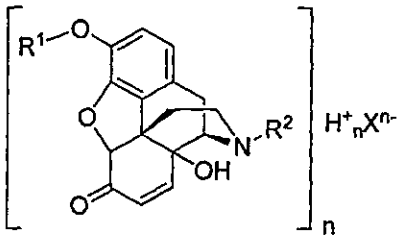
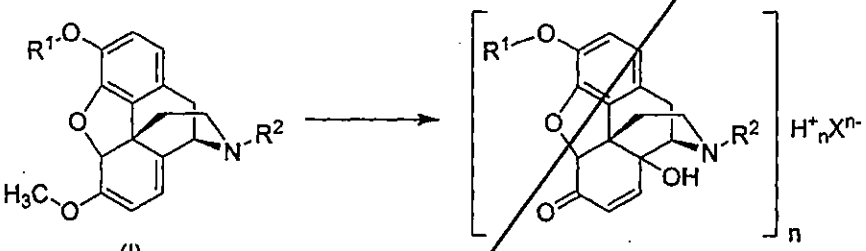
CLAIMS

1. A process for preparing a compound of formula V or a solvate thereof



(V)

from a compound of formula I or a salt or solvate thereof, the process comprising:



(I) (V)

(a) oxidizing the compound of formula I; and

(b) adding an acid $H^+_nX^{n-}$ to the reaction mixture before, during and/or after the oxidation reaction,

wherein,

R^1 is -H, -(C_1-C_7)alkyl, aralkyl, -(C_2-C_6)alkenyl, -SiR^3_3, -(C_3-C_7)cycloalkyl, -(C_1-C_7)alkyl-(C_3-C_7)cycloalkyl, -(C_3-C_7)cycloalkenyl, -(C_1-C_7)alkyl-(C_3-C_7)cycloalkenyl, -CR^4_2-O-(C_1-C_6)alkyl, -C(halo)$_3$, -CH_2(halo), -CH(halo)$_2$,-SO_2R^5, or an O-protecting group;

R^2 is -H, -CH_3, -(C_2-C_7)alkyl, -(C_2-C_4)alkenyl, benzyl, -(C_1-C_7)alkyl-(C_3-C_7)cycloalkyl, -CN, or an N-protecting group;

each R^3 is independently selected from aryl, –(C_1-C_6)alkyl and –(C_1-C_6)alkoxy;

each R^4 is independently selected from –H and –(C_1-C_6)alkyl;

R^5 is -(C_6-C_{14})aryl or –(C_1-C_6)alkyl;

X^{n-} is an anion selected from the group consisting of Cl^-, HSO_4^-, SO_4^{2-}, methanesulfonate, tosylate, trifluoroacetate, $H_2PO_4^-$, HPO_4^{2-}, PO_4^{3-}, oxalate, perchlorate, and any mixtures thereof; and

n is 1, 2 or 3.

2. The process of claim 1, wherein R^2 is -CH_3, -CH_2-cyclopropyl, -CH_2-cyclobutyl, or allyl.

3. The process of claim 1, wherein R^2 is –CH_3.

4. The process of claim 1, wherein R^2 is –H.

5. The process of any one of the preceding claims, wherein R^1 is –H.

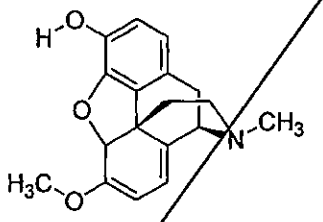
6. The process of any one of the preceding claims, wherein n is 1 or 2, preferably n is 2.

7. The process of any one of the preceding claims, wherein X^{n-} is SO_4^{2-} or trifluoroacetate.

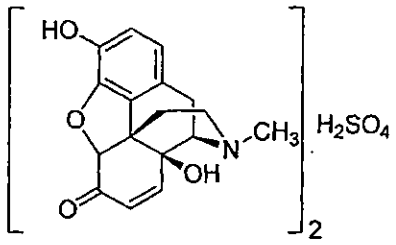
8. The process of any one of the preceding claims, wherein X^{n-} is SO_4^{2-}.

9. The process of any one of the preceding claims, wherein the acid $H^+_nX^{n-}$ is H_2SO_4.

10. The process of any one of the preceding claims, wherein the compound of formula I is

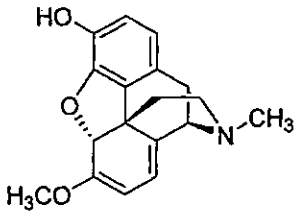


and the compound of formula V is

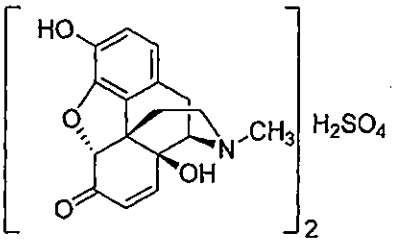


or a solvate thereof.

11. The process of any one of the preceding claims, wherein the compound of formula I is



and the compound of formula V is



or a solvate thereof.

12. The process of any one of the preceding claims, wherein the compound of formula V is a hydrate of the compound of formula V.

13. The process of claim 12, wherein the hydrate is a hydrate containing from 0.5 to 10.0 water molecules per molecule of the compound of formula V.

14. The process of claim 12, wherein the hydrate is the monohydrate or the pentahydrate of the compound of formula V.

15. The process of any one of the preceding claims, wherein the acid $H^+_nX^{n-}$ is added to the reaction mixture before the oxidation reaction of step (a).

16. The process of any one of the preceding claims, wherein the acid $H^+_nX^{n-}$ is added during

the oxidation reaction.

17. The process of any one of the preceding claims, wherein the acid $H^+_nX^{n-}$ is added after the oxidation reaction.

18. The process of any one of the preceding claims, wherein the reaction mixture is maintained at a temperature of from about 30°C to about 38°C, preferably of from about 32°C to about 36°C, more preferably of about 35°C during the oxidation reaction.

19. The process of any one of the preceding claims, comprising the additional step:
(c) precipitating the compound of formula V or solvate thereof.

20. The process of claim 19, wherein the precipitation is caused by the presence of the acid $H^+_nX^{n-}$ in the reaction mixture.

21. The process of claim 19 or 20, wherein the precipitation takes place during and/or after the oxidation reaction.

22. The process of any one of claims 19 to 21, wherein the precipitation is initiated and/or enhanced by adding an additional amount of the acid $H^+_nX^{n-}$ during step (b).

23. The process of any one of claims 19 to 22, wherein said precipitation is initiated and/or enhanced by one or more of the following:
(i) adjusting the temperature of the reaction mixture to the precipitation temperature;
(ii) addition of an antisolvent;
(iii) addition of a seed crystal;
(iv) lowering the pH;
(v) changing the ionic strength of the reaction mixture;
(vi) concentrating the reaction mixture;
(vii) reducing or stopping agitation of the reaction mixture.

24. The process of any one of claims 19 to 23, wherein the precipitation is initiated and/or enhanced by adjusting the temperature of the reaction mixture to reach the precipitation temperature.

25. The process of any one of claims 19 to 24, wherein the precipitation temperature is a temperature of ≤ 40 °C, and preferably is ≤ 35 °C, ≤ 30 °C, ≤ 25 °C, ≤ 20 °C, ≤ 18°C, ≤ 15 °C, ≤ 10 °C, ≤ 5 °C, or ≤ 0 °C.

