PROCESS FOR PREPARING OXYMORPHONE, NALTREXONE, AND BUPRENORPHINE

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ABSTRACT

Methods are provided which include converting oripavine to other opiates, including converting oripavine to naltrexone, buprenorphine, 14-hydroxymorphinone and/or converting 14-hydroxymorphinone to oxymorphone. Purification and salt formation are optionally included.
PROCESS FOR PREPARING OXYMORPHONE, NALTREXONE, AND BUPRENORPHINE

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority to U.S. Provisional Application No. 60/829,817, filed Oct. 17, 2006, and to U.S. Provisional Application No. ______ (Attorney Docket No. P31168), for which a Request to Convert Non-Provisional Application to Provisional Application Under 37 C.F.R. § 1.53(e)(2) was filed Oct. 11, 2007, from U.S. application Ser. No. 11/611,049, filed Dec. 14, 2006, the disclosures of each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] This invention relates to preparation of opiates such as 14-hydroxyoxymorphone, oxymorphone, naltrexone, methylnaltrexone, buprenorphine, nalmefine, nalorphine, and naloxone from oripavine.

[0004] 2. Background of the Invention and Related Art

[0005] Oxymorphone, a potent opiate analgesic, is a semi-synthetic substitute for morphine. It is about ten times as potent as morphine. In the United States, FDA has approved oxymorphone hydrochloride in oral, parenteral and suppository forms. Naltrexone, methylnaltrexone, buprenorphine, nalmefine, nalorphine, and naloxone are other useful opiates.

[0006] Oxymorphone can also be converted to these and other useful compounds, such as nal-componds, including naltrexone.

[0007] Oxymorphone is typically synthesized using thebaine, morphine or another compound as a starting material. Thebaine, when used, is generally obtained from the concentrated poppy straw (CPS-T), a poppy extract relatively rich in thebaine. Reaction schemes for producing oxymorphone from thebaine take several steps, to intermediates such as oxycodeone, then conversion of the 3-methoxy group of oxycodeone to the 3-hydroxy group of oxymorphone. U.S. Pat. No. 6,291,675, for example, discloses a method for O-demethylation of the 3-methoxy group of opiates by use of a lithium hydride compound, providing a yield of O-demethylated opioid of at least 25%. U.S. Pat. No. 5,922,876 discloses preparation of oxymorphone from morphine. The process includes protection of the 3-hydroxy group of morphine with an aceto or benzyl group.

[0008] Naltrexone is a narcotic antagonist; it also has been used to treat opioid abuse and alcoholic abuse. It can be prepared from thebaine (U.S. Pat. No. 3,332,950) or morphine (U.S. Pat. No. 6,013,796). Buprenorphine is a narcotic agonist/antagonist; it has been used for the treatment of opioid abuse. It can be prepared from thebaine (U.S. Pat. No. 3,433,791).

[0009] Features and advantages of the present invention will be set forth in the description of invention that follows, and will be apparent, in part, from the description or may be learned by practice of the invention. The invention will be realized and attained by the compositions, products, and methods particularly pointed out in the written description and claims hereof.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0010] Unless otherwise stated, a reference to a compound or component includes the compound or component by itself, as well as in combination with other compounds or components, such as mixtures of compounds.

[0011] As used herein, the singular forms “a,” “an,” and “the” include the plural reference unless the context clearly dictates otherwise.

[0012] Except where otherwise indicated, all numbers expressing quantities of ingredients, reaction conditions, and so forth used in the specification and claims are to be understood as being modified in all instances by the term “about.” Accordingly, unless indicated to the contrary, the numerical parameters set forth in the following specification and attached claims are approximations that may vary depending upon the desired properties sought to be obtained by the present invention. At the very least, and not to be considered as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should be construed in light of the number of significant digits and ordinary rounding conventions.

[0013] Additionally, the recitation of numerical ranges within this specification is considered to be a disclosure of all numerical values and ranges within that range. For example, if a range is from about 1 to about 50, it is deemed to include, for example, 1, 7, 34, 46.1, 23.7, or any other value or range within the range.

