrier, such as an isotonic buffer. The emollients, as described above for the lotions, can also be used in the cream compositions. The cream may also contain a suitable emulsifier, as described above. The emulsifier is included in the composition at a level from 3% to 50%, preferably from 5% to 20%.

These compositions that are formulated as solutions or suspensions may be
10 applied to the skin, or, may be formulated as an aerosol or foam and applied to the skin as a spray-on. The aerosol compositions typically contain [by weight] from 25% to 80%, preferably from 30% to 50%, of a suitable propellant. Examples of such propellants are the chlorinated, fluorinated and chlorofluorinated lower molecular weight hydrocarbons. Nitrous oxide, carbon dioxide, butane, and propane are also
15 used as propellant gases. These propellants are used as understood in the art in a quantity and under a pressure suitable to expel the contents of the container.

Suitably prepared solutions and suspensions may also be topically applied to the eyes and mucosa. Solutions, particularly those intended for ophthalmic use, may be formulated as 0.01%-10% isotonic solutions, pH about 5-7, with appropriate salts,
20 and preferably containing one or more of the compounds herein at a concentration of about 0.1%, preferably greater than 1%, up to 50% or more. Suitable ophthalmic solutions are known [see, e.g., U.S. Pat. No. 5,116,868, which describes typical compositions of ophthalmic irrigation solutions and solutions for topical application]. Such solutions, which have a pH adjusted to about 7.4, contain, for example, 90-100
25 mM sodium chloride, 4-6 mM dibasic potassium phosphate, 4-6 mM dibasic sodium phosphate, 8-12 mM sodium citrate, 0.5-1.5 mM magnesium chloride, 1.5-2.5 mM calcium chloride, 15-25 mM sodium acetate, 10-20 mM D.L.-sodium, β -hydroxybutyrate and 5-5.5 mM glucose.

Gel compositions can be formulated by simply admixing a suitable thickening
30 agent to the previously described solution or suspension compositions. Examples of suitable thickening agents have been previously described with respect to the lotions.

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The gelled compositions contain an effective amount of therapeutic agent(s) of the invention, typically at a concentration of between about 0.1-50% by weight or more of one or more of the compounds provided herein.; from 5% to 75%, preferably from 10% to 50%, of an organic solvent as previously described; from 0.5% to 20%, preferably from 1% to 10% of the thickening agent; the balance being water or other aqueous or non-aqueous carrier, such as, for example, an organic liquid, or a mixture of carriers.

The formulations can be constructed and arranged to create steady state plasma levels. Steady state plasma concentrations can be measured using HPLC techniques, as are known to those of skill in the art. Steady state is achieved when the rate of drug availability is equal to the rate of drug elimination from the circulation. In typical therapeutic settings, the therapeutic agent(s) of the invention will be administered to patients either on a periodic dosing regimen or with a constant infusion regimen. The concentration of drug in the plasma will tend to rise immediately after the onset of administration and will tend to fall over time as the drug is eliminated from the circulation by means of distribution into cells and tissues, by metabolism, or by excretion. Steady state will be obtained when the mean drug concentration remains constant over time. In the case of intermittent dosing, the pattern of the drug concentration cycle is repeated identically in each interval between doses with the mean concentration remaining constant. In the case of constant infusion, the mean drug concentration will remain constant with very little oscillation. The achievement of steady state is determined by means of measuring the concentration of drug in plasma over at least one cycle of dosing such that one can verify that the cycle is being repeated identically from dose to dose. Typically, in an intermittent dosing regimen, maintenance of steady state can be verified by determining drug concentrations at the consecutive troughs of a cycle, just prior to administration of another dose. In a constant infusion regimen where oscillation in the concentration is low, steady state can be verified by any two consecutive measurements of drug concentration.

FIG. 8 shows a kit according to the invention. The kit 10 includes a vial 12 containing an opioid tablet. The kit 10 also includes a vial 14 containing R-MNTX

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tablets which contain pellets, some of which are enterically coated with pH sensitive material and some of which are constructed and arranged to release the R-MNTX immediately in the stomach. The kit also includes instructions 20 for administering the tablets to a subject who is constipated or who has symptoms of constipation or
5 gastrointestinal immotility. The instructions include indicia, for example writing, indicating that the R-MNTX is pure R-MNTX free of S-MNTX.

In some aspects of the invention, the kit 10 can include optimally or alternatively a pharmaceutical preparation vial 16, and a pharmaceutical preparation diluents vial 18. The vial containing the diluents for the pharmaceutical preparation is
10 optional. The diluents vial contains diluents such as physiological saline for diluting what could be a concentrated solution or lyophilized powder of R-MNTX. The instructions can include instructions for mixing a particular amount of the diluents with a particular amount of the concentrated pharmaceutical preparation, whereby a final formulation for injection or infusion is prepared. The instructions 20 can include
15 instructions for treating a patient with an effective amount of R-MNTX. It also will be understood that the containers containing the preparations, whether the container is a bottle, a vial with a septum, an ampoule with a septum, an infusion bag, and the like, can contain additional indicia such as conventional markings which change color when the preparation has been autoclaved or otherwise sterilized.

20 This invention is not limited in its application to the details of construction and the arrangement of components set forth in the following description or illustrated in the drawings. The invention is capable of other embodiments and of being practiced or of being carried out in various ways. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The
25 use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

EXAMPLES

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Example 1**HPLC Analysis of R- and S-MNTX**

HPLC analysis was performed on a Varian ProStar HPLC controlled by Varian Star software using the following method:

5 HPLC Method I:

Column: Luna C18(2), 150 × 4.6 mm, 5 μ
Flow Rate: 1 mL/min
Detection: UV @ 230 nm

10 Gradient Program:

Time (min)	%A	%B
0:00	95	5
8:00	65	35
12:00	35	65
15:00	0	100
16:00	95	5
18:00	95	5

Mobile phase A = 0.1% Aqueous TFA
Mobile phase B = 0.1% Methanolic TFA
TFA = trifluoroacetic acid

15**HPLC Method II:**

Chromatographic Conditions and Parameters: Analytical Column

Description: Phenomenex Inertsil ODS-3 150 x 4.6 mm, 5 μm; Column Temperature: 50.0 °C; Flow Rate: 1.5 mL/min; Injection Volume: 20 μL; Detection Wavelength:

20 280 nm Mobile Phase:

A = Water : MeOH : TFA (95:5:0.1%; v/v/v) B = Water : MeOH : TFA (35:65:0.1%; v/v/v) Analysis Time: 50 min

Quantitation limit: 0.05%

Detection limit: 0.02%

25

Gradient Profile:

Time (min)	%A	%B	Curve
0:00	100	0	Initial
45	50	50	Linear

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48	100	0	Linear
55	100	0	Hold

Mobile Phase A (Water : MeOH : TFA :: 95 : 5 : 0.1%, v/v/v)

Mobile Phase B (Water : MeOH : TFA :: 35 : 65 : 0.1%, v/v/v)

MeOH = Methanol TFA = trifluoroacetic acid

5 The synthesis and purification of R-MNTX were monitored using the above HPLC protocol. S-MNTX is distinguished from R-MNTX using the HPLC conditions described. Authentic S-MNTX for use as a standard may be made using the protocol as described herein. In a typical HPLC run, S-MNTX elutes about 0.5 minutes before R-MNTX elutes. The retention time of S-MNTX is approximately 9.3 minutes; the
10 retention time of R-MNTX is about 9.8 minutes.

As illustrated in FIG. 2, the S and R forms of MNTX can be distinguished clearly on an HPLC chromatogram. FIG. 3 is an HPLC chromatogram of a mixture of 0.1% by weight of authentic S form added to 99.5% by weight of authentic R form; FIG. 4 is a chromatogram of 1.0% by weight of authentic S form added to 99.0% by
15 weight of authentic R form. FIG. 5 is a chromatogram of 3.0% by weight of authentic S form added to 98.0% by weight of authentic R form. This has permitted applicants to devise and test for the first time stereoselective protocols for synthesis and purification that yield highly pure R-MNTX from 3-*O*-protected-naltrexone.

20 Example 2

Stereoselective Synthesis of R-MNTX

The synthetic scheme for Example 2 is shown in FIG. 6.

General. All anhydrous reactions were carried out in oven-dried (130 °C) glassware under an atmosphere of dry nitrogen (N₂). All commercial reagents and
25 solvents were used without any additional purification. Nuclear magnetic resonance (NMR) spectra were obtained using either a Varian Gemini or Varian Mercury 300 MHz spectrometer. Mass spectra were determined on a Finnigan LCQ. HPLC purity was determined using a Waters 717 Autosampler and Waters 996 Photodiode Array Detector.

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3-O-Isobutyryl-Naltrexone (2). To a solution of compound (1) (1.62 g, 4.75 mmol) in anhydrous tetrahydrofuran (THF) (120 mL) at 0 °C was added triethylamine (NEt₃) (1.4 mL, 10 mmol). After the reaction was stirred for 15 min. at 0 °C, isobutyryl chloride (1.05 mL, 10 mmol) was added dropwise. Reaction mixture was stirred at 0 °C for 1 hr, then at room temperature for 18 hr before being quenched with saturated sodium bicarbonate (NaHCO₃) (aq) (70 mL) and 30 ml of H₂O. The reaction was extracted with methylene chloride (CH₂Cl₂) (2 x 200 mL). The extracts were combined, washed with brine (130 ml), dried over sodium sulfate (Na₂SO₄) (50g), filtered and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel (column size 40X450 mm, silica gel was loaded 40X190mm) (9.8:0.2 → 9.6:0.4 → 9.4:0.6 CH₂Cl₂/MeOH) to give compound (2) (1.5 g 76.8%) as a white solid.

¹H NMR (300M Hz, CDCl₃) δ 6.82 (d, J=8.0 Hz, 1H), 6.67 (d, J=8.0 Hz, 1H), 4.69 (s, 1H), 3.21 (d, J=6.0 Hz, 1H), 3.12-2.96 (m, 2H), 2.93-2.82 (m, 1H), 2.71 (dd, J=4.5 Hz, 1H), 2.62 (dd, J=6.2 Hz, 1H), 2.48-2.28 (m, 4H), 2.19-2.10 (m, 1H), 1.93-1.86 (m, 1H), 1.68-1.59 (m, 2H), 1.34 (d, J=0.8 Hz, 3H, CH₃-isobutyryl), 1.31 (d, J=0.8 Hz, 3H, CH₃-isobutyryl), 0.90-0.83 (m, 1H, CH-cyclopropyl), 0.60-0.54 (m, 2H, CH₂-cyclopropyl), 0.18-0.13 (m, 2H, CH₂-cyclopropyl). ¹³C NMR (75.5 MHz, CDCl₃) δ 207.6 (CO), 174.7 (COO/Pr) 147.8, 132.8, 130.1, 130.0, 122.8, 119.2, 90.5, 70.0, 61.9, 59.2, 50.6, 43.4, 36.1, 33.8, 31.2, 30.7, 22.9, 19.0, 18.9, 9.4, 4.0, 3.8. MS[M+H]⁺ : 412.