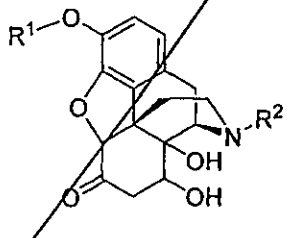
26. The process of claim 25, wherein the precipitation temperature is in a range of from about 0 °C to about 40 °C, preferably from about 0 °C to about 35 °C.

27. The process of claim 26, wherein the precipitation temperature is in a range of from about 5 °C to about 22 °C; preferably from about 8 °C to about 15 °C.

28. The process of any one of claims 19 to 27, wherein the precipitation is initiated and/or enhanced by adding an antisolvent, preferably an antisolvent selected from the group consisting of *tert*-butyl methyl ether, diethyl ether, hexane(s), *tert*-amyl alcohol, methanol, ethanol, isopropanol, 2-butanol, heptanes, xylenes, toluene, acetone, 2-butanone, ethyl acetate, tetrahydrofuran, 1,2-dichloroethane, chloroform, dichloromethane, 1-methoxy-2-propanol, 2-ethoxyethanol, n-propanol, 1-butanol, *tert*-butanol, isobutanol, isopropyl acetate, 1,4-dioxane, 2-methyl-tetrahydrofuran, methyl formate, methyl acetate, and any mixtures of two or more of any of the foregoing, more preferably selected from the group consisting of methanol, isopropanol, 2-butanol, *tert*-butyl methyl ether, tetrahydrofuran and any mixtures thereof, even more preferably selected from the group consisting of isopropanol, 2-butanol, and any mixtures thereof.

29. The process of any one of claims 19 to 28, comprising the additional step:
(d) isolating the precipitate from the reaction mixture.

30. The process of claim 29, wherein the isolated precipitate is washed and/or (re)crystallized with a solvent which is suitable to remove from the precipitate a compound of formula III or a salt or solvate thereof



(III)

wherein R^1 and R^2 are defined as in any one of claims 1 to 5.

31. The process of claim 30, wherein the solvent is selected from the group consisting of an ether, a ketone, an ester, an alcohol, water, an alkane (which may be halogenated), an aromatic solvent (which may be halogenated) and any combination of the foregoing.

32. The process of claim 31, wherein the solvent is selected from the group consisting of methanol, ethanol, isopropanol, 1-butanol, 2-butanol, *tert*-butanol, isobutanol, acetone, tetrahydrofuran, ethyl acetate, heptane, *tert*-butyl methyl ether, 1,2-dichloroethane, toluene, 2-butanone (MEK), *tert*-amyl alcohol, chloroform, xylene, water, and any mixture of the foregoing.

33. The process of claim 30, 31 or 32, wherein the solvent is *tert*-butyl methyl ether, tetrahydrofuran, methanol, ethanol, acetone, isopropanol, 2-butanol, or a mixture of methanol:water, THF:water, acetone:water, isopropanol:water, 2-butanol:water, or ethanol:water.

34. The process of claim 30, 31 or 32, wherein the solvent is *tert*-butyl methyl ether, tetrahydrofuran, methanol, 2-butanol, a 2-butanol:water mixture, or a methanol:water mixture.

35. The process of any one of the preceding claims, wherein the oxidation in step (a) is performed in the presence of an oxidizing agent.

36. The process of claim 35, wherein the oxidizing agent is selected from the group consisting of peracids, peroxides including H_2O_2 and peroxide salts, periodinanes, singlet oxygen and any combinations of the foregoing.

37. The process of claim 36, wherein the oxidizing agent comprises or is at least one peracid.

38. The process of claim 37, wherein the at least one peracid is generated in situ in the reaction mixture of step (a) from hydrogen peroxide and at least one acid.

39. The process of claim 38, wherein the at least one acid is selected from the group consisting of formic acid, acetic acid, 3-chlorobenzoic acid, potassium monosulfate, trifluoroacetic acid, and sulfuric acid.

40. The process of any one of claims 37 to 39, wherein the at least one peracid is selected from the group consisting of performic acid, peracetic acid, 3-chloroperoxybenzoic acid, potassium peroxymonosulfate, trifluoro peracetic acid, persulfuric acid, and any combinations of the foregoing.

41. The process of claim 40, wherein the at least one peracid is performic acid, which is generated in situ in step (a) from hydrogen peroxide and formic acid.

42. The process of claim 40, wherein the at least one peracid is a combination of performic acid and persulfuric acid, which is generated in situ in step (a) from hydrogen peroxide, sulfuric acid and formic acid.

43. The process of claim 37, wherein the peracid is generated ex situ and then added to the reaction mixture.

44. The process of any one of claims 35 to 43, wherein from about 1 to about 1.4 moles of the oxidizing agent per mole of the compound of formula I are used, and preferably from about 1.2 to about 1.4 moles of the oxidizing agent per mole of the compound of formula I are used, and more preferably from about 1.2 to about 1.3 moles of the oxidizing agent per mole of the compound of formula I are used.

45. The process of any one of claims 35 to 43, wherein from about 1 to about 1.4 moles of hydrogen peroxide per mole of the compound of formula I are used, and preferably from about 1.2 to about 1.4 moles of hydrogen peroxide per mole of the compound of formula I are used, and more preferably from about 1.2 to about 1.3 moles of hydrogen peroxide per mole of the compound of formula I are used.

46. The process of any one of the preceding claims, wherein X^{n-} is an anion selected from the group consisting of HSO_4^-, SO_4^{2-}, methanesulfonate, tosylate, trifluoroacetate, and combinations of the foregoing.

47. The process of any one of the preceding claims, wherein X^{n-} is HSO_4^-, SO_4^{2-}, methanesulfonate, or trifluoroacetate.

48. The process of any one of the preceding claims, wherein X^{n-} is HSO_4^- or SO_4^{2-}.

49. The process of any one of the preceding claims, wherein X^{n-} is SO_4^{2-}.

50. The process of any one of the preceding claims, wherein X^{n-} is polymer-supported.

51. The process of any one of the preceding claims, wherein X^{n-} is not polymer-supported.

52. The process of any one of the preceding claims, wherein $H^+_nX^{n-}$ is generated in situ by adding a salt containing X^{n-} to the reaction mixture, wherein the salt containing X^{n-} has the formula $M^{m+}(H^+)_{(n-m)}X^{n-}$, or $M^{m+}_{((n-l)/m)}(H^+)_lX^{n-}$, and wherein

M^{m+} is a monovalent or polyvalent metal cation;
m and n are independently an integer selected from 1, 2, and 3, provided that $m \leq n$; and
l is an integer selected from 0, 1, and 2, provided that $l < n$.

53. The process of any one of the preceding claims, wherein step (b) is performed by adding a Lewis acid to the reaction mixture instead of the acid $H^+_nX^{n-}$.

54. The process of any one of the preceding claims, wherein n is 2 and the acid $H^+_nX^{n-}$ added in step (b) is added in an amount of from about 0.1 to about 1.5 molar equivalents, preferably of from about 0.1 to about 1.2 molar equivalents, more preferably of from about 0.1 to about 1 molar equivalents, even more preferably of from about 0.25 to about 0.75 molar equivalents, even more preferably of from about 0.4 to about 0.6 molar equivalents, even more preferably of from about 0.5 to about 0.6 molar equivalents per molar equivalent of the compound of formula I.