[0014] Unless otherwise noted, all reactions are run under inert conditions, such as under nitrogen or argon for safety and/or to avoid the formation of N-oxide by-products.

[0015] The present inventor has discovered that oripavine can be economically converted to other opiates, such as oxymorphone, naltrexone, and buprenorphine and derivatives thereof. Any starting material comprising oripavine may be used. The starting material preferably comprises greater than about 50% by weight oripavine, preferably greater than about 70%, more preferably greater than about 95%. The starting material is preferably purified oripavine, or a concentrate of poppy straw comprising oripavine as the main alkaloid (hereinafter, “CPS—O”).

[0016] Preferably, the oripavine comprises “natural oripavine,” but can comprise oripavine from any source. By “natural oripavine” is meant oripavine obtained from a natural source (e.g., botanical, bioengineered bacterial, etc.), and is meant to distinguish from oripavine obtained in a laboratory or factory setting by partial or total chemical synthesis, e.g., synthetic or semi-synthetic oripavine. Natural oripavine includes, without limitation, CPS—O, and purified oripavine obtained from CPS—O or other poppy straw.

Preparation of Oxymorphone

[0017] Preferably, oripavine is oxidized with an oxidizing agent to obtain 14-hydroxyoxymorphone. The 14-hydroxyoxymorphone is then preferably reduced with a reducing agent to obtain oxymorphone. The 14-hydroxyoxymorphone can also be used in other ways, preferably to prepare other products.
The oxidizing agent can comprise any oxidizing agent that permits the conversion of oripavine to 14-hydroxy-morphinone, including, but not limited to, peroxo acids, such as performic acid, peracetic acid, and m-chloroperbenzoic acid (MCPBA). Mixtures of oxidizing agents may be used. When a peroxo acid is used, it may be added, or prepared in situ.

When the oxidizing agent comprises a peroxo acid prepared in situ, it may be prepared in any manner, preferably by combining a peroxide and an acid. Any peroxide or combination of peroxides that can provide a peroxo acid can be used, preferably hydrogen peroxide, for example, aqueous hydrogen peroxide. Any acid or combination of acids that can provide a peroxo acid can be used, preferably formic acid, or acetic acid, for example, aqueous solutions of formic and/or acetic acid. Performic acid may be obtained, for example, by combining hydrogen peroxide and formic acid, and peracetic acid may be obtained by combining hydrogen peroxide with acetic acid.

The reaction may be carried out in any appropriate solvent, preferably an aqueous solvent. When the oxidizing agent includes a peroxo acid, it is preferred to use a solvent comprising the corresponding acid. For example, when the oxidizing agent comprises performic acid, it is preferred to use a solvent comprising formic acid, and when the oxidizing agent comprises peracetic acid, it is preferred to use a solvent comprising acetic acid. When MCPBA is used, it is preferred to use a solvent comprising acetic acid.
Any temperature that permits the reaction to proceed may be used. The temperature need not remain constant, and may vary during the reaction. Higher reaction temperatures speed up the reaction, but may increase formation of by-products. Different oxidation agents may run optimally at different temperatures. Reactions employing performic acid, for example are preferably run in the range of about 20 to 60° C., more preferably about 40-50° C., even more preferably at about 50° C. Reactions employing MCPBA are preferably run in the range of about 0 to 40° C., more preferably about 10-30° C., even more preferably at ambient temperature, e.g., about 25° C.

The reaction is run under conditions to convert oripavine to 14-hydroxymorphinone. Preferably, at least about 90% of the oripavine is converted to 14-hydroxymorphinone, more preferably, about 95%, even more preferably about 98% or 99%. Preferably, the conversion of oripavine to 14-hydroxymorphinone will be about 100%.

The remaining amount of oripavine in the reaction mixture, as well as the amount of 14-hydroxymorphinone produced, can be determined by any method, such as by TLC or HPLC.

Any reducing agent may be used to convert 14-hydroxymorphinone to oxymorphone. Catalytic hydrogenation is a preferred method, e.g., with a palladium catalyst, preferably palladium, or palladium hydroxide, on activated carbon (e.g., Pd/C).