3-O-Isobutyryl-N-Methylnaltrexone Iodide salt (3). Compound (2) (689 mg, 1.67 mmol) was transferred by spatula into a glass pressure vessel. The vessel was purged gently with nitrogen on the manifold for 5 minutes and was then evacuated under high vacuum. When the vacuum was constant, the lower part of the vessel was immersed in liquid nitrogen. Methyl iodide (973 mg, 6.85 mmol) was dispensed into a separate flask on the manifold into a nitrogen atmosphere and frozen in liquid nitrogen. The frozen methyl iodide vessel was evacuated under high vacuum. The main manifold chamber was isolated from the high vacuum pump. The methyl iodide was allowed to warm to ambient temperature and sublime via the main chamber onto the liquid nitrogen cooled 3-O-Isobutyryl-Naltrexone. When

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sublimation was complete, nitrogen was slowly allowed to leach into the glass pressure vessel. The vessel was then sealed tight, removed from the manifold and heated in an oil bath at 88-90°C for 17 hrs. The vessel was allowed to cool to ambient temperature before allowing nitrogen to flow into the vessel. The vessel was then
5 evacuated under high vacuum to remove residues of unreacted methyl iodide giving a white solid. A sample of the solid was removed for ^1H NMR analysis. This showed good conversion to product. Thin layer chromatography (TLC) of the product [dichloromethane / methanol 9:1 (v/v), normal phase silica, UV detection] showed a trace of starting material (2) ($R_f = 0.8$) and a diffuse region ($R_f = 0-0.4$). The solid was
10 dissolved in dichloromethane / methanol (4:1, minimum volume) and applied to a silica gel column (ultrapure silica gel, 22 g in dichloromethane, bed dimensions: 200mm x 20mm id). The column was eluted as follows:
Dichloromethane / methanol 98:2 (300 ml)
Dichloromethane / methanol 97:3 (300 ml)
15 Dichloromethane / methanol 94:6 (200 ml)
Dichloromethane / methanol 92:8 (400 ml)
Fractions were analyzed by TLC [dichloromethane / methanol 9:1 (v/v), normal phase silica, UV detection]. Fractions containing exclusively the principal component ($R_f = 0.4$) were combined rinsing together with methanol, and concentrated to yield 867 mg
20 of white solid. This represents a 91% yield based on 3-*O*-Isobutyryl-Naltrexone. ^1H NMR is consistent.

***N*-Methylnaltrexone Bromide/Iodide salt (4).** Compound (3) (862 mg, 1.56 mmol) was dissolved in methanol (13 ml). To this mixture was added sterile water (11.5 ml) followed by 48% aqueous hydrobromic acid (1.5 ml). The resultant mixture
25 was stirred under nitrogen and heated in an oil bath at 64-65°C for 6.5 hr. TLC analysis of a sample (dispersed in methanol) of the reaction mixture showed no starting material (3) remaining ($R_f = 0.4$) and conversion to material at $R_f = 0-0.15$. The mixture was concentrated on the rotary evaporator with the bath at 22-25°C until approximately 1 ml of oily liquid remained. Acetonitrile (10 ml) was added and the
30 mixture was reconcentrated. This was repeated a further three times, using 10 ml of acetonitrile, to give a ginger colored crisp foam (590 mg, 86% crude yield).

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Preparation of Anion Exchange Resin Column. 30 g of AG 1-X8 resin was packed into an medium pressure liquid chromatography (MPLC) column (20 mm id) using 100 ml water to create a resin slurry. The resin bed was washed with 1.0N aqueous hydrobromic acid (200 ml) and then sterile water until the pH of the aqueous eluate was pH 6-7. Approximately 1.5 L of water was required.

***N*-Methylnaltrexone Bromide (5).** The foam (4) (597 mg) was dispersed in water (6 ml) / methanol (2 ml). Some dark oil remained undissolved. The clear supernatant liquid was decanted and applied to the prepared anion exchange resin column. The residue was washed twice with methanol (0.2 ml) / water (3 ml). The supernatant liquors were applied to the column. The column was eluted with 4.2 L of sterile water and fractions of ~20 ml were collected. The presence of *N*-Methylnaltrexone salt was detected by liquid chromatography/mass spectrometry (LC/MS). The majority of *N*-Methylnaltrexone was located in the initial 1.5 L of eluate of which the first 600 ml contained the most pure material by TLC (4:1 dichloromethane / methanol, normal phase silica). The first 600 ml of eluate was combined and concentrated on the rotary evaporator to give a whitish glass. The water bath was maintained at ~35°C. Care was needed to control foaming of the eluate while evaporating.

Purification of *N*-Methylnaltrexone Bromide (5). Recrystallization from methanol. The residue was warmed in methanol (60 ml) under nitrogen to just below reflux and then filtered through a glass sinter to remove a small amount of insoluble material. This filtrate was then blown down in a stream of nitrogen to approximately 10 ml and then cooled under nitrogen in ice / water. Some white precipitate was formed but clearly much solid remained in solution. The mixture was then concentrated by evaporation to give a slightly colored gum. This was triturated with methanol (3 ml x 2). Methanol was cautiously decanted by pipette between triturations. The white residue was dissolved in methanol (60 ml) and filtered through a glass sinter. The filtrate was concentrated to approximately 1 ml and a further portion of methanol (1 ml) was added to triturate the solid. The supernatant liquors were decanted as before. The solid was dried to give a white solid, batch A (178.0 mg). HPLC analysis showed 97.31% of R-MNTX, and 2.69% of S-MNTX.

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All filtrates / supernatant liquors in methanol were combined and concentrated to give a white glass. This residue was triturated with methanol (3 ml x 2) and the supernatant liquors were removed carefully as before. The residue was dissolved in methanol (50 ml) and filtered through a glass sinter. The filtrate was concentrated to approximately 1 ml solution and a further portion of methanol (1 ml) was added to triturate the solid. The supernatant liquors were decanted as before and the residue was triturated further with methanol (2 ml). The supernatant liquors were decanted and the residue was dried to give a white solid, batch B (266.0 mg). HPLC analysis of batch B showed 97.39% of R-MNTX, and 2.61% of S-MNTX. Batches A and B together represent a total yield of 436.8 mg (64%). ¹H NMR is consistent. MS [M+H]⁺: 356.

As demonstrated in batches A and B, recrystallization from methanol yields product with high percentage of R-MNTX. In a reaction carried out under the same conditions with ¹⁴CH₃-labelled material, it was found that the composition of the crude reaction mixture before recrystallization from methanol was 94.4% R-MNTX* and 4.7% S-MNTX*. Recrystallization from methanol yielded product containing 98.0% R-MNTX* and 1.5% S-MNTX*. A second recrystallization from methanol yielded 98.3% R-MNTX* and 1.2% S-MNTX*.

It should be understood that it is believed that the synthetic protocol results in greater than 94% R form with only a small percentage of the S form. Using synthesis Scheme 1, the substantially pure material, could be processed further on a chromatography column, preparative HPLC or recrystallization. In one recrystallization following ion exchange, the purity of the R form was greater than 98%. A second recrystallization yielded 98.3% R-MNTX. It is understood that further recrystallizations and/or chromatography, anywhere between one and four, (or even six or as many as ten) times ensures greater than 99.95% R form and eliminates traces of the S form, if present.

Example 3

Stereoselective Synthesis of R-MNTX

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The synthetic scheme for Example 3 is shown in FIG. 7. In Example 3, the method taught by Goldberg et al for protecting groups was followed. Acetyl, Goldberg et al's preferred protecting group, instead of isobutyryl was used as the protecting group. The reactions were carried out as described in Example 2. It was surprisingly found using the scheme shown in FIG. 7 that the acetyl protecting group tended to fall off during purification of intermediate 2 (O-acetyl-naltrexone). This made it difficult to obtain pure intermediate 2. The yield of intermediate 2 with the acetyl group was only 36.3% rendering the scheme shown in FIG. 7 unsuitable for commercial scale-up. In contrast using the synthetic scheme with isobutyryl as the protecting group (FIG. 6), intermediate 2 (3-O-isobutyryl-naltrexone) was quite stable during purification resulting in a yield of 76.8%.

Example 4

Manufacturing Process for a Pharmaceutical Formulation

of R-MNTX

A manufacturing process can be outlined as follows:

1. Add required amount of water for injection (~80% or final volume) to a stainless steel tank.
2. Add chelating agent to the tank and stir till dissolved.
3. Add buffering agent to the tank and stir till dissolved.
4. Add R-MNTX to the tank and stir till dissolved.
5. Add isotonicity agent to the tank and stir till dissolved.
6. Adjust the pH of the solution to pH 3.25.
7. Add water for injection to increase the volume to the required amount.
8. Transfer material to supply pressure vessel.
9. Sterile filter into a sterile stainless steel pressure vessel.
10. Fill into bottles/vials, purge with nitrogen and then stopper the bottles/vials.
11. Sterilize the filled vials by autoclaving.

Exact amount of excipients to be used:

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Disodium edetate = 0.75 mg/ml Added in step 2

Sodium citrate = 0.199 mg/ml Added in step 3

Citric acid = 0.35 mg/ml Added in step 3

Sodium chloride = 8.5 mg/ml Added in step 5

5 The order of addition of excipients is described above. Steps 2 to 5 can take place in any order.

When all excipients and drug have been added, step 6, pH of the solution is adjusted by addition of acid. If a buffering agent is used in the solution, pH adjustment may not be required.

10 There are no specifics on the temperature or the stirring speed during the formulation. The temperature during formulation can be as high as 80 °C.

Example 5

Preferred Manufacturing Process for a Pharmaceutical Formulation of R-MNTX

15

A preferred manufacturing process for 100 ml of 20 mg/ml solution of R-MNTX solution is as follows:

1. Add 80 ml of water for injection (~80% or final volume) to a stainless steel
20 tank.
2. Add 75 mg of disodium edetate, a chelating agent, to the tank and stir till dissolved.
3. Add 19.9 mg of sodium citrate and 35 mg of citric acid (as buffering agents) to the tank and stir till dissolved.
- 25 4. Add 2000 mg of R-MNTX to the tank and stir till dissolved.
5. Add 850 mg of sodium chloride, an isotonicity agent, to the tank and stir till dissolved.
6. Adjust the pH of the solution if necessary.
7. Add water for injection to increase the volume to 100 ml.
- 30 8. Transfer the material to supply pressure vessel.

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9. Sterile filter using a 0.22 micron filter into a sterile stainless steel pressure vessel.
10. Fill, purge with nitrogen and then stopper the bottles/vials.
11. Sterilize the filled vials by autoclaving.

5

Example 6

Preparation of a Subcutaneous Formulation of R-MNTX

A formula for a low citrate/EDTA formulation is listed below:

10

<u>Ingredient</u>	<u>mg/mL</u>
R-MNTX	30 mg
Sodium chloride	4 mg
Citric acid	0.0875 mg
15 Trisodium citrate	0.0496 mg
Disodium edetate	0.75 mg
Water for injection	q.s. to 1 g

The pH of this solution is 3.5 and can withstand an autoclaving process.

20

Example 7

Manufacturing Process for a Lyophilized Pharmaceutical Formulation of R-MNTX

25 The lyophilization cycle is used for the preparation of lyophilized preparation of R-MNTX. Forty milligrams of R-MNTX is mixed with 32 mg of the cryoprotecting agent, mannitol and q.s. to 1mL using water for injection.

1. Load chamber at room temperature (20-25°C)
2. Lower shelf temp to -45 degrees C at 1.0 degrees C/min
- 30 3. Hold shelf temp at -45 for 120 minutes
4. When condenser is below -50 degrees C, evacuate the chamber to 100-125 mt.