55. The process of claim 54, wherein the acid $H^+_nX^{n-}$ added in step (b) is added in an amount of from about 0.51 to about 0.55 molar equivalents per molar equivalent of the compound of formula I.

56. The process of claim 54 or 55, wherein H_2SO_4 is the acid $H^+_nX^{n-}$ added in step (b).

57. The process of any one of the preceding claims, wherein n is 1 and the acid $H^+_nX^{n-}$ added in step (b) is added in an amount of from about 0.2 to about 3 molar equivalents, preferably of from about 0.7 to about 2.4 molar equivalents, more preferably of from about 0.8 to about 2 molar equivalents, even more preferably of from about 0.8 to about 1.6 molar equivalents,

even more preferably of from about 0.8 to about 1.2 molar equivalents, even more preferably of from about 0.9 to about 1.1 molar equivalents per molar equivalent of the compound of formula I.

58. The process of claim 57, wherein the acid $H^+_nX^{n-}$ added in step (b) is added in an amount of about 1 molar equivalents per molar equivalent of the compound of formula I.

59. The process of claim 57 or 58, wherein the acid $H^+_nX^{n-}$ added in step (b) is methanesulfonic acid or trifluoroacetic acid.

60. The process of any one of the preceding claims, wherein n is 3 and the acid $H^+_nX^{n-}$ added in step (b) is added in an amount of from about 0.07 to about 1 molar equivalents, preferably of from about 0.23 to about 0.8 molar equivalents, more preferably of from about 0.26 to about 0.66 molar equivalents, even more preferably of from about 0.26 to about 0.53 molar equivalents, even more preferably of from about 0.26 to about 0.4 molar equivalents, even more preferably of from about 0.3 to about 0.36 molar equivalents per molar equivalent of the compound of formula I.

61. The process of claim 60, wherein the acid $H^+_nX^{n-}$ added in step (b) is added in an amount of about 0.33 molar equivalents per molar equivalent of the compound of formula I.

62. The process of claim 60 or 61, wherein H_3PO_4 is the acid $H^+_nX^{n-}$ added in step (b).

63. The process of any one of the preceding claims, wherein in step (b) the $H^+_nX^{n-}$ is added in an amount of about 1/n molar equivalents per molar equivalent of the compound of formula I.

64. The process of any one of the preceding claims, wherein the oxidation is performed with an oxidizing agent, and the oxidizing agent comprises or is at least one peracid generated in situ from hydrogen peroxide and at least one acid in the reaction mixture.

65. The process of claim 64, wherein the at least one acid used for generating the peracid comprises or is formic acid.

66. The process of claim 64 or 65, wherein the amount of the at least one acid used for generating the peracid is from about 0.5 to about 14 molar equivalents, preferably from about 1 to about 12 molar equivalents, more preferably from about 1 to about 7 molar equivalents,

more preferably from about 1.5 to about 6 molar equivalents, more preferably from about 2 to about 5 molar equivalents, more preferably from about 2.5 to about 4.5 molar equivalents, even more preferably from about 2.5 to 4 molar equivalents per molar equivalent of the compound of formula I.

67. The process of any one of claims 64 to 66, wherein the total amount of acid in the reaction mixture, including the acid $H^+_nX^{n-}$ and the at least one acid used for generating the peracid, is from about 0.6 to about 14.0 molar equivalents of total acid per molar equivalent of the compound of formula I.

68. The process of claim 67, wherein the total amount of acid is from about 1 to about 12, from about 1 to about 10, from about 1 to about 8, from about 1 to about 7, from about 1 to about 6.5, from about 1 to about 6, from about 1 to about 5.5, from about 1 to about 4.5, from about 1 to about 4, from about 1 to about 3.5, or from about 1.5 to about 3.5 molar equivalents of total acid per molar equivalent of the compound of formula I.

69. The process of claim 67, wherein the total amount of acid is from about 1 to about 8 molar equivalents of total acid per molar equivalent of the compound of formula I.

70. The process of claim 69, wherein the total amount of acid is from about 1.5 to about 4.5 molar equivalents of total acid per molar equivalent of the compound of formula I.

71. The process of claim 69, wherein the total amount of acid is from about 2.5 to about 5.5, preferably from about 3 to about 5 molar equivalents of total acid per molar equivalent of the compound of formula I.

72. The process of any one of claims 64 to 71, wherein the molar ratio of the acid $H^+_nX^{n-}$ to the at least one acid used for generating the peracid is from about 1:20 to about 1:0.5, from about 1:17 to about 1:1, from about 1:15 to about 1:1, from about 1:14 to about 1:1, from about 1:12 to about 1:1, from about 1:10 to about 1:1, from about 1:9 to about 1:2, from about 1:8 to about 1:3, from about 1:7 to about 1:3, , from about 1:7 to about 1:5, or is a numeric value lying within these ranges.

73. The process of claim 72, wherein the molar ratio of the acid $H^+_nX^{n-}$ to the at least one acid used for generating the peracid is from about 1:9 to about 1:4, preferably from about 1:7.5 to about 1:4, more preferably from about 1:7 to about 1:5, or is a numeric value lying within these ranges.

74. The process of claim 72, wherein the molar ratio of the acid $H^+_nX^{n-}$ to the at least one acid used for generating the peracid is about 1:7, about 1:6.5, about 1:6, about 1:5.5, or about 1:5.

75. The process of any one of claims 64 to 74, wherein the molar amount of the acid used for generating the peracid in situ is from about 2.5 to about 4.5 equivalents per molar equivalent of the compound of formula I, and the molar amount of the peroxide is from about 1 to about 1.4 moles, preferably from about 1.2 to about 1.4 moles, more preferably from about 1.2 to about 1.3 moles per mole of the compound of formula I.

76. The process of claim 75, wherein the acid used for generating the peracid is formic acid, and wherein the peroxide is hydrogen peroxide.

77. The process of any one of claims 64 to 76, wherein the molar amount of the acid used for generating the peracid is from about 2.5 to about 4.5 molar equivalents per molar equivalent of the compound of formula I, n is 2, and the molar amount of the acid $H^+_nX^{n-}$ is from about 0.5 to about 0.6 molar equivalents per molar equivalent of the compound of formula I.

78. The process of claim 77, wherein the acid used for generating the peracid is formic acid, and the acid $H^+_nX^{n-}$ is sulfuric acid.

79. The process of any one of the preceding claims, wherein the compound of formula V or the solvate thereof is precipitated and wherein the precipitation temperature is ≤ 40 °C, and the total amount of acid present in the reaction mixture is from about 0.6 to about 14.0 molar equivalents of total acid per molar equivalent of the compound of formula I.