Catalytic hydrogenation may be performed at any suitable pressure, and is preferably done completely, or in part, in a low pressure environment. Catalytic hydrogenation preferably includes hydrogenation at or greater than, about 1 atmosphere pressure. By “low pressure” is preferably meant less than about 10 atm, or less than about 4 atm. Catalytic hydrogenation reactions, therefore, include hydrogenation at, e.g., at about 1-10 atm or about 1-4 atm. Low pressure hydrogenation generally requires less expensive processing and/or lower equipment costs than hydrogenation at higher pressures.

The oxidizing and reduction may be performed as a “one pot” process, or may be done in separate vessels. The 14-hydroxymorphinone may be isolated, but need not be isolated, prior to reduction. In a preferred embodiment, the 14-hydroxymorphinone is not isolated in solid form prior to reduction.

Preferably, the opiate, e.g., oxymorphone, or a salt thereof, is purified. Preferably, crude oxymorphone is isolated, purified, and converted to a salt, preferably the hydrochloride salt. An exemplary process for purifying crude oripavine base is:

Purification aids may be used in the purification process. Preferred purification aids include adsorbents. Some preferred purification aids include activated carbon (commercially available as, e.g., DARCO), and/or powdered cellulose (commercially available as, e.g., SOLKA-FLOC). The reducing agent sodium bisulfite may be used, e.g., when performing the reaction in the presence of oxidants, e.g., under an oxidizing atmosphere. When the reaction is run under a non-oxidizing atmosphere, e.g., nitrogen gas, it may be possible to omit sodium bisulfite. Other purification aids, including purification aids known in the art, may be selected and used by a person of ordinary skill in the art. Purified oxymorphone, containing very little 14-hydroxymorphinone, is especially desirable because the impurity (14-hydroxymorphinone) is an alpha-beta-unsaturated ketone, which may be a carcinogen.

Opiate salts, e.g., of oxymorphone, may also be prepared. Any salt, preferably a therapeutically acceptable salt, may be included in the present invention. The hydrochloride is a preferred salt. Methods for preparing salts of compounds are known in the art. An exemplary process for preparing the hydrochloride salt of purified oxymorphone is:
Generally, oxymorphone, preferably purified oxymorphone, is suspended or dissolved in a liquid, preferably an alcohol and/or water; and more preferably ethanol, 2-propanol, combinations thereof, and combinations with water. Then, an acid, such as hydrochloric acid (preferably concentrated or gaseous HCl), is added to the mixture at a higher temperature. After cooling for a period of time, preferably once the reaction is complete or substantially complete, the oxymorphone salt is separated from the mixture, washed, and dried.

Oxymorphone can also be converted to other compounds, such as naloxone. Methods for effecting this conversion are known in the art.

Preparation of Naltrexone

Oripavine can also be converted to naltrexone. One scheme for performing this conversion is shown in Scheme 1, below:
Generally, the phenolic hydroxyl group in the 3-position of oripavine can be protected, for example by a benzyl group (or a substituted benzyl group, etc.) to 3-benzyl-oripavine, (1-1), followed by N-demethylation with a demethylation agent such as 1-chloroethyl chloroformate (ACE-C1), and then reacting with methanol to obtain 3-benzyl-nororipavine, (1-2). The nor-product is alkylated with (chloromethyl)cyclopropane (or other halomethylcyclopropane, or tosylmethylecyclopropane, for example) to give 3-benzyl-17-cyclopropylmethylnororipavine, (1-3). This is oxidized to 3-benzyl-17-cyclopropylmethyl-14-hydroxynororipavine, (1-4), by reacting with an oxidation agent such as a peroxy acid like peroxyformic acid, peroxycetic acid, or MCPBA. The product, which may or may not be isolated, can be hydrogenated to reduce the 7,8-double bond and to de-benzylate at the same time to give naltrexone, which can be converted to a salt.