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5. Ramp shelf to -20 degrees C at 0.5 degrees C/min.
6. Hold at -20 degrees C for 16 hours
7. Ramp shelf to +27 degrees C at 0.10 degrees C/min.
8. Hold for a minimum of 8 hours. Maintain chamber pressure at 100-125mt for
5 the entire cycle.
9. Restore chamber to 11.0 PSIA + or- 1.0 with sterile filtered Nitrogen and then
seat the closures (2" Hg), then bleed to atmospheric pressure with N₂ to unload. The
pH of the solution after lyophilization and reconstitution is 5.0.

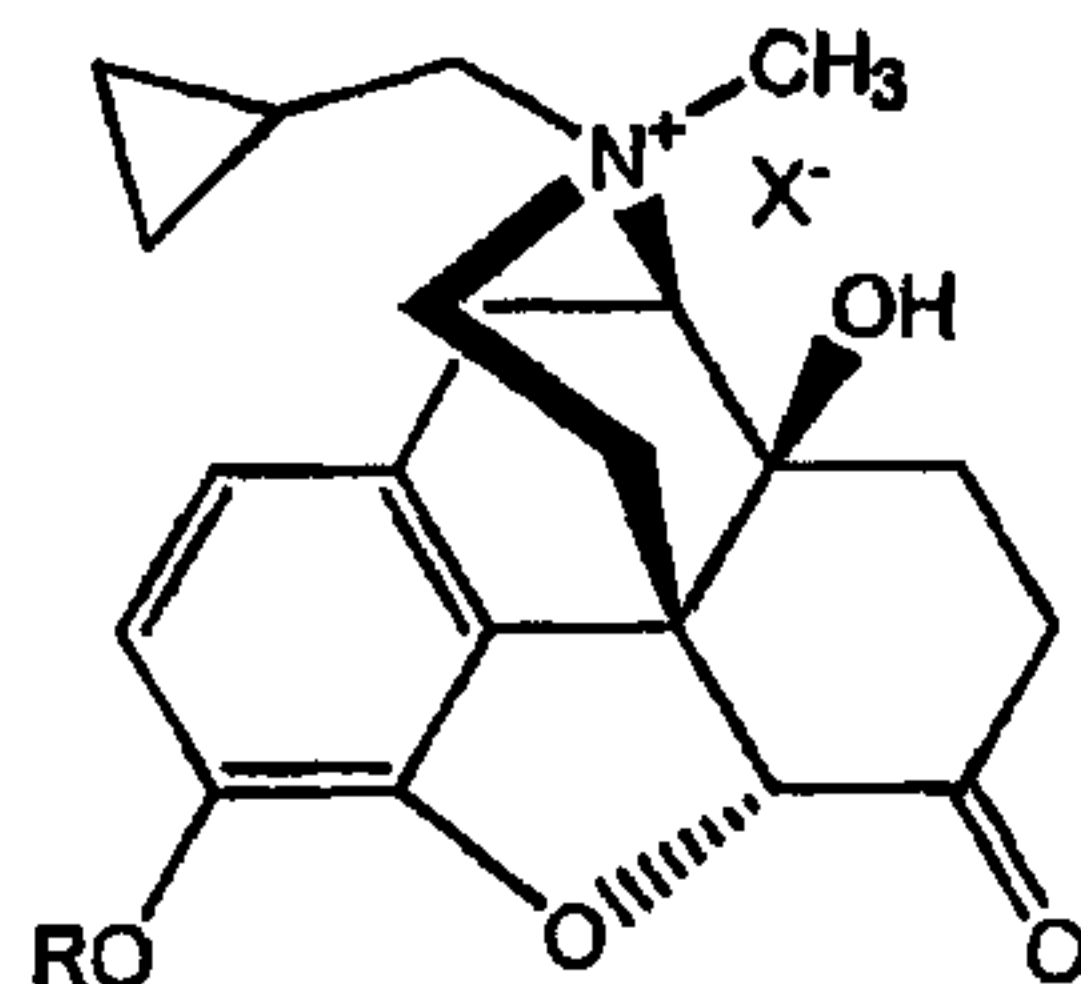
10 Having thus described several aspects of at least one embodiment of this
invention, it is to be appreciated various alterations, modifications, and improvements
will readily occur to those skilled in the art. Such alterations, modifications, and
improvements are intended to be part of this disclosure, and are intended to be within
the scope of the invention. Accordingly, the foregoing description and
15 drawings are by way of example only.

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CLAIMS:

1. An isolated 3-O-protected-R-methylnaltrexone (MNTX) salt of the formula



wherein

- 5 R is a hydroxyl protecting group selected from the group consisting of isobutyryl, 2-methyl butyryl, and tertbutyl carbonyl, or R, taken together with the oxygen atom to which it is attached, is a silyl ether, a 2-tetrahydropyranyl ether, or an alkyl carbonate; and

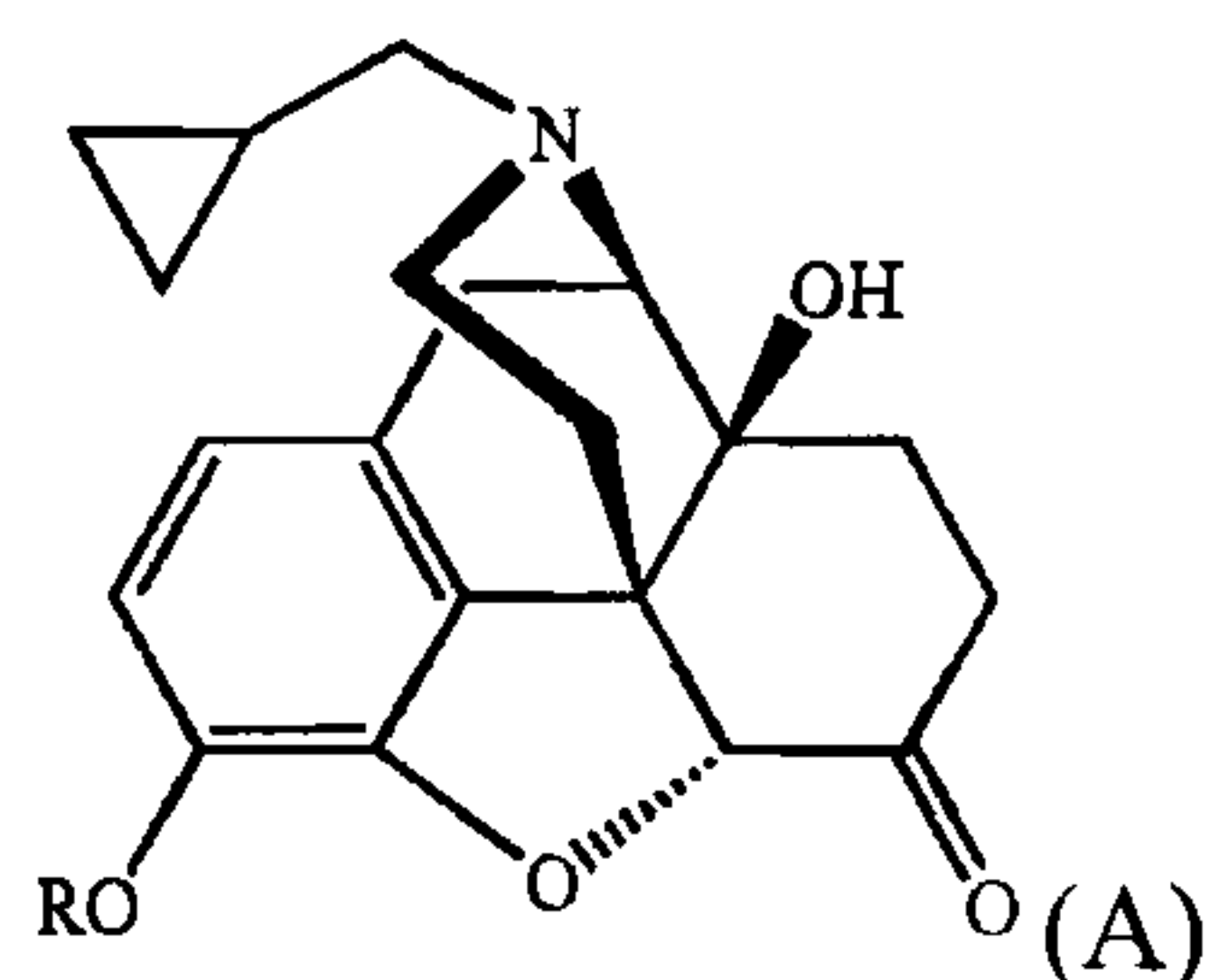
X⁻ is a counterion.

- 10 2. The 3-O-protected-R-MNTX salt of claim 1, wherein R is isobutyryl.
3. The 3-O-protected-R-MNTX salt of claim 1 or 2, wherein X⁻ is selected from the group consisting of a halide, sulfate, phosphate, nitrate, an organic anionic-charged species, a sulfonate, a carboxylate, mesylate, besylate, tosylate, triflate, formate, acetate, citrate, and fumarate.
- 15 4. The 3-O-protected-R-MNTX salt of claim 3, wherein X⁻ is a halide selected from the group consisting of bromide, iodide, chloride and fluoride.
5. The 3-O-protected-R-MNTX salt of claim 4, wherein X⁻ is bromide.
6. A method for stereoselective synthesis of R-methylnaltrexone (MNTX) comprising:

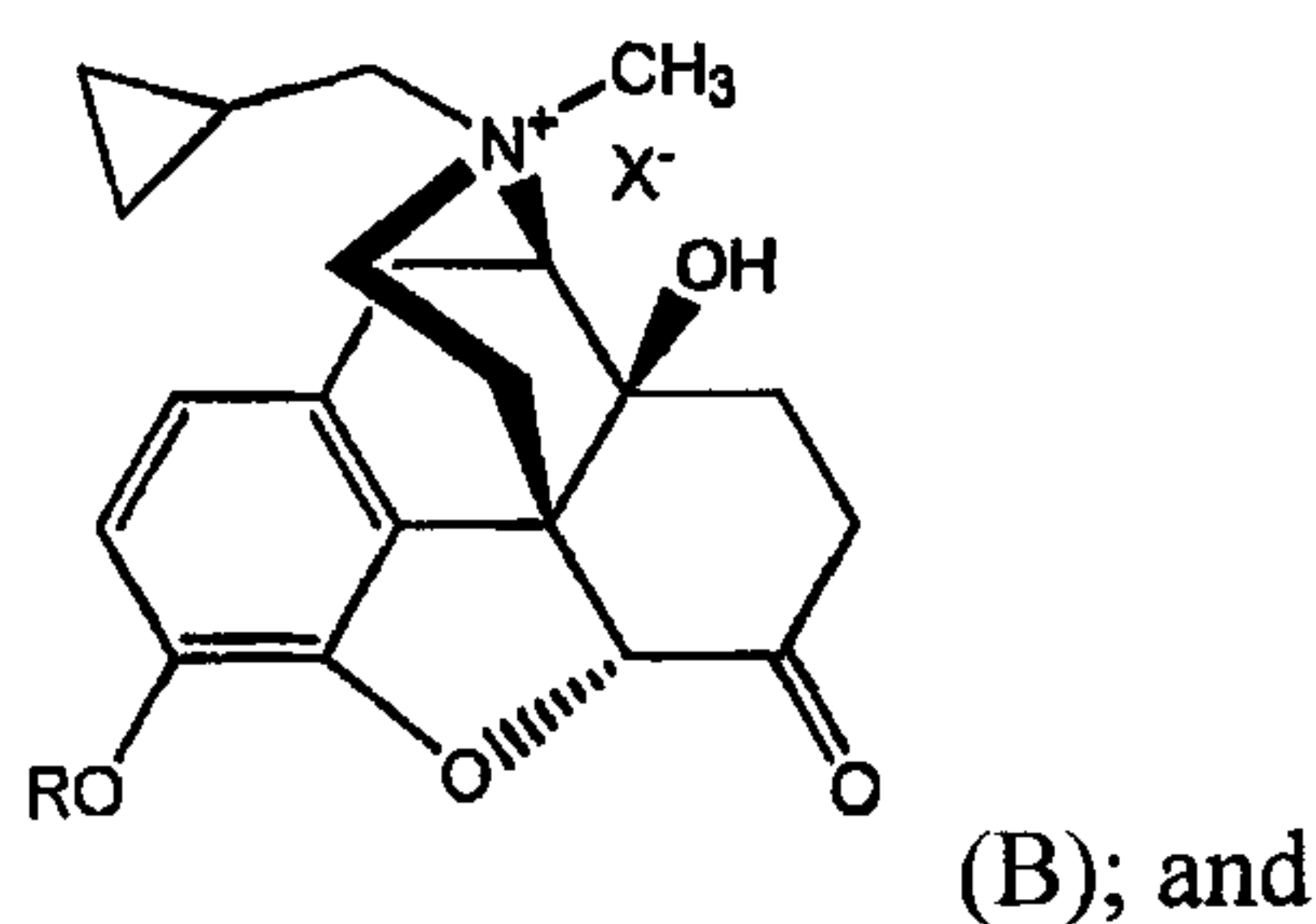
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(a) methylating a compound of formula A:



with a methylating agent to yield a compound of formula B:



- 5 (b) removal of the 3-hydroxyl protecting group R to yield R-MNTX, wherein R is a hydroxyl protecting group selected from the group consisting of isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, or R, taken together with the oxygen atom to which it is attached, is a silyl ether, a 2-tetrahydropyranyl ether, or an alkyl carbonate; and

X^- is a counterion.

- 10 7. The method of claim 6, wherein X^- is selected from the group consisting of a halide, sulfate, phosphate, nitrate, an organic anionic-charged species, a sulfonate, a carboxylate, mesylate, besylate, tosylate, triflate, formate, acetate, citrate, and fumarate.
8. The method of claim 7, wherein X^- is a halide selected from the group consisting of bromide, iodide, chloride and fluoride.
- 15 9. The method of claim 8, wherein X^- is bromide.

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10. The method of any one of claims 6-9, further comprising exchanging X^- with a different anion.
11. The method of any one of claims 6-10, wherein the methylating agent comprises a methyl group susceptible to nucleophilic attack, and a leaving group.
- 5 12. The method of claim 11, wherein the methylating agent is selected from the group consisting of methyl halide, dimethyl sulfate, methyl nitrate, methyl sulfonate, methyl mesylate, methyl besylate, methyl tosylate, and methyl triflate.
13. The method of any one of claims 6-12, wherein the removal of the 3-hydroxyl protecting group R is catalyzed by an acid.
- 10 14. The method of claim 13, wherein the acid is selected from the group consisting of sulfuric acid, hydrochloric acid or hydrobromic acid.
15. The method of any one of claims 6-12, wherein the removal of the 3-hydroxyl protecting group R is catalyzed by a base.
- 15 16. The method of claim 15, wherein the base is sodium hydroxide or potassium hydroxide.
17. The method of any one of claims 6-16, wherein R is isobutyryl.
18. The method of any one of claims 6-17, wherein the methylation is conducted at a temperature range from about 70°C to about 100°C.
19. The method of claim 18, wherein the methylation is conducted at a temperature
20 range from about 80°C to about 90°C.
20. The method of any one of claims 6-19, wherein the methylation reaction is conducted for about 1 hour to about 24 hours.
21. The method of claim 20, wherein the methylation reaction is conducted for about 5 hours to 16 hours.

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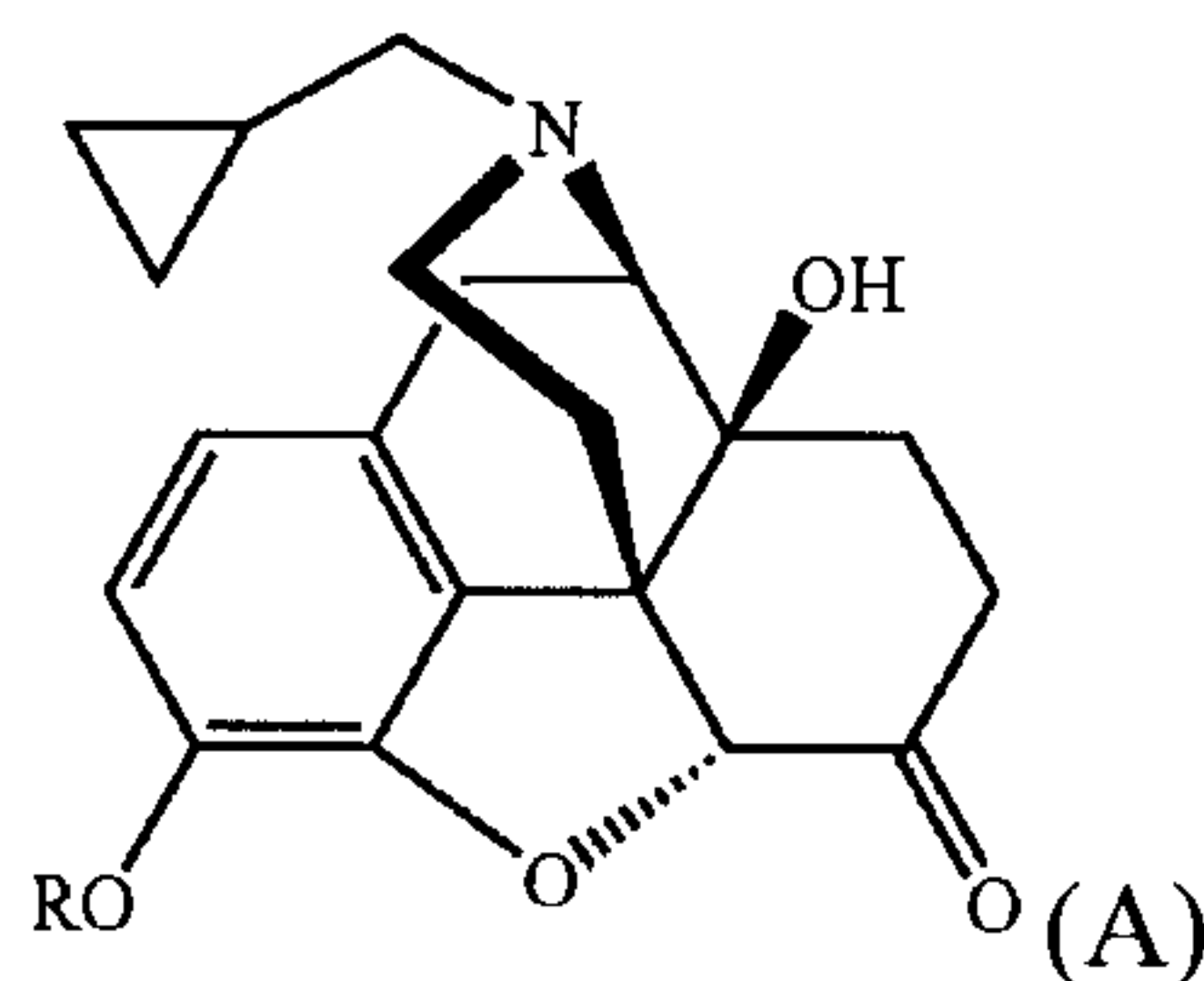
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22. The method of any one of claims 6-21, further comprising purifying the R-MNTX by chromatography or recrystallization, or a combination thereof.

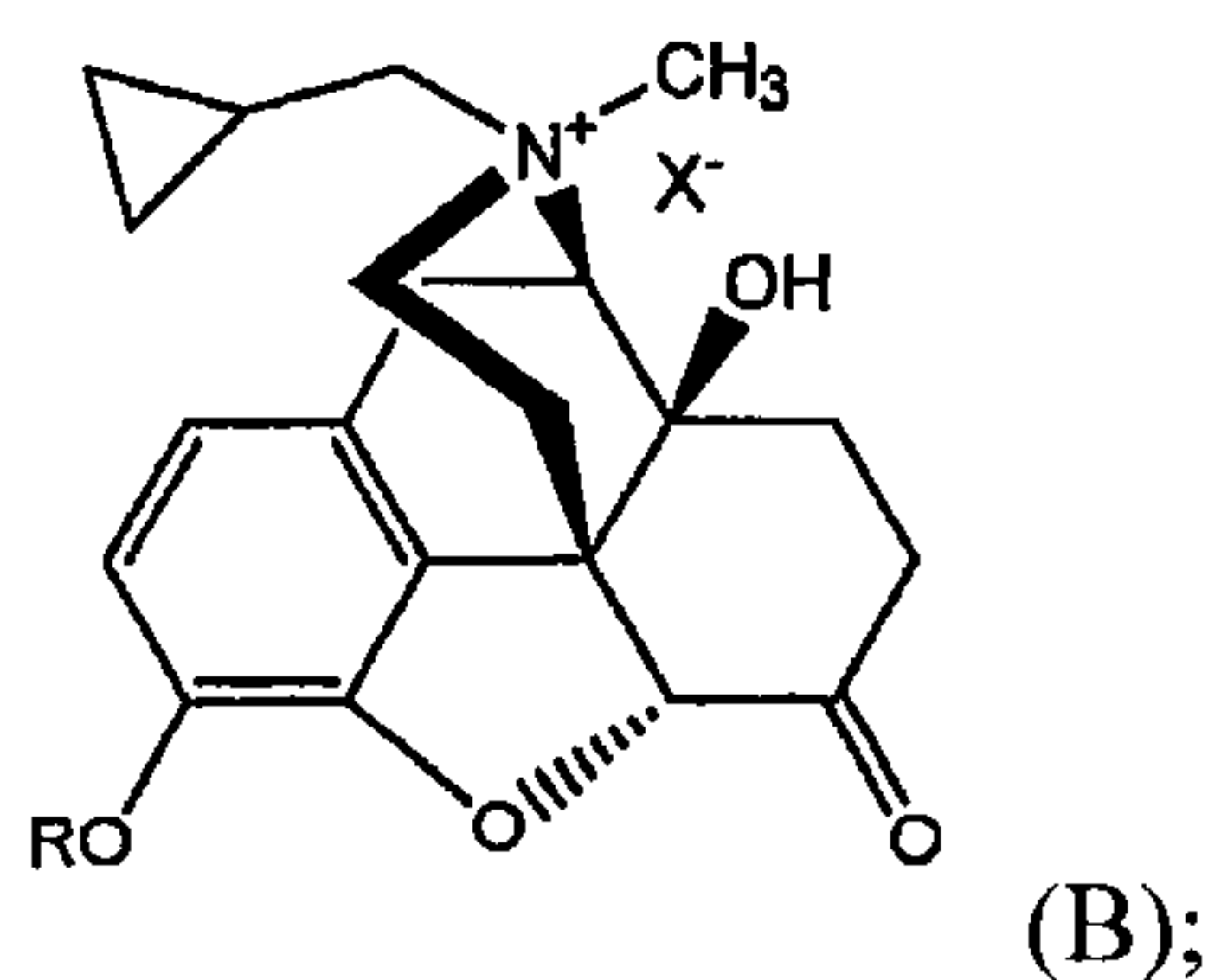
23. The method of claim 22, wherein the purification is performed by reverse phase chromatography or regular phase chromatography.