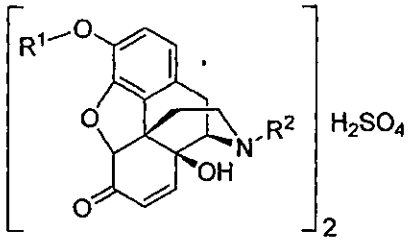
80. The process of claim 79, wherein the precipitation temperature is in a range of from about 0 °C to about 40 °C, preferably from about 0 °C to about 35 °C, and the total amount of acid present in the reaction mixture is from about 1 to about 8 molar equivalents, preferably from about 1 to about 5 molar equivalents, more preferably from about 1 to about 3 molar

equivalents of total acid per molar equivalent of the compound of formula I.

81. The process of claim 79, wherein the precipitation temperature is in a range of from about 5 °C to about 22 °C, and the total amount of acid present in the reaction mixture is from about 1 to about 7 molar equivalents, preferably from about 1 to about 5 molar equivalents of total acid per molar equivalent of the compound of formula I.

82. The process of any one of the preceding claims, wherein the pH in step (a) and (b) is less than 7, preferably the pH is 4 or less, more preferably 2.5 or less, even more preferably from 1 to 2.

83. The process of any one of the preceding claims, wherein X^{n-} in step (b) is SO_4^{2-} and the compound of formula V is



or a solvate thereof.

84. The process of claim 83, wherein the SO_4^{2-} is provided by addition of sulfuric acid as acid $H^+_nX^{n-}$ in step (b).

85. The process of claim 83, wherein the SO_4^{2-} is provided by addition of $NaHSO_4$ instead of the acid $H^+_nX^{n-}$ in step (b).

86. The process of any one of claims 83 to 85, wherein the compound of formula V is 14-hydroxymorphinone sulfate.

87. The process of any one of claims 83 to 85, wherein the compound of formula V is a solvate of 14-hydroxymorphinone sulfate.

88. The process of any one of claims 83 to 85 and 87, wherein the solvate of the compound of formula V is a hydrate.

89. The process of claim 88, wherein the hydrate is a hydrate containing from 0.5 to 10 water molecules per molecule of the compound of formula V.

90. The process of claim 88 or 89, wherein the hydrate is a monohydrate, dihydrate, trihydrate, tetrahydrate, pentahydrate, or hexahydrate.

91. The process of claim 90, wherein the hydrate is a monohydrate or a pentahydrate.

92. The process of any one of the preceding claims, wherein the reaction mixture comprises a solvent.

93. The process of claim 92, wherein the solvent is selected from the group consisting of water, alcohols, aromatic hydrocarbons (which are optionally halogenated), aliphatic hydrocarbons (which are optionally halogenated), ethers, (C_1-C_4) alkyl esters of (C_1-C_4) alkanoic acids, amides, N-methylpyrrolidone, formylmorpholine, and any combinations of the foregoing.

94. The process of claim 92, wherein the solvent is selected from the group consisting of water, ethers, alcohols, (C_1-C_4) alkanes (which are optionally chlorinated), and combinations of the foregoing.

95. The process of claim 93, wherein the solvent is water, tetrahydrofuran, isopropanol, methanol, ethanol, 1-butanol, 2-butanol, *tert*-butanol, isobutanol, *tert*-amyl alcohol, n-propanol, chloroform, or a combination of two or more of the foregoing.

96. The process of any one of claims 92 to 95, wherein the solvent is water or a combination of water with another solvent listed in claim 93, 94 or 95.

97. The process of any one of claims 92 to 95, wherein the solvent is isopropanol or a combination of isopropanol with water, or wherein the solvent is 2-butanol or a combination of 2-butanol with water.

98. The process of any one of claims 92 to 97, wherein the oxidation reaction is performed in the presence of at least one peracid generated from at least one acid, and wherein the at least one acid used for generating the peracid acts as a solvent.

99. The process of claim 98, wherein the acid used for generating the peracid is formic acid.

100. The process of any one of claims 92 to 99, wherein the acid $H^+_nX^{n-}$ acts as a solvent.

101. The process of claim 100, wherein the acid $H^+_nX^{n-}$ is sulfuric acid.

102. The process of any one of claims 92 to 101, wherein the molarity of the compound of formula I in relation to the solvent is ≥ 0.8, and preferably is from 0.8 to 1.8, more preferably from 1.2 to 1.7, more preferably from 1.2 to 1.6 and even more preferably from 1.3 to 1.5.

103. The process of claim 96, wherein the ratio of the compound of formula I (in mmol) to water (in ml) is preferably from about 1:1 to about 5:1, more preferably from about 1.2:1 to about 4:1, more preferably from about 1.5:1 to about 3:1, more preferably from about 1.6:1 to about 2.4:1, even more preferably from about 1.7:1 to about 2.2:1.

104. The process of any one of the preceding claims, wherein the compound of formula I is oripavine or a salt or solvate thereof.

105. The process of claim 104, wherein the oripavine, or the salt or solvate thereof is contained in CPS-O.

106. The process of any one of the preceding claims, wherein
the compound of formula (I) is oripavine or a salt or solvate thereof,
the oxidation agent comprises or is performic acid formed from hydrogen peroxide and formic acid,
the acid $H^+_nX^{n-}$ in step (b) is sulfuric acid which is added to the reaction mixture, and
the compound of formula V is 14-hydroxymorphinone sulfate or a solvate thereof.

107. The process of claim 106, wherein the total amount of acid in the reaction mixture, including the acid $H^+_nX^{n-}$ and the at least one acid used for generating the peracid, is from about 0.6 to about 14.0 molar equivalents of total acid per molar equivalent of the compound of formula I.

108. The process of claim 106, wherein the total amount of acid in the reaction mixture, including the acid $H^+_nX^{n-}$ and the at least one acid used for generating the peracid, is from

about 1 to about 10 molar equivalents, more preferably from about 1 to about 8 molar equivalents, more preferably from about 1 to about 7, more preferably from about 1 to about 6, more preferably from about 1 to about 5.5 molar equivalents, more preferably from about 1 to about 4.5 molar equivalents, even more preferably from about 1 to about 3.5 molar equivalents of total acid per molar equivalent of the compound of formula I.

109. The process of claim 108, wherein the total amount of acid is from about 1 to about 8 molar equivalents of total acid per molar equivalent of the compound of formula I.

110. The process of claim 109, wherein the total amount of acid is from about 1.5 to about 4.5 molar equivalents of total acid per molar equivalent of the compound of formula I.

111. The process of claim 109, wherein the total amount of acid is from about 2.5 to about 5.5, preferably from about 3 to about 5 molar equivalents of total acid per molar equivalent of the compound of formula I.

112. The process of any one of claims 106 to 111, wherein the sulfuric acid added in step (b) is added in an amount of from about 0.1 to about 1.5 molar equivalents, preferably of from about 0.1 to about 1.2 molar equivalents, more preferably of from about 0.1 to about 1 molar equivalents, even more preferably of from about 0.25 to about 0.75 molar equivalents, even more preferably of from about 0.4 to about 0.6 molar equivalents, even more preferably of from about 0.5 to about 0.6 molar equivalents per molar equivalent of the compound of formula I.

113. The process of claim 112, wherein the sulfuric acid is added in an amount of from about 0.5 to about 0.55 molar equivalents per molar equivalent of the compound of formula I.

114. The process of claim 113, wherein the sulfuric acid is added in an amount of about 0.55 molar equivalents per molar equivalent of the compound of formula I.

115. The process of claim 113, wherein the sulfuric acid is added in an amount of about 0.54 molar equivalents per molar equivalent of the compound of formula I.