Preparation of Buprenorphine

Oripavine can also be converted to buprenorphine. One scheme for performing this conversion is shown in Scheme 2, below:

Scheme 2. Synthesis of Buprenorphine from Oripavine (such as obtained from CPS-O)
Generally, oripavine can be reacted with methyl vinyl ketone under Diels-Alder conditions to give 7α-acetyl-6,7,8,14-tetrahydro-6,14-endotoxicoripavine, (2-1), which can be protected for the 3-phenolic hydroxyl group by, for example, a benzyl group (or a substituted benzyl group, etc.) to 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endotoxicoripavine, (2-2). This is de-methylated by reacting with a demethylating agent, such as ACE-CI, and then refluxing in methanol to the nor product 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoinnororipavine, (2-3), which is alkylated with (chloromethyl)-cyclopropane (or other halomethylcyclopropane, or tosylmethylcyclopropanone, for example) to 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoxnororipavine, (2-4). This is reacted with a Grignard reagent, tert-butyl magnesium chloride (or tert-butyl lithium), in THF to 3-benzyl-17-cyclopropylmethyl-6,14-endotheno-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydronororipavine, (2-5), which is reduced and de-benzylated at the same time by hydrogenation with Pd/C or Pd(OH)₂ in hydrogen to buprenorphine, which can be converted to a salt.

Alternatively, the hydroxyl group of oripavine is protected with a benzyl group first and then reacted with methyl vinyl ketone under Diels-Alder conditions.

Oxymorphone, naltraxone, or buprenorphine, or salts thereof, preferably HCl salts, may be prepared into pharmaceutical dosage forms. Pharmaceutical dosage forms include, but are not limited to, tablets, pills, capsules (including hard or soft gelatin capsules), parenteral formulations, suppositories, patches, and powders. Generally, a salt, e.g., the hydrochloride, is preferred. Oxymorphone base may be used, e.g., for transdermal patches. Preferred dosage forms include parenteral formulations and suppositories.

**EXAMPLES**

**Synthesis of Oxymorphone**

**Example 1**

**Crude Oxymorphone from Oripavine**

To a stirred oripavine (166.7 mg; 0.561 mmol) solution in 0.5 ml 30% formic acid (4.185 mmol) was added 0.1 ml 30% hydrogen peroxide (0.979 mmol), and the resulting mixture was stirred at 50°C. After complete transformation as indicated by TLC, the reaction mixture was transferred to a Parr Shaker, and 5% Pd/C (51.9 mg) was added. The mixture was hydrogenated at room temperature under 28 inch-Hg overnight, filtered, basified with NH₄OH, and extracted with methylene chloride (5×15 ml). The extract was evaporated under reduced pressure to give 113.4 mg of a pale yellow solid, yield 67.1%. The product has an identical retention time in HPLC and same R₂ value in TLC to oxymorphone standard.

**Example 2**

**Crude Oxymorphone from Oripavine**

Oripavine (50.0 g, 168 mmol), de-ionized water (70 ml), and 90% formic acid (42.0 g, 0.821 mol) were charged into a 500 ml 3-necked round bottom flask. The solution was stirred at 30-40°C, and to the composition was added 35% hydrogen peroxide, drop-wise (19.7 g, 0.203 mol), while keeping the temperature below 40°C. Upon completion of the addition, the mixture was stirred at 40-50°C for 4 hours. The reaction mixture was transferred to a 1-L hydrogenation vessel and 5% Pd/C (3.2 g) and 2-propanol (160 ml) were added. Hydrogenation proceeded at 46-52 psig at room temperature overnight (about 18 h). The catalyst in the mixture was filtered off. The filtrate and washings are combined and basified with 50% NaOH (59.6 g) to pH 9.16. The temperature was kept at below 30°C during the basification. The slurry was stirred at room temperature for 1 hour, and filtered to give a brown solid, which was then dried at 90°C and 25°C Hg vacuum overnight to provide the crude oxymorphone as light brown solids (48.2 g, 160 mmol, 95.2% yield).