5 24. A method for stereoselective synthesis of R-methylnaltrexone (MNTX) halide comprising:

(a) methylating a compound of formula A



with a methyl halide methylating agent to yield a compound of formula B:



10

(b) removal of the 3-hydroxyl protecting group R to yield R-MNTX halide, wherein R is a hydroxyl protecting group selected from the group consisting of isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, or R, taken together with the oxygen atom to which it is attached, is a silyl ether, a 2-tetrahydropyranyl ether, or an alkyl carbonate; and

15

X⁻ is a halide.

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25. The method of claim 24, further comprising exchanging the halide with a different halide.

26. The method of claim 25, wherein the halide is iodide and the different halide is bromide.

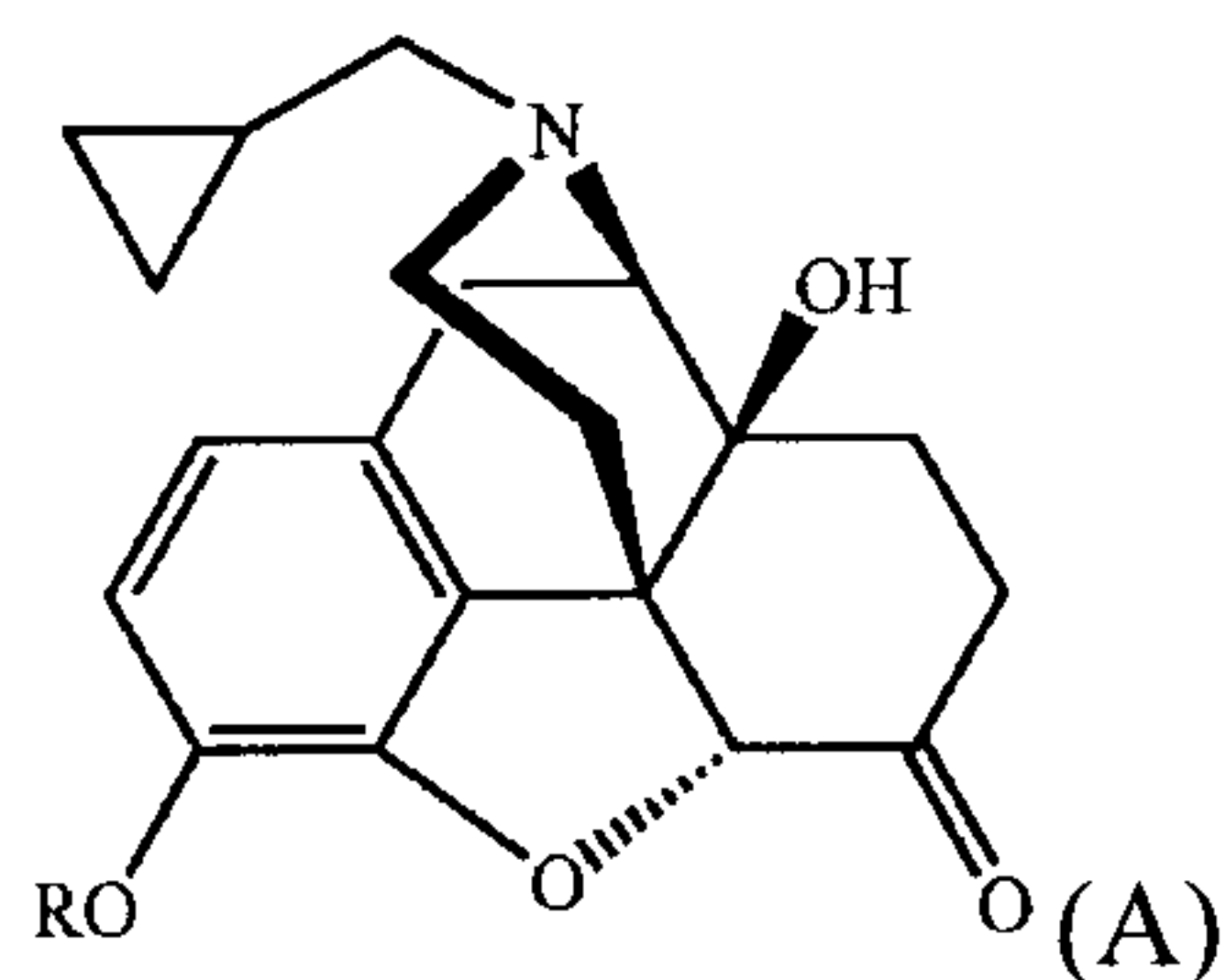
5 27. The method of any one of claims 24-26, further comprising purifying the R-MNTX by chromatography or recrystallization, or a combination thereof.

28. The method of claim 27, wherein the purification is performed by reverse phase chromatography or regular phase chromatography.

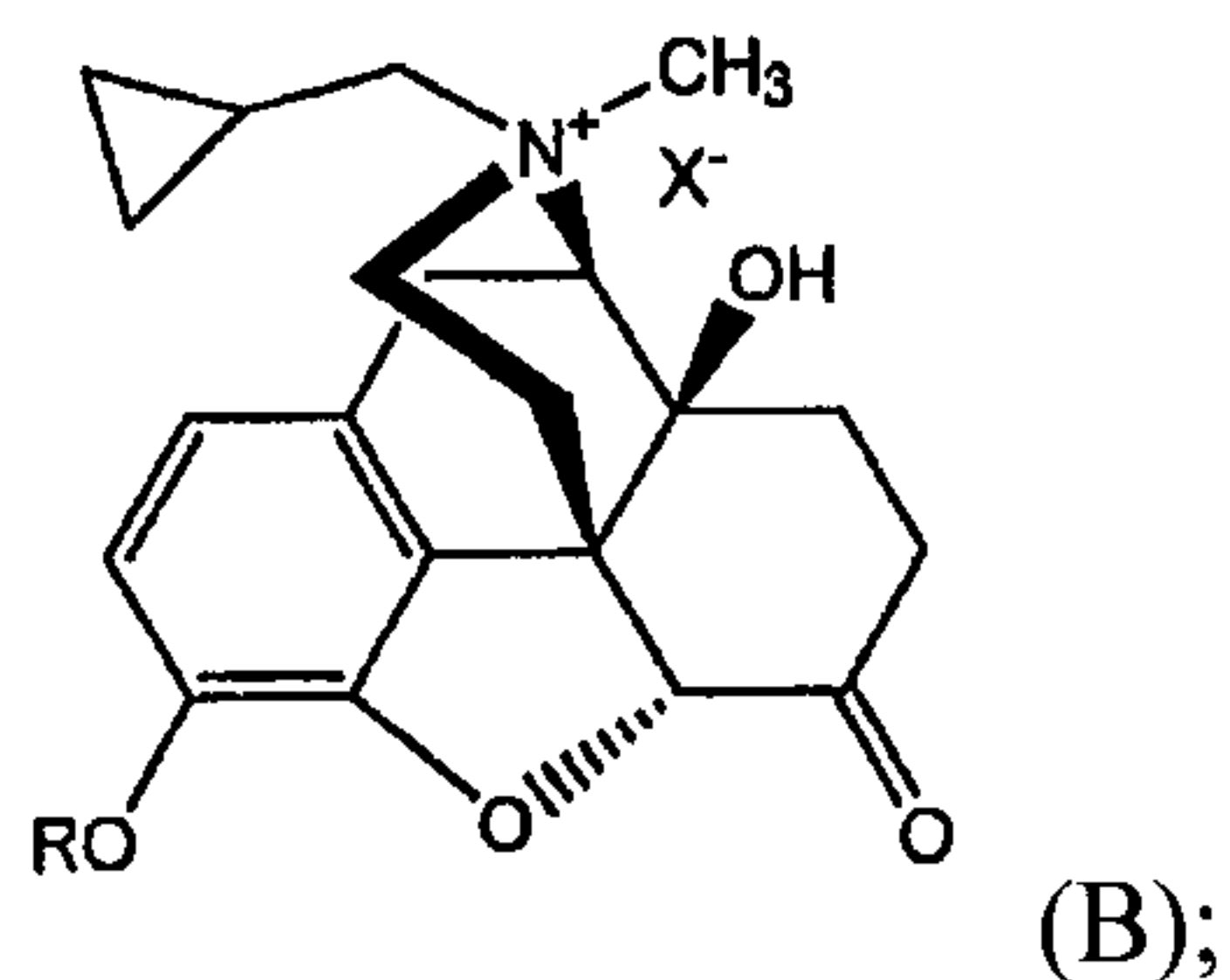
29. A method for stereoselective synthesis of R-methylnaltrexone (MNTX)

10 bromide salt comprising:

(a) methylating a compound of formula A:



with methyl iodide to yield a compound of formula B:



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wherein R is a hydroxyl protecting group selected from the group consisting of isobutyryl, 2-methyl butyryl, tertbutyl carbonyl, or R, taken together with the oxygen atom to which it is attached, is a silyl ether, a 2-tetrahydropyranyl ether, or an alkyl carbonate; and

X⁻ is iodide;

5 (b) hydrolysis with hydrobromic acid to remove R to yield R-MNTX bromide/iodide salt; and

(c) passing the R-MNTX bromide/iodide salt through anion exchange (bromide form) to yield R-MNTX bromide salt.

30. The method of claim 29, further comprising purifying the R-MNTX by
10 chromatography or recrystallization, or a combination thereof.

31. The method of claim 30, wherein the purification is performed by reverse phase chromatography or regular phase chromatography.

32. The method of claim 30 or 31, wherein the R-MNTX bromide salt has a purity of greater than 98% after purification.

15 33. A composition comprising the isolated 3-O-protected-R-MNTX salt of any one of claims 1-5 and a carrier.

34. A pharmaceutical composition comprising the salt of any one of claims 1-5 or the composition of claim 33, and a pharmaceutically acceptable carrier.

35. The pharmaceutical composition of claim 34, wherein the pharmaceutical
20 composition is a sustained release formulation, a lyophilized preparation, or a solution.

36. The pharmaceutical composition of claim 34 or 35, further comprising an opioid, optionally selected from the group consisting of alfentanil, anileridine, asimodiline, bremazocine, burprenorphine, butorphanol, codeine, dezocine, diacetylmorphine (heroin), dihydrocodeine, diphenyloxylate, fedotozine, fentanyl, funaltrexamine, hydrocodone,

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hydromorphone, levallorphan, levomethadyl acetate, levorphanol, loperamide, meperidine (pethidine), methadone, morphine, morphine-6-glucoronide, nalbuphine, nalorphine, opium, oxycodone, oxymorphone, pentazocine, propiram, propoxyphene, remifentanyl, sufentanil, tilidine, trimebutine, tramadol, and combinations thereof.