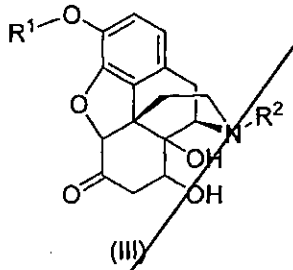
116. The process of claim 113, wherein the sulfuric acid is added in an amount of about 0.51 molar equivalents per molar equivalent of the compound of formula I.

117. The process of any one of claims 106 to 116, wherein the solvent comprises or consists of water.

118. The process of claim 106, which is performed by:
(i) forming a solution or a suspension comprising the compound of formula I, from about 1.5 to about 2.0 ml water per g compound of formula I, and from about 2.5 to about 4.5 molar equivalents of formic acid per molar equivalent of compound of formula I,
(ii) adding from about 0.5 to about 0.6 molar equivalents of sulfuric acid per molar equivalent of the compound of formula I to the solution or the suspension,
(iii) adding from about 1.0 to about 1.4 molar equivalents, preferably from about 1.2 to about 1.4 molar equivalents, more preferably from about 1.2 to about 1.3 molar equivalents of hydrogen peroxide to the solution or the suspension from (ii), then incubating the mixture at a temperature of from about 30 °C to about 38 °C, preferably of from about 32 °C to about 36 °C, more preferably of about 35 °C, until the conversion is complete, and
(iv) precipitating the compound of formula V from the resulting solution or suspension, preferably by adding an antisolvent to the solution.

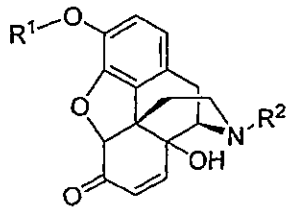
119. The process of claim 118, wherein the antisolvent is an alcohol or an ether, preferably methanol, isopropanol, 2-butanol, *tert*-butyl methyl ether and/or tetrahydrofuran, more preferably isopropanol or 2-butanol.

120. The process of any one of the preceding claims, wherein in the product containing the compound of formula V the amount of a compound having the formula III



(III)

wherein R^1 and R^2 are defined as in the compound of formula V,
or a salt or solvate thereof
in relation to the amount of the component of formula V which has the formula II



(II)

in the product resulting from step (b) and/or step (c) is reduced in comparison to a process performed without $H^+_nX^{n-}$.

121. The process of claim 120, wherein the amount of the compound having the formula III in relation to the amount of the compound having the formula II in the product is reduced by precipitating the compound of formula V or a solvate thereof and isolating it from the reaction mixture.

122. The process of claim 120 or 121, wherein the amount of the compound having the formula III in relation to the amount of the compound having the formula II in the product is reduced because of the presence of $H^+_nX^{n-}$ during the oxidation reaction.

123. The process of claim 120 or 121, wherein the amount of the compound having the formula III in relation to the amount of the compound having the formula II in the product is reduced by using sulfuric acid as the acid $H^+_nX^{n-}$.

124. The process of any one of claims 120 to 123, wherein the total amount of acid in the reaction mixture is from about 0.6 to about 14.0 molar equivalents of total acid per molar equivalent of the compound of formula I, preferably from about 1 to about 10 molar equivalents, more preferably from about 1 to about 8 molar equivalents, more preferably from about 1 to about 7, more preferably from about 1 to about 6, more preferably from about 1 to about 5.5 molar equivalents, more preferably from about 1 to about 4.5 molar equivalents, even more preferably from about 1 to about 3.5 molar equivalents of total acid per molar equivalent of the compound of formula I.

125. The process of claim 124, wherein the total amount of acid is from about 1 to about 8 molar equivalents of total acid per molar equivalent of the compound of formula I.

126. The process of claim 125, wherein the total amount of acid is from about 1.5 to about 4.5 molar equivalents of total acid per molar equivalent of the compound of formula I.

127. The process of claim 125, wherein the total amount of acid is from about 2.5 to about 5.5, preferably from about 3 to about 5 molar equivalents of total acid per molar equivalent of the compound of formula I.

128. The process of any one of claims 120 to 127, wherein the amount of the compound having the formula III in relation to the amount of the compound having the formula II in the product is less than about 2500 ppm, less than about 2250 ppm, less than about 2000 ppm, less than about 1750 ppm, less than about 1500 ppm, or less than about 1250 ppm.

129. The process of claim 128, wherein the amount of the compound having the formula III in relation to the amount of the compound of formula II in the product is less than about 1000 ppm, less than about 750 ppm, less than about 500 ppm, less than about 400 ppm, less than about 300 ppm, less than about 275 ppm, less than about 250 ppm, less than about 225 ppm, less than about 200 ppm, less than about 175 ppm, less than about 150 ppm, or less than about 125 ppm.

130. The process of claim 128, wherein the amount of the compound having the formula III in relation to the amount of the compound of formula II in the product is from about 0.01 ppm to about 2500 ppm, from about 0.05 to about 2250 ppm, from about 0.1 ppm to about 2000 ppm, from about 0.3 to about 1750 ppm, from about 0.5 ppm to about 1500 ppm, or from about 1 ppm to about 1250 ppm.

131. The process of any one of claims 120 to 129, wherein the compound having the formula III is 8-hydroxyoxymorphone and wherein the compound having the formula II is 14-hydroxymorphinone, and wherein the amount of the compound having the formula III in relation to the amount of the compound having the formula II in the product is less than about 300 ppm, less than about 250 ppm, less than about 200 ppm, less than about 150 ppm, less than about 100 ppm, less than about 80 ppm, less than about 60 ppm, less than about 40 ppm, less than about 30 ppm, or less than about 20 ppm.

132. The process of any one of the preceding claims, with the proviso that the compound of

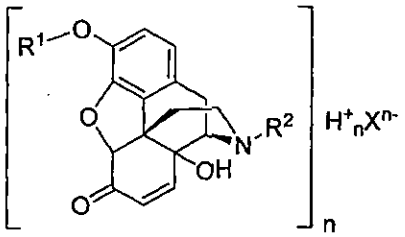
formula V is not

14 -hydroxymorphinone triflate

133. The process of any one of the preceding claims, with the proviso that the compound of formula V is not 14-hydroxymorphinone chloride.

134. The process of any one of the preceding claims, with the proviso that the compound of formula V is not precipitated by adding the reaction mixture after the oxidation reaction to a solvent containing sulfuric acid, methanesulfonic acid, phosphoric acid or HCl, when
R^1 is –H; and
R^2 is selected from -H, $-CH_3$, optionally unsaturated $-(C_2-C_6)$alkyl, and $-(C_1-C_4)$alkyl substituted with a cycloalkyl group.

135. A compound having the formula V or a solvate thereof



(V)

wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 8.

136. The compound having the formula V of claim 135, wherein n is 1 or 2, preferably n is 2.

137. The compound having the formula V of claim 136, wherein X^{n-} is SO_4^{2-} or trifluoroacetate.

138. The compound having the formula V of any one of claims 135 to 138, wherein X^{n-} is SO_4^{2-}.

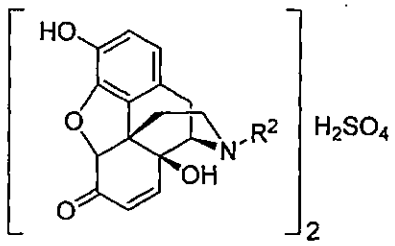
139. The compound having the formula V of any one of claims 135 to 138, wherein R^1 is –H.