**Example 2b**

**Crude Oxymorphone from Oripavine**

Oripavine (50.0 g, 168 mmol), was converted to 14-hydroxymorphone as in Example 2 through and including addition of hydrogen peroxide. Upon completion of the addition, the mixture was stirred at 40-50°C. By HPLC, it was determined that the area ratio of 14-hydroxymorphone: oripavine is 27.2:72.8 after 1 hour, and 99.3:0.7 after 4 hours. After 4 hours 40 minutes, the reaction mixture was tran-
ferred to a 1-L hydrogenation vessel and 5% Pd/C (3.2 g) (Degussa E101 o/w, H₂O 56.2%) was added. Hydrogenation proceeds at 46-52 psig at room temperature overnight (about 18 h). The mixture was filtered, and rinsed with about 50 ml water. 250 ml of filtrate was obtained, to which was added 25 ml butanol, yielding a mixture having pH of 2.86. While kept at less than 30° C, or at about 19.6° C, the filtrate was basified with 57.5 g of 50% NaOH, resulting in a pH of 9.05. The mixture was stirred for about one hour at room temperature, filtered, washed with water (4x50 ml), yielding a brown solid. The wet cake was dried at 93° C. at 25 °Hg overnight, yielding 44.2 g, 87.2% yield, of oxymorphone as a light brown solid.

Example 3
Crude Oxymorphone from CPS—O

[0044] A mixture of CPS—O (6.92 g contains 76% (5.26 g, 17.7 mmol) of oripavine), meta-chloroperoxybenzoic acid (MCPBA, 4.30 g) and gluacial acetic acid (52 ml) is stirred at room temperature for 5 hours. The amount of oripavine is then expected to be not more than 1% by HPLC analysis. To the resulting 14-hydroxymorphine mixture is added 5% Pd/C (0.55 g) and hydrogenation proceeds at room temperature at 48 psig of hydrogen for about 18 hours. The amount of unreacted 14-hydroxymorphine is expected to be not more than 0.5% by HPLC analysis. The mixture is filtered to remove the catalyst and the filtrate is evaporated to almost dryness. The residue is dissolved in water and basified to pH 9 by ammonium hydroxide. The solids are collected by filtration and dried at 90° C. and under 25-inch Hg of vacuum for 3 hours to give crude oxymorphone (approximately 95% yield expected).

Example 4
Purified Oxymorphone

[0045] A suspension of the crude oxymorphone (20.0 g, 66 mmol) and water (120 ml) was stirred at 45-55° C. Tartaric acid (5.5 g) was added to adjust the pH to 4.35 to complete dissolution. DARCO (1.0 g) and SOLKA-FLOC (1.0 g) were then added and stirred at 45-55° C. for 1 hour. The mixture was filtered and rinsed with water (10 ml). The filtrate and washings were combined and to this were added DARCO (1.0 g), SOLKA-FLOC (1.0 g) and sodium bisulfite (0.4 g). The mixture was stirred for 1 hour at 45-55° C., filtered and rinsed with water (10 ml). 1-BuOH (12 ml) was added to the filtrate and stirred at 45-55° C. 50% NaOH (6.1 g) was added to adjust the pH to 8.56 at 45-55° C., in particular, 50.5° C. The shuxy was cooled to room temperature and filtered. Light brown solids were collected and dried at 65° C. and 25° Hg vacuum overnight to give purified oxymorphone (18.2 g, 60 m mol, 91.0% yield).

Example 5
Oxymorphone HCl from Purified Oxymorphone

[0046] Purified oxymorphone (17.8 g, 59 mmol) was suspended in 94%aq. ethanol (107 ml) and stirred at 50-60° C. Concentrated hydrochloric acid (32%) was added slowly to adjust the pH to 2.58. The mixture was allowed to cool to room temperature, and then cooled further to 0-10° C., stirred for 2 hours and filtered then washed with ethanol (3x20 ml). The isolated solids were dried at 75° C. under 25 inches-Hg overnight to give oxymorphone HCl as white solids (17.3 g, 51 mmol, 86.7% yield).

[0047] This Oxymorphone HCl meets the specifications in the USP 2006 monograph for Oxymorphone Hydrochloride.