5 37. The pharmaceutical composition of claim 34 or 35, further comprising at least one pharmaceutical agent that is not an opioid or an opioid antagonist, optionally selected from the group consisting of an antiviral agent, an anti-infective agent, an anticancer agent, an antispasmodic agent, an anti-muscarinic agent, an anti-inflammatory agent, a pro-motility agent, a 5HT₁ agonist, a 5HT₃ antagonist, a 5HT₄ antagonist, a 5HT₄ agonist, a bile salt
10 sequestering agent, a bulk-forming agent, an alpha2-adrenergic agonist, a mineral oil, an antidepressant, a herbal medicine, an anti-emetic agent, an anti-diarrheal agent, a laxative, a stool softener, a fiber or a hematopoietic stimulating agent.

38. The composition of claim 37, wherein the anti-inflammatory agent is selected from the group consisting of non-steroidal anti-inflammatory drugs (NSAIDS), tumor necrosis
15 factor inhibitors, basiliximab, daclizumab, infliximab, mycophenolate, mofetil, azothioprine, tacrolimus, steroids, sulfasalazine, olsalazine, mesalamine, and combinations thereof.

39. The use of the pharmaceutical composition of claim 34 in the manufacture of a medicament for the treatment or prevention of an opioid-induced side effect wherein the medicament comprises an amount effective to treat or prevent the side effect.

20 40. The use of claim 39, wherein the patient is a chronic opioid patient.

41. The use of claim 39, wherein the opioid-induced side effect is induced by an endogenous opioid.

42. The use of claim 39, 40 or 41, wherein the side effect is selected from the group consisting of constipation, immune suppression, inhibition of gastrointestinal motility,
25 inhibition of gastric emptying, nausea, emesis, incomplete evacuation, bloating, abdominal

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distension, increased gastroesophageal reflux, hypotension, bradycardia, gastrointestinal dysfunction, pruritus, dysphoria, and urinary retention.

43. The use of the pharmaceutical composition of claim 34 in the manufacture of a medicament for the treatment or prevention of a condition selected from the group consisting
5 of idiopathic constipation, irritable bowel syndrome and post-operative bowel dysfunction, wherein the medicament comprises an amount effective to prevent or treat the condition.

44. The use of claim 43, wherein the post-operative bowel dysfunction is delayed gastric emptying or inhibition of gastrointestinal motility.

45. The use of the pharmaceutical composition of claim 34 in the manufacture of a
10 medicament for inducing laxation in a patient, wherein the medicament comprises an amount effective to induce laxation.

46. A patient-controlled injection device comprising the pharmaceutical composition of claim 34.

47. A kit comprising a package containing a sealed container comprising the
15 pharmaceutical composition of claim 34 and instructions for use.

48. A package containing the pharmaceutical composition of claim 34 and indicia on or contained within the package indicating a level of S-MNTX in the composition.

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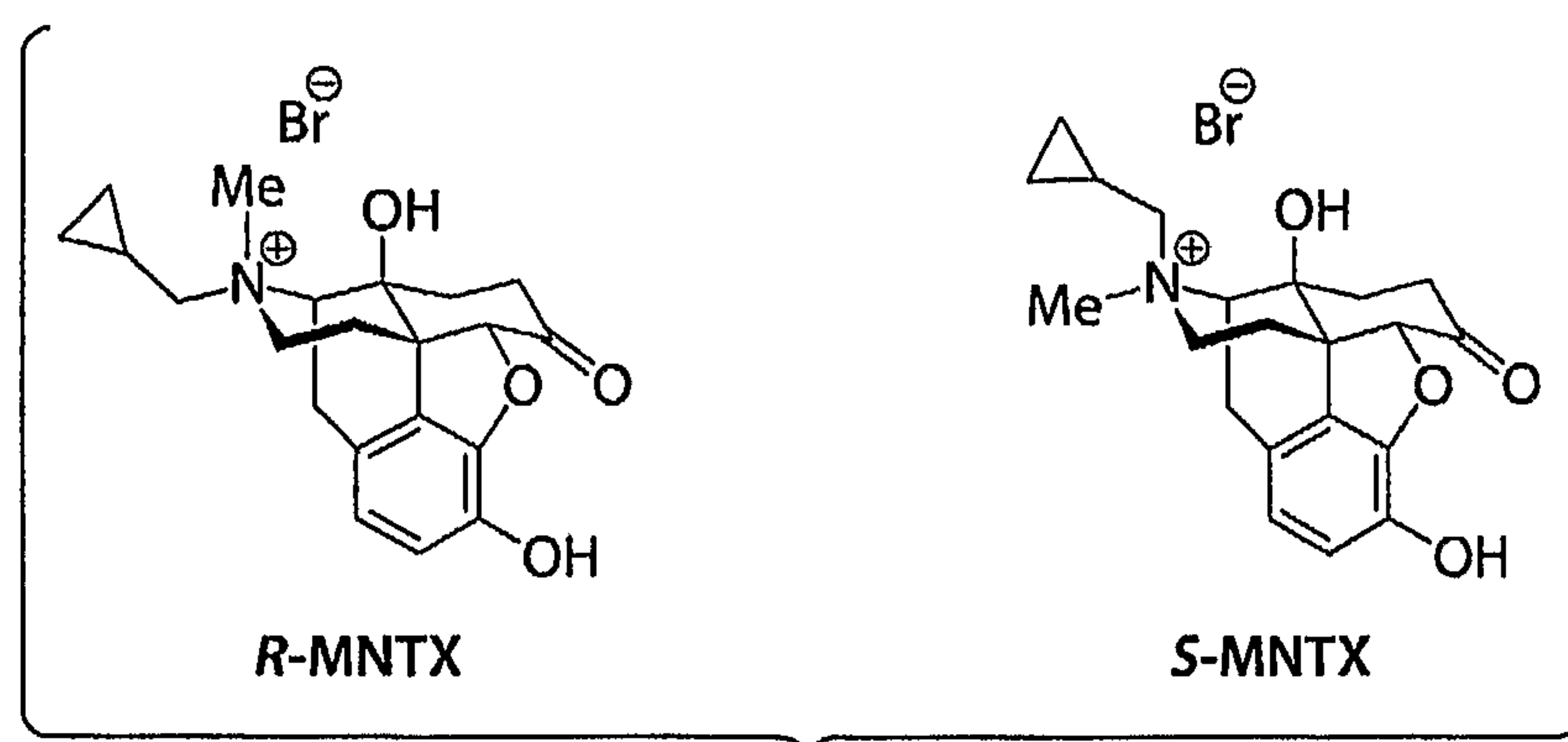
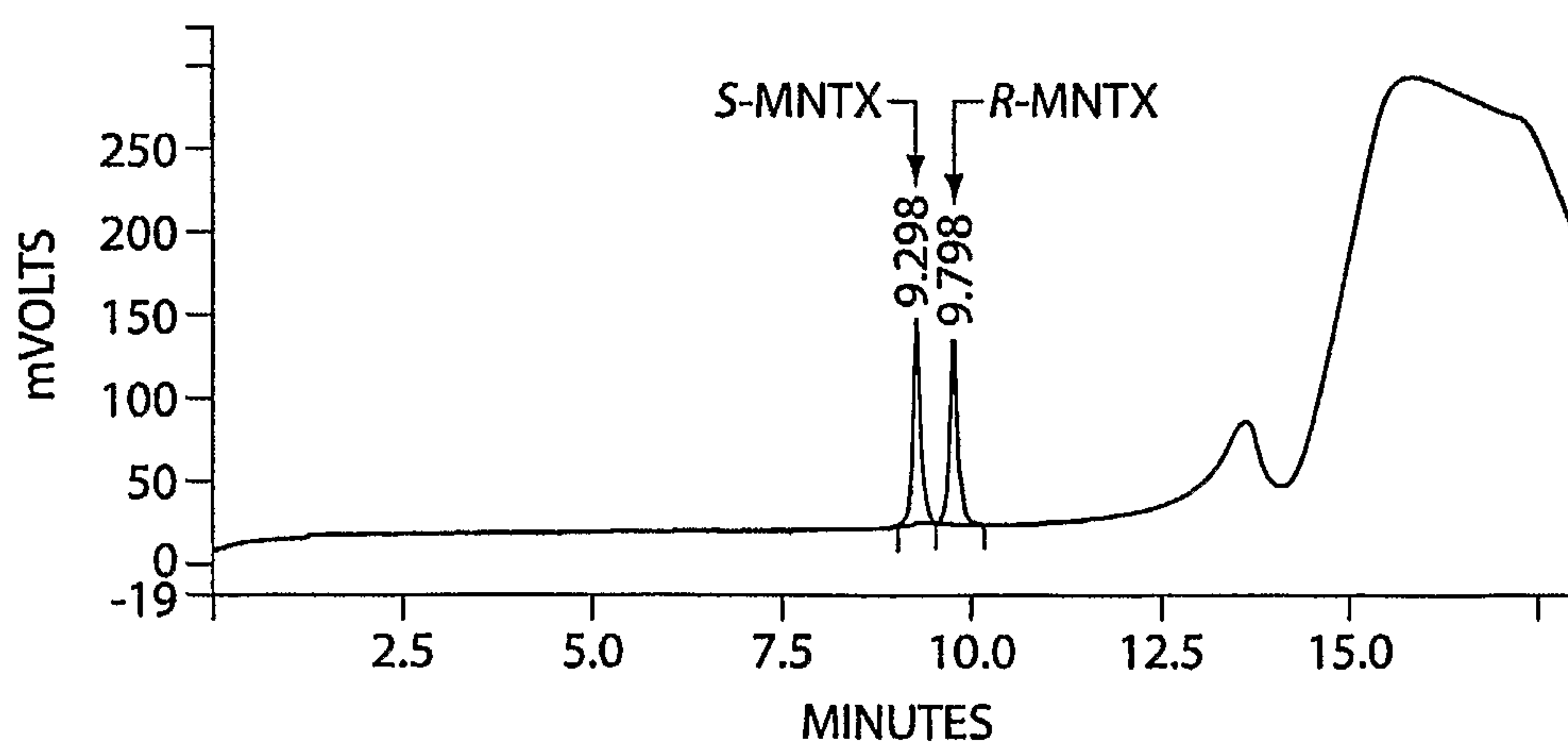