140. The compound having the formula V of any one of claims 135 to 139, wherein R^2 is -

CH_3.

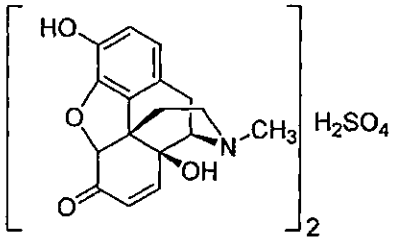
141. The compound having the formula V of any one of claims 135 to 139, wherein R^2 is –H.

142. The compound having the formula V of any one of claims 135 to 141, which is



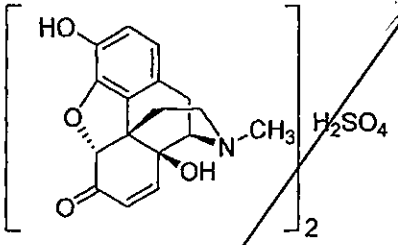
or a solvate thereof.

143. The compound having the formula V of claim 135, which is



or a solvate thereof.

144. The compound having the formula V of claim 135, which is



or a solvate thereof.

145. The compound having the formula V of any one of claims 135 to 144, which is the hydrate of the compound of formula V.

146. The compound having the formula V of claim 145, wherein the hydrate is a hydrate containing from 0.1 to 6.9 water molecules per molecule of the compound of formula V.

147. The compound of claim 145, which is a monohydrate, dihydrate, trihydrate, tetrahydrate, pentahydrate, or hexahydrate.

148. The compound of claim 145, which is a monohydrate or a pentahydrate.

149. The compound having the formula V of any one of claims 135 to 148, with the proviso that the compound is not 14 -hydroxymorphinone triflate.

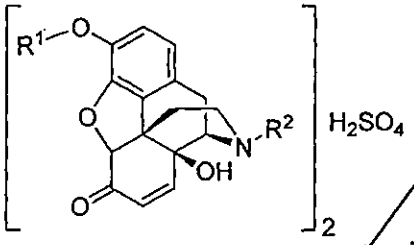
150. The compound having the formula V of any one of claims 135 to 148, with the proviso that the compound is not 14-hydroxymorphinone chloride.

151. The compound having the formula V of any one of claims 135 to 148, with the proviso that when

R^1 is –H; and

R^2 is selected from -H, $-CH_3$, optionally unsaturated $-(C_2-C_6)$alkyl, and $-(C_1-C_4)$alkyl substituted with a cycloalkyl group, then

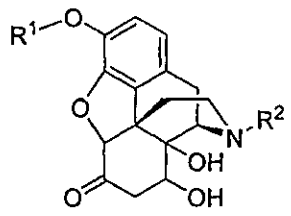
the compound having the formula V is not



152. The compound having the formula V of any one of claims 135 to 151, which is obtainable by the process according to any one of claims 1 to 103.

153. A composition comprising the compound of formula V according to any one of claims 135 to 152.

154. The composition of claim 153, which additionally comprises a compound of formula III



(III)

wherein R^1 and R^2 are defined as in the compound of formula V,
or a salt or solvate thereof.

155. The composition of claim 154, wherein the amount of the compound of formula III in the composition is less than about 2500 ppm, less than about 2250 ppm, less than about 2000 ppm, less than about 1750 ppm, less than about 1500 ppm, or less than about 1250 ppm of the compound of formula V (HPLC peak area ratio).

156. The composition of claim 154, wherein the amount of the compound of formula III in the composition is less than about 1000 ppm, less than about 750 ppm, less than about 500 ppm, less than about 400 ppm, less than about 300, less than about 250 ppm, less than about 200 ppm, or less than about 150 ppm of the compound of formula V (HPLC peak area ratio).

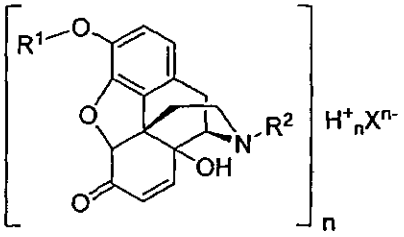
157. The composition of claim 154, wherein the amount of the compound of formula III in the composition is less than about 100 ppm, less than about 90 ppm, less than about 80 ppm, less than about 70 ppm, less than about 60 ppm, less than about 50 ppm, less than about 40 ppm, less than about 30 ppm, or less than about 20 ppm of the compound of formula V (HPLC peak area ratio).

158. The composition of claim 154, wherein the amount of the compound of formula III in the composition is less than about 10 ppm, less than about 8 ppm, less than about 6 ppm, less than about 4 ppm, or less than about 2 ppm of the compound of formula V (HPLC peak area ratio).

159. The composition of claim 154, wherein the amount of the compound of formula III in the composition is less than about 1 ppm, less than about 0.8 ppm, less than about 0.6 ppm, less than about 0.4 ppm, less than about 0.3 ppm, less than about 0.2 ppm, or less than about 0.1 ppm of the compound of formula V (HPLC peak area ratio).

160. Use of the compound of formula V according to any one of claims 135 to 159 or a solvate thereof as an intermediate or starting material for preparing an opioid or a pharmaceutically acceptable salt or solvate thereof, and/or a medicament containing an opioid or a pharmaceutically acceptable salt or solvate.

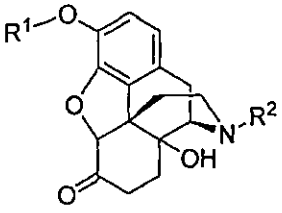
161. Use of a compound of formula V or a solvate thereof



(V)

wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 8,

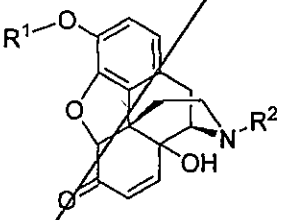
for the reduction of at least one by-product in the synthesis of a compound of formula IV or a salt or solvate thereof



(IV)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4.

162. The use of claim 161, wherein the at least one by-product is a compound of formula II



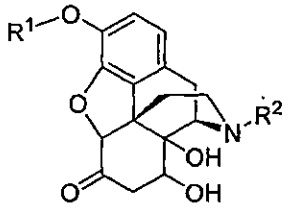
(II)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,

or a salt or solvate thereof.

163. The use of claim 162, wherein the amount of the compound of formula II in relation to the amount of the compound having the formula IV in the synthesis product is less than about 500 ppm, less than about 250 ppm, less than about 200 ppm, less than about 100 ppm, less than about 50 ppm, less than about 40 ppm, less than about 30 ppm, less than about 25 ppm, less than about 20 ppm, les than about 15 ppm, less than about 10 ppm, less than about 5 ppm, less than about 2.5 ppm, or less than about 1 ppm (HPLC peak area ratio).