Synthesis of Naltrexone

Example 6
Preparation of 3-Benzylripavine (1-1) from CPS—O

[0048] A mixture of CPS—O (76% Oripavine, 13.16 g, 44 m mol), benzy1 bromide (9.2 g) and potassium bicarbonate (17.6 g) in toluene (200 ml) is heated to reflux for 4 hours, then cooled and filtered. The filtrate is extracted with dilute acetic acid. Immediately, the extract is basified with ammonium hydroxide to collect 3-benzylripavine (expected yield: 16.19 g; 95% yield).

Example 7
Preparation of 3-Benzyl-17-cyclopentylmethylnorripavine (1-3) through 3-Benzylnorripavine (1-2) from 3-Benzylripavine (1-1)

[0049] A solution of 3-benzylripavine (11.62 g, 30 mmol), 1-chlorolnethyl chlorofomate (5.52 g, 37.8 mmol) and proton sponge (1.1 g) in methylene chloride (80 ml) is heated at reflux for 2 hours. The reaction mixture is evaporated in vacuo to dryness. The residue is dissolved in methanol (50 ml), heated to reflux for 30 minutes, basified with ammonium hydroxide, and then evaporated to dryness. To the residue is added (chloromethyl)-cyclopropane (5.14 g, 55.6 m mol), sodium carbonate (14.7 g, 139 mmol), and potassium iodide (4.6 g, 28 mmol) in ethanol (250 ml) and heating proceeds at reflux for 20 hours. The mixture is cooled and evaporated in vacuo to dryness. The residue is basified with ammonium hydroxide and extracted with methylene chloride. The extract is washed with water, dried with anhydrous sodium sulfate, and evaporated in vacuo to dryness. The residue is chromatographed on silica gel with a eluting solvent system of methanol/ethyl acetate (10/90 v/v) to give 3-benzyl-17-cyclopentylmethylnorripavine (expected yield: 10.93 g; 85% yield).

Example 8
Preparation of naltrexone through 3-benzyl-17-cyclopentylmethyl-14-hydroxynorripavine (1-4) from 3-benzyl-17-cyclopentylmethylnorripavine (1-3)

[0050] A mixture of 3-benzyl-17-cyclopentylmethylnorripavine (10 g, 23 mmol), formic acid (90%, 60 ml), D.I. water (3 ml), methanol (10 ml) and hydrogen peroxide (31%, 3.3 ml) is stirred and heated at 40-50° C. for 5 hours. The mixture is allowed to cool, then 5% Pd/C (0.5 g) is added, and the mixture is hydrogenated under 25-inch-Hg for 8 hours. The catalyst is filtered off. The residue is evaporated in vacuo to dryness to give a crude product, which is re-crystallized from acetone/water to give a white crystalline solid. It is dissolved at 90° C. under 25 inch-Hg of vacuum for 4 hours to give naltrexone (expected yield: 6.8 g; 86% yield). This product is identical to a USP standard of Naltrexone.
Synthesis of Buprenorphine from CPS — O or Oripavine

Example 9
Preparation of 7α-Acetyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (2-1) from Oripavine

[0051] A mixture of oripavine (28.7 g, 96.5 mmol) and methyl vinyl ketone (18 ml) in 2-propanol (90 ml) is stirred and heated at reflux for 6 hours. The mixture is cooled to 10°C, and the solids filtered off, washed with cold 2-propanol and dried at 50°C to produce an anticipated yield of 32.9 g (93% yield) of 7α-acetyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine.

Example 10
Preparation of 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (2-2) from 7α-acetyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (2-1)

[0052] A mixture of 7α-acetyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (20.5 g, 55.8 mmol), benzyl bromide (11.5 g), and sodium carbonate (23.6 g) in toluene (350 ml) is heated at reflux for 4 hours. The reaction mixture is cooled and washed with water. The organic layer is evaporated in vacuo to dryness to give 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (24.5 g, 96% yield).