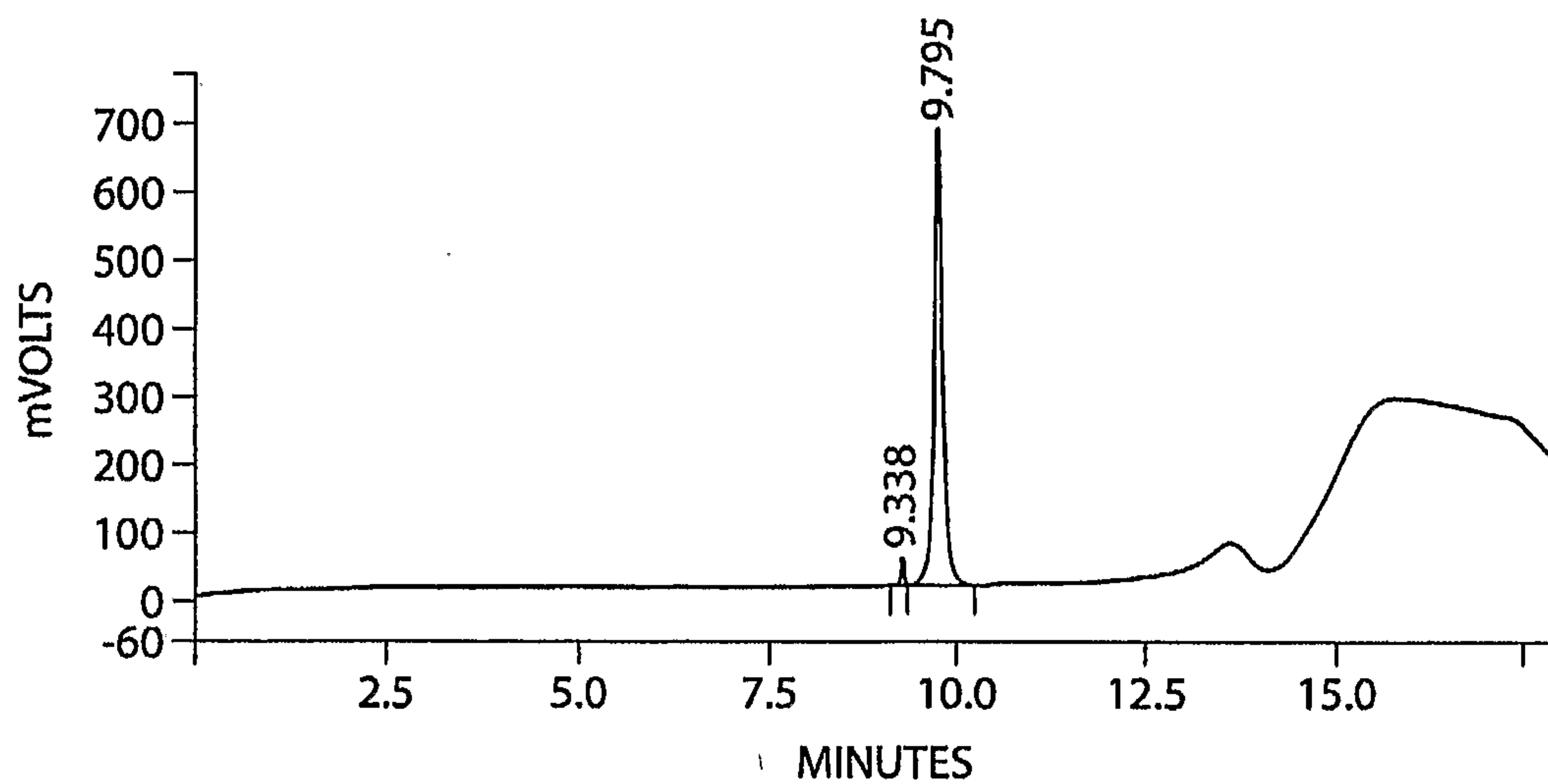
Fig. 1



PEAK NO	RET. TIME (MIN)	AREA (COUNTS)	SEP. CODE	WIDTH 1/2 (SEC)	RESULT 0
1	9.298	908375	BB	7.4	55.32
2	9.798	733746	BB	6.7	44.68
1642121					100.00

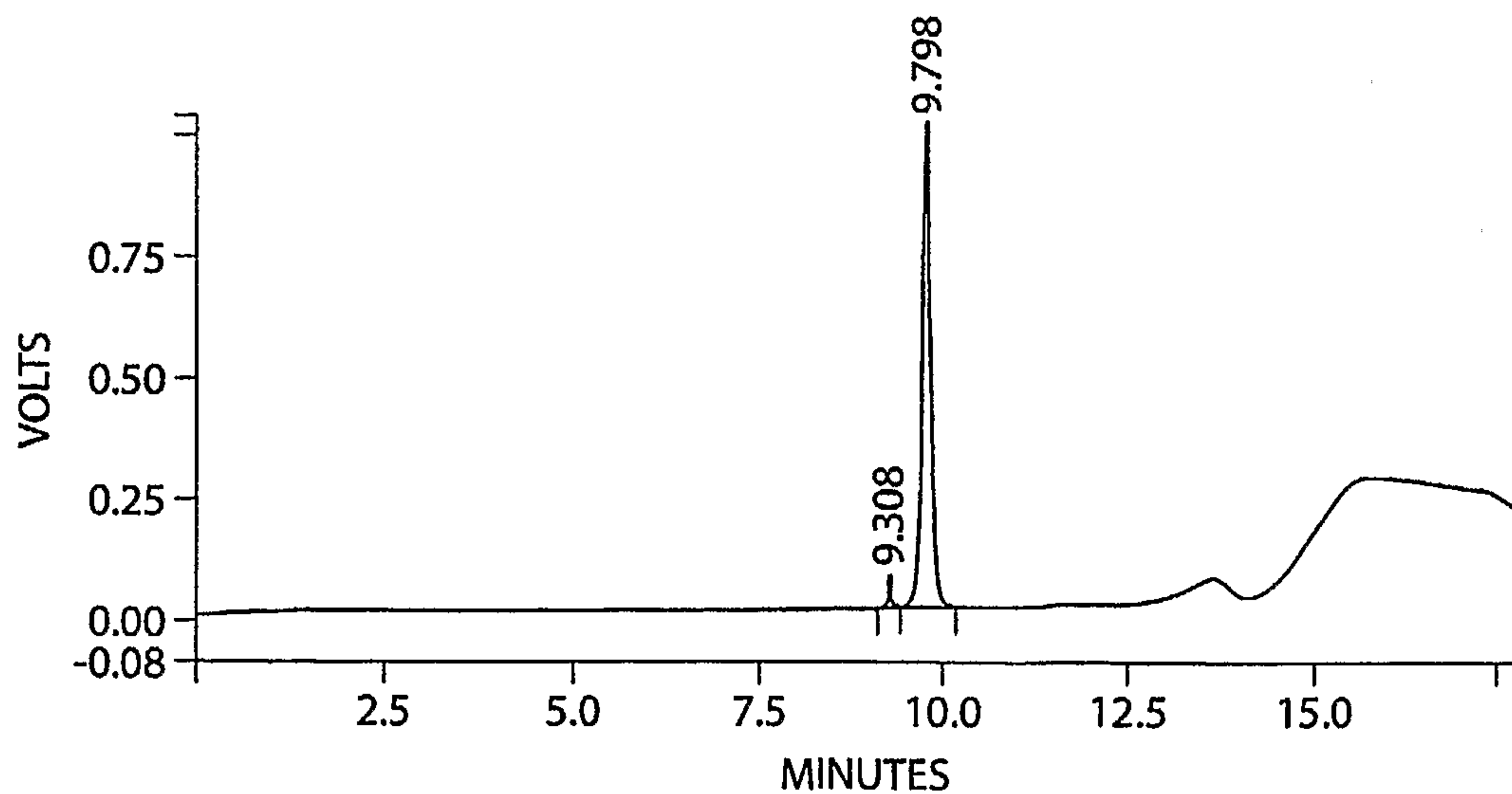
Fig. 2

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PEAK NO	RET. TIME (MIN)	AREA (COUNTS)	SEP. CODE	WIDTH 1/2 (SEC)	RESULT 0
1	9.338	6746	BB	-14.2	0.12
2	9.795	5851533	BB	7.3	99.88
5858279					100.00

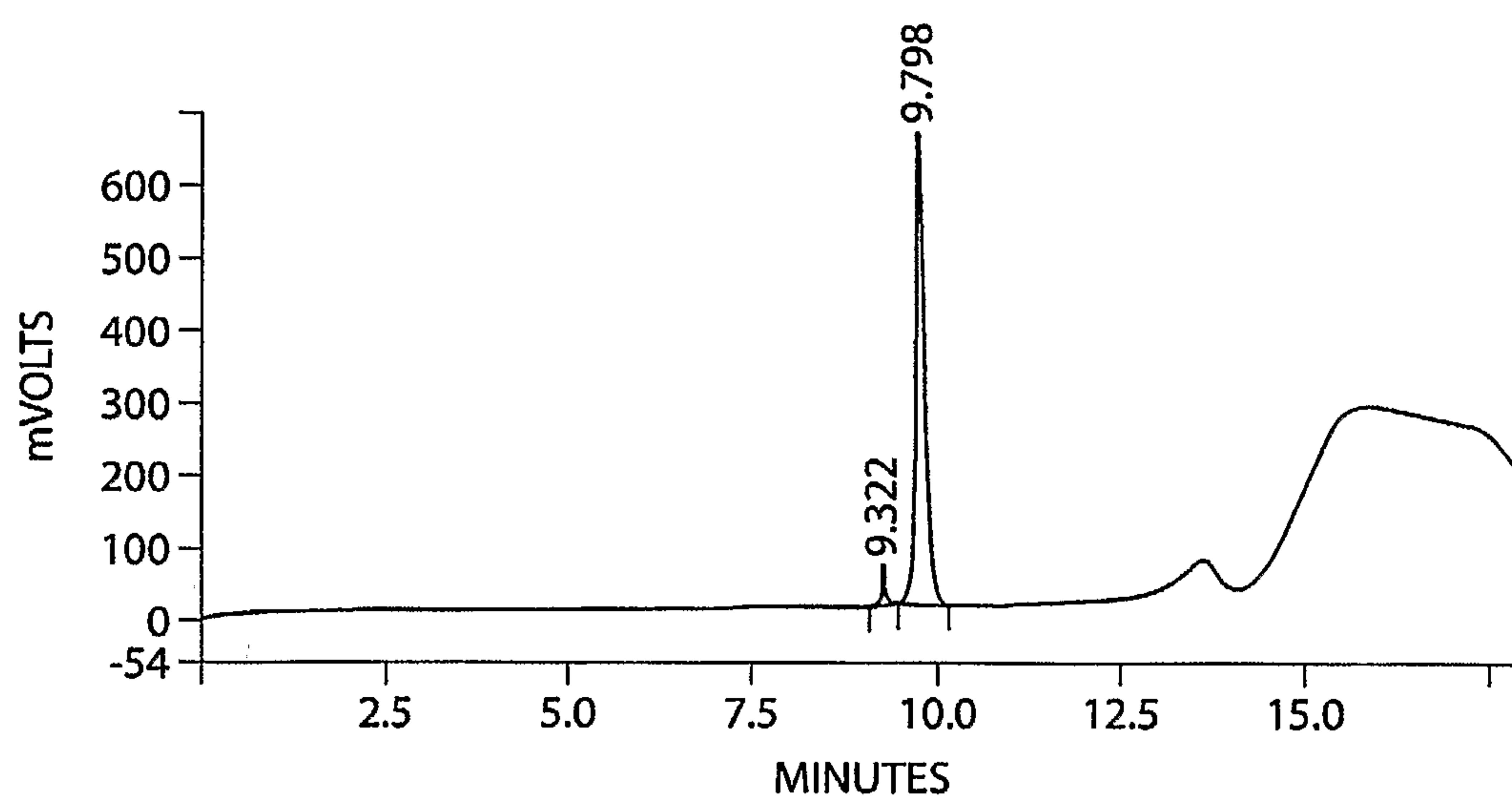
Fig. 3



PEAK NO	RET. TIME (MIN)	AREA (COUNTS)	SEP. CODE	WIDTH 1/2 (SEC)	RESULT 0
1	9.308	96051	BB	8.1	1.12
2	9.798	8465857	BB	7.8	98.88
8561908					100.00

Fig. 4

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PEAK NO	RET. TIME (MIN)	AREA (COUNTS)	SEP. CODE	WIDTH 1/2 (SEC)	RESULT 0
1	9.322	149670	BB	7.6	2.83
2	9.798	5144966	BB	7.2	97.17
5294636					100.00