164. The use of any one of claims 161 to 163, wherein the at least one by-product is a compound of formula III



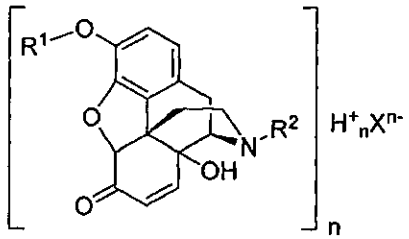
(III)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,
or a salt or solvate thereof.

165. The use of claim 164, wherein the amount of the compound of formula III in relation to the amount of the compound having the formula IV in the synthesis product is less than about 1000 ppm, less than about 500 ppm, less than about 300 ppm, less than about 250 ppm, less than about 200 ppm, less than about 150 ppm, less than about 100 ppm, less than about 50 ppm, less than about 20 ppm, or less than about 10 ppm of the compound of formula IV (HPLC peak area ratio).

166. Use of the composition comprising the compound of formula V or a salt or solvate thereof according to any one of claims 153 to 159 as an intermediate or starting material for preparing an opioid or a pharmaceutically acceptable salt or solvate thereof, and/or a medicament containing an opioid or a pharmaceutically acceptable salt or solvate.

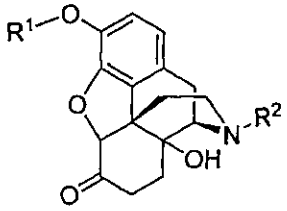
167. Use of the composition comprising the compound of formula V or a salt or solvate thereof according to any one of claims 153 to 159



(V)

wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 8,

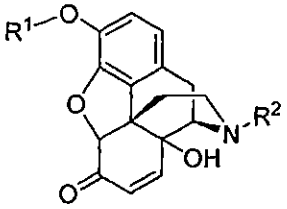
for the reduction of at least one by-product in the synthesis of a compound of formula IV or a salt or solvate thereof



(IV)

wherein R^1 and R^2 are defined as in any one of claims 1 to 6.

168. The use of claim 167, wherein the at least one by-product is a compound of formula II



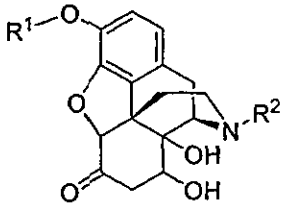
(II)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,
or a salt or solvate thereof.

169. The use of claim 168, wherein the amount of the compound of formula II in relation to the amount of the compound having the formula IV in the synthesis product is less than about 500 ppm, less than about 250 ppm, less than about 200 ppm, less than about 100 ppm, less than about 50 ppm, less than about 40 ppm, less than about 30 ppm, less than about 25 ppm,

less than about 20 ppm, les than about 15 ppm, less than about 10 ppm, less than about 5 ppm, less than about 2.5 ppm, or less than about 1 ppm (HPLC peak area ratio).

170. The use of any one of claims 167 to 169, wherein the at least one by-product is a compound of formula III

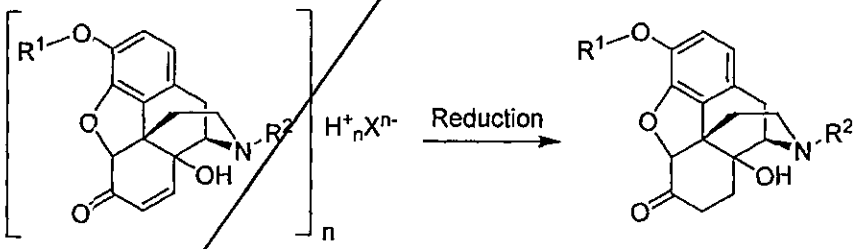


(III)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,
or a salt or solvate thereof.

171. The use of claim 170, wherein the amount of the compound of formula III in relation to the amount of the compound having the formula IV in the synthesis product is less than about 1000 ppm, less than about 500 ppm, less than about 300 ppm, less than about 250 ppm, less than about 200 ppm, less than about 150 ppm, less than about 100 ppm, less than about 50 ppm, less than about 20 ppm, or less than about 10 ppm of the compound of formula IV (HPLC peak area ratio).

172. A process for preparing a compound of formula IV or a salt or solvate thereof from a compound having formula V or a solvate thereof



(V) (IV)

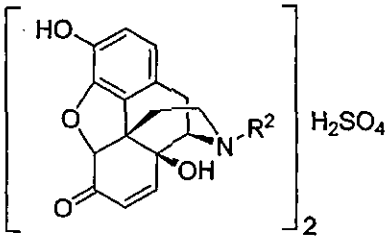
the process comprising the steps of
(e) providing a solution or suspension of the compound having formula V or a solvate thereof as defined in any one of claims 135 to 152; and
(f) reducing the compound of formula V to the compound of formula IV,

wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 8.

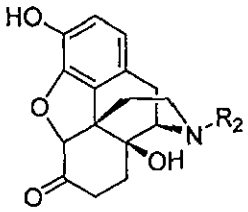
173. The process of claim 172, wherein the reduction reaction in step (f) is performed by hydrogenation.

174. The process of claim 173, wherein the hydrogenation is transfer hydrogenation or hydrogenation with H_2.

175. The process of any one of claims 172 to 174, wherein the compound of formula V is



or a solvate thereof,
and the compound of formula IV is

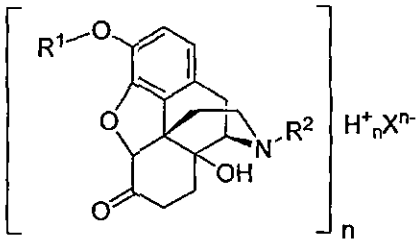


or a salt or solvate thereof.

176. The process of any one of claims 172 to 175, wherein the compound of formula V is 14-hydroxymorphinone sulfate or a solvate thereof, and the compound of formula IV is oxymorphone or a salt or solvate thereof.

177. The process of any one of claims 172 to 176, wherein the salt or solvate of the compound of formula IV is a pharmaceutically acceptable salt or solvate.

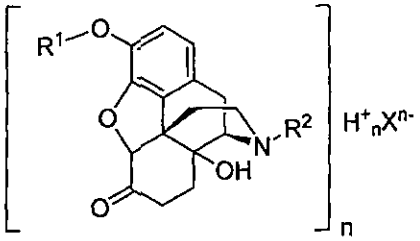
178. The process of any one of claims 172 to 176, wherein the compound of formula IV is prepared in the form of its salt



wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 8, or a solvate thereof.

179. The process of claim 178, additionally comprising the step

(g) isolating the salt



or the solvate thereof.

180. The process of claim 179, wherein the salt is isolated by precipitation.

181. The process of claim 180, wherein the precipitation is performed by adding an antisolvent during and/or after the reduction reaction.

182. The process of any one of claims 178 to 181, wherein X^{n-} is SO_4^{2-}.

183. The process of any one of claims 178 to 181, wherein X^{n-} is trifluoroacetate.

184. The process of any one of claims 178 to 182, wherein the salt of the compound of formula IV is oxymorphone sulfate or a solvate thereof.

185. The process of any one of claims 178 to 182, wherein the salt of the compound of formula IV is oxymorphone trifluoroacetate or a solvate thereof.

186. The process of any one of claims 172 to 185, additionally comprising the step of

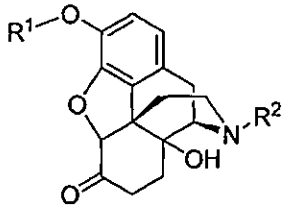
preparing the salt or solvate of formula V according to the process of any one of claims 1 to 134.