Example 11
Preparation of 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (2-4) through 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (2-3) from 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (2-2)

[0053] A solution of 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (6.9 g, 15 mmol), 1-chloroethyl chloroformate (2.76 g, 19 mmol) and proton sponge (0.5 g) in methylene chloride (50 ml) is heated at reflux for 2 hours. The reaction mixture is evaporated in vacuo to dryness. The residue is dissolved in methanol (30 ml). To this is added a few drops of concentrated hydrochloric acid and heated to reflux for 30 minutes and basified with ammonium hydroxide. This is evaporated to dryness. To the residue is added (chloromethyl)cyclopropane (2.07 g, 28 mmol), sodium carbonate (7.4 g, 64 mmol), and potassium iodide (2.3 g, 14 mmol) in ethanol (150 ml) and heated at reflux for 20 hours. The resulting mixture is cooled and evaporated in vacuo to dryness. The residue is basified with ammonium hydroxide and extracted with methylene chloride. The extract is washed with water, dried with anhydrous sodium sulfate and evaporated in vacuo to dryness. The residue is chromatographed on silica gel with a eluting solvent system of methanol/ethyl acetate (10/90 v/v) to give 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (expected yield: 6.9 g, 92% yield).

Example 12
Preparation of 3-benzyl-17-cyclopropylmethyl-6,14-endootheno-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydro-6,14-endoothenoropavine (2-5) from 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (2-4)

[0054] To 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoothenoropavine (6.6 g, 13 mmol) in dry THF (100 ml) is added tert-butyl magnesium chloride (2.0 M in THF, 8 ml, 16 mmol). The mixture was heated to reflux for 18 hours, cooled, THF (100 ml) is added and the mixture is quenched with saturated magnesium sulfate solution. The solution is separated from the semisolids and evaporated in vacuo to dryness to give 3-benzyl-17-cyclopropylmethyl-6,14-endootheno-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydronoropavine (expected yield: 7.5 g, 90% yield).

Example 13
Preparation of Buprenorphine from 3-benzyl-17-cyclopropylmethyl-6,14-endootheno-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydronoropavine (2-5)

[0055] A mixture of 3-benzyl-17-cyclopropylmethyl-6,14-endootheno-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydronoropavine (7.2 g, 13 mmol), glacial acetic acid (42 ml), and 5% Pd/C (0.36 g) is hydrogenated at 25 psig hydrogen pressure at 40°C for 16 hours. The catalyst is filtered off and the filtrate evaporated in vacuo to dryness. The residue is re-crystallized from ethanol to give buprenorphine (expected yield: 5.2 g, 86% yield).

Example 14
Preparation of Buprenorphine Hydrochloride

[0056] To a solution of buprenorphine (5.1 g, 11 mmol) in ethanol (60 ml) at 50-60°C, is added concentrated hydrochloric acid to pH 2.5, the heating is maintained at 50-60°C for 2 hours, and cooled to 10-15°C. The mixture is filtered to collect the solid. The solid is washed with cold ethanol and dried at 80°C under 25 inch Hg of vacuum for 4 hours to give the final product (expected yield: 5.3 g, 96% Yield). This product is identical to a USP standard of Buprenorphine Hydrochloride.

[0057] Although the present invention has been described in considerable detail with regard to certain versions thereof, other versions are possible, and alterations, permutations, and equivalents of the version shown will become apparent to those skilled in the art upon a reading of the specification and study of the drawings. Also, the various features of the version herein can be combined in various ways to provide additional versions of the present invention. Furthermore, certain terminology has been used for the purposes of descriptive clarity, and not to limit the present invention. Therefore, any appended claims should not be limited to the description of the preferred versions contained herein and should include all such alterations, permutations, and equivalents as fall within the true spirit and scope of the present invention.

[0058] Having now fully described this invention, it will be understood to those of ordinary skill in the art that the methods of the present invention can be carried out with a wide and equivalent range of conditions, formulations, and other parameters without departing from the scope of the invention or any embodiments thereof.