Fig. 5

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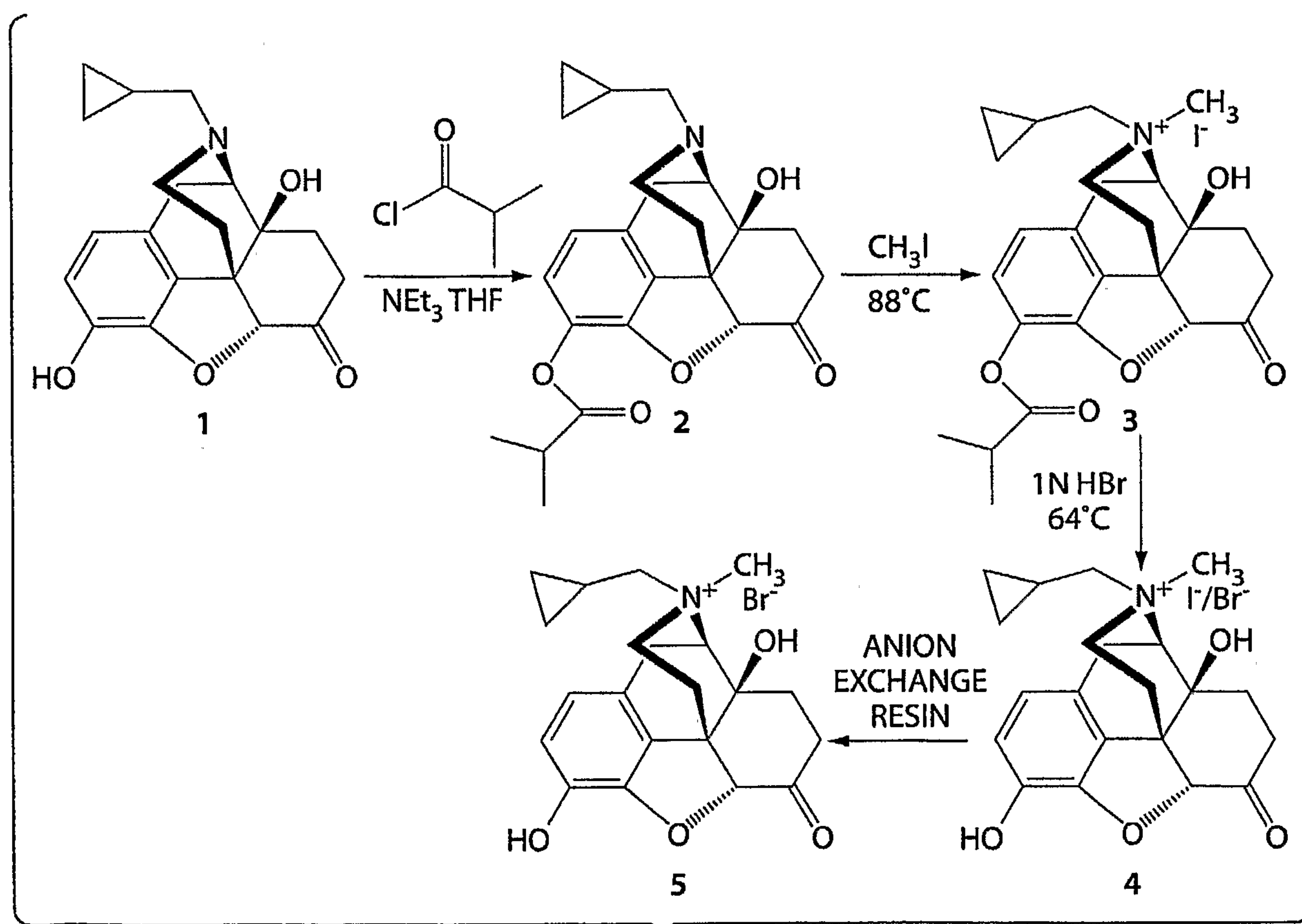


Fig. 6

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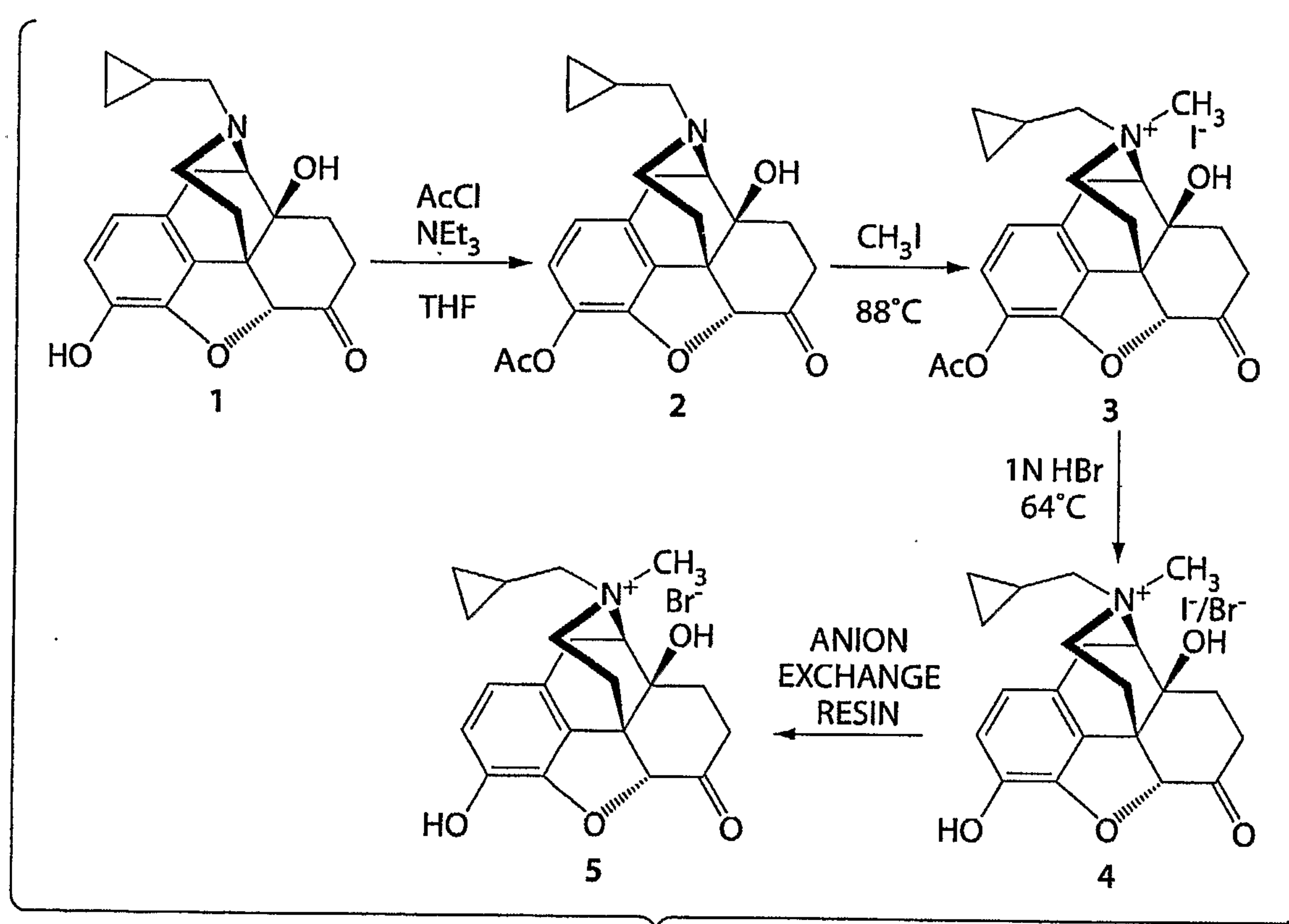


Fig. 7

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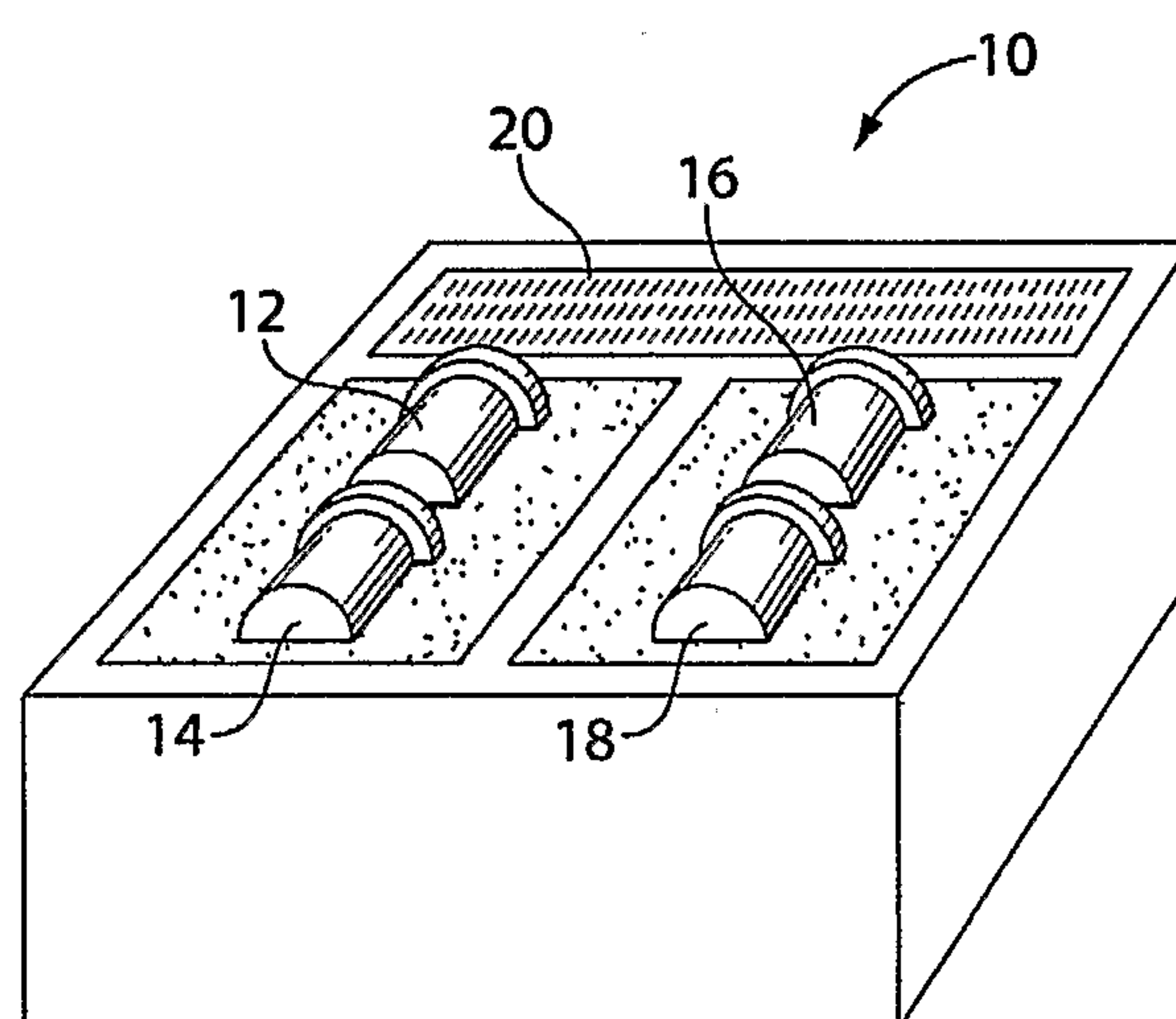


Fig. 8