What is claimed is:
1. A method of preparing oxymorphone or a salt thereof comprising:
   oxidizing oripavine to obtain 14-hydroxymorphonine; and
   reducing the 14-hydroxymorphonine to obtain oxymorphone.
2. The method of claim 1 wherein the oxidizing comprises combining oripavine and an oxidizing agent.
3. The method of claim 2 wherein the oxidizing agent comprises a peroxy acid.
4. The method of claim 2 wherein the oxidizing agent comprises perfolinic acid.
5. The method of claim 2 wherein the oxidizing agent comprises m-chloroperoxybenzoic acid.
6. The method of claim 1 wherein the reducing includes catalytic hydrogenation.
7. The method of claim 1 wherein the reducing comprises palladium-catalyzed hydrogenation.
8. The method of claim 6 wherein the hydrogenation includes hydrogenation at lower pressure.
9. The method of claim 1 further comprising converting the oxymorphone to an oxymorphine salt.
10. The method of claim 9 wherein the oxymorphone salt comprises oxymorphone hydrochloride.
11. The method of claim 1 further comprising purifying the oxymorphol or salt thereof.
12. The method of claim 11 comprising recrystallizing the oxymorphol or salt thereof.
13. A method of preparing oxymorphol or a salt thereof comprising converting 14-hydroxymorphol to oxymorphol or a salt thereof.
14. The method of claim 13 wherein the converting comprises hydrogenation.
15. The method of claim 14 wherein the hydrogenation comprises palladium-catalyzed hydrogenation.
16. The method of claim 14 wherein the hydrogenation includes hydrogenation at lower pressure.
17. A method of preparing oxymorphol or a salt thereof comprising converting oripavine to oxymorphol or a salt thereof.
19. The method of claim 1 wherein the oripavine includes oripavine present in a concentrate of poppy straw comprising oripavine as the main alkaloid.
20. The method of claim 17 which includes converting oripavine in a concentrate of poppy straw comprising oripavine as the main alkaloid to oxymorphol or a salt thereof.
21. A method of preparing naltrexone or a salt thereof comprising converting oripavine to naltrexone or a salt thereof.
22. The method according to claim 21, comprising: protecting a hydroxyl group of oripavine with a benzyl group to 3-benzyloripavine; reacting 3-benzyloripavine with 1-chloroethyl chloroformate and then reacting with methanol to obtain 3-benzyl-nororipavine; alkylation of the 3-benzyl-nororipavine with (chloromethyl)cyclopropane to produce 3-benzyl-17-cyclopropylmethyloripavine; oxidizing the 3-benzyl-17-cyclopropylmethyloripavine with a peroxy acid to produce 3-benzyl-17-cyclopropylmethyl-14-hydroxynororipavine; and reducing the 3-benzyl-17-cyclopropylmethyl-14-hydroxynororipavine with catalytic hydrogenation to produce naltrexone.
23. A method of preparing buprenorphine or a salt thereof comprising converting oripavine to buprenorphine or a salt thereof.
24. The method according to claim 23, comprising: reacting the oripavine with methyl vinyl ketone to produce 7α-acetyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine; protecting a hydroxyl group of 7α-acetyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine with a benzyl group to 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine; de-methylating the 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine with ACE-Cl to 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine; alkylation of the 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine with (chloromethyl)cyclopropane to obtain 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine; reacting the 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine with tert-butyl magnesium chloride or tert-butyl lithium to produce 3-benzyl-17-cyclopropylmethyl-6,14-endoethano-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydrooripavine; and reducing the 3-benzyl-17-cyclopropylmethyl-6,14-endoethano-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydrooripavine by catalytic hydrogenation to produce buprenorphine.
25. The method according to claim 23, comprising: protecting a hydroxyl group of oripavine with a benzyl group to 3-benzyloripavine; reacting the 3-benzyloripavine with methyl vinyl ketone to produce 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine; de-methylating the 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine with ACE-Cl to 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine; alkylation of the 7α-acetyl-3-benzyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine with (chloromethyl)cyclopropane to obtain 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine; reacting the 7α-acetyl-3-benzyl-17-cyclopropylmethyl-6,7,8,14-tetrahydro-6,14-endoethnornororipavine with tert-butyl magnesium chloride or tert-butyl lithium to produce 3-benzyl-17-cyclopropylmethyl-6,14-endoethano-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydrooripavine; and reducing the 3-benzyl-17-cyclopropylmethyl-6,14-endoethano-7α-(2-hydroxy-3,3-dimethyl-2-butyl)-6,7,8,14-tetrahydrooripavine by catalytic hydrogenation to produce buprenorphine.