187. The process of claim 186, wherein
the compound of formula (I) is oripavine or a salt or solvate thereof,
the oxidation agent comprises or is performic acid formed in situ from hydrogen peroxide and formic acid,
the acid $H^+_nX^{n-}$ in step (b) is sulfuric acid which is added to the reaction mixture,
the compound having formula V is 14-hydroxymorphinone sulfate or a solvate thereof, and
the compound of formula IV is oxymorphone or a salt or solvate thereof.

188. The process of any one of claims 178 to 187, wherein the compound having formula V or a solvate thereof is precipitated and isolated before the reduction step.

189. The process of any one of claims 178 to 188, wherein the component of the compound having formula V which is a compound of formula II is liberated from the compound of formula V as free base before the reduction step.

190. A compound of formula IV



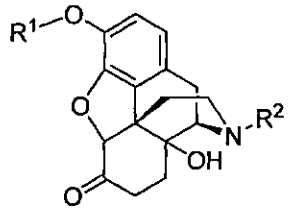
(IV)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,
or a pharmaceutically acceptable salt or solvate thereof,
obtainable by the process according to any one of claims 172 to 189.

191. Oxymorphone trifluoroacetate or a pharmaceutically acceptable solvate thereof.

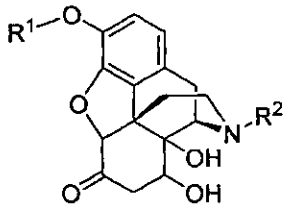
192. Oxymorphone sulfate or a pharmaceutically acceptable solvate thereof.

193. A composition comprising a compound of formula IV



(IV)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,
or a pharmaceutically acceptable salt or solvate thereof,
which additionally comprises an amount of a compound of formula III



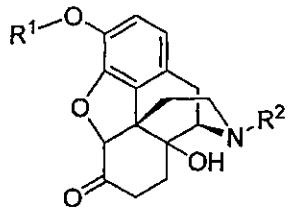
(III)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,
or a salt or solvate thereof,
wherein the amount of the compound having the formula III in relation to the amount of the compound having the formula IV is less than about 2500 ppm, less than about 2000 ppm, less than about 1500 ppm, less than about 1000 ppm, or less than about 500 ppm (HPLC peak area ratio).

194. The composition of claim 193, wherein the amount of the compound having the formula III in relation to the amount of the compound having the formula IV is less than about 300 ppm, less than about 250 ppm, less than about 200 ppm, less than about 150 ppm, less than about 100 ppm, less than about 50 ppm, or less than about 20 ppm (HPLC peak area ratio).

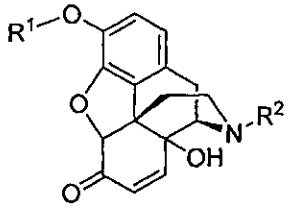
195. The composition of claim 193, wherein the amount of the compound having the formula III in relation to the amount of the compound having the formula IV is less than about 10 ppm, less than about 6 ppm, less than about 2 ppm, less than about 1 ppm, less than about 0.8 ppm, less than about 0.6 ppm, less than about 0.4 ppm, less than about 0.3 ppm, less than about 0.2 ppm, or less than about 0.1 ppm (HPLC peak area ratio).

196. A composition comprising a compound of formula IV



(IV)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,
or a pharmaceutically acceptable salt or solvate thereof,
which additionally comprises an amount of a compound of formula II

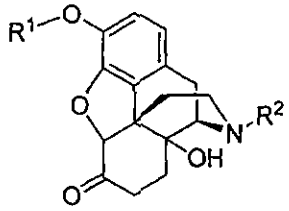


(II)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,
or a pharmaceutically acceptable salt or solvate thereof,
wherein the amount of the compound of formula II in relation to the amount of the compound having the formula IV is less than about 500 ppm, less than about 250 ppm, less than about 200 ppm, less than about 100 ppm, less than about 50 ppm, less than about 40 ppm, or less than about 30 ppm (HPLC peak area ratio).

197. The composition of claim 196, wherein the amount of the compound of formula II in relation to the amount of the compound having the formula IV is less than about 25 ppm, less than about 20 ppm, less than about 15 ppm, less than about 10 ppm, less than about 5 ppm, less than about 2.5 ppm, or less than about 1 ppm (HPLC peak area ratio).

198. A composition comprising a compound of formula IV

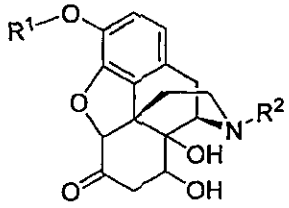


(IV)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,

or a pharmaceutically acceptable salt or solvate thereof,

which additionally comprises an amount of a compound of formula III

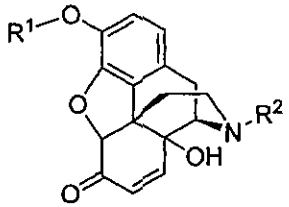


(III)

wherein R^1 and R^2 are defined as in any one of claims 1 to 4,

or a salt or solvate thereof, and

which additionally comprises an amount of a compound of formula II



(II)

wherein R^1 and R^2, are defined as in any one of claims 1 to 4,

or a pharmaceutically acceptable salt or solvate thereof, wherein the combined amount of the compound of formula II and III in the composition is less than about 3000 ppm, less than about 2500 ppm, less than about 2000 ppm, less than about 1500 ppm, less than about 1000 ppm, less than about 500 ppm, less than about 400 ppm, or less than about 300 ppm in relation to the amount of the compound of formula IV (HPLC peak area ratio).

199. The composition of claim 198, wherein the combined amount of the compound of formula II and III in the composition is less than about 250 ppm, less than about 200 ppm,

less than about 150 ppm, less than about 100 ppm, less than about 50 ppm, or less than about 20 ppm in relation to the amount of the compound of formula IV (HPLC peak area ratio).

200. The composition of claim 198,
wherein the amount of the compound of formula III in relation to the amount of the compound of formula IV is less than about 1000 ppm, less than about 500 ppm, less than about 300 ppm, less than about 250 ppm, less than about 200 ppm, less than about 150 ppm, less than about 100 ppm, less than about 50 ppm, less than about 20 ppm, or less than about 10 ppm of the compound of formula IV (HPLC peak area ratio), and
wherein the amount of the compound of formula II in relation to the amount of the compound of formula IV is less than about 200 ppm, less than about 100 ppm, less than about 50 ppm, less than about 25 ppm, less than about 20 ppm, less than about 15 ppm, less than about 10 ppm, less than about 5 ppm, less than about 2.5 ppm, or less than about 1 ppm of the compound of formula IV (HPLC peak area ratio).

201. The composition of claim 198,
wherein the amount of the compound of formula III in relation to the amount of the compound of formula IV is less than about 10 ppm, less than about 5 ppm, less than about 4 ppm, less than about 3 ppm, less than about 2 ppm, less than about 1 ppm, or less than about 0.5 ppm, and
wherein the amount of the compound of formula II in relation to the amount of the compound of formula IV is less than about 10 ppm, less than about 5 ppm, less than about 3 ppm, less than about 2 ppm, less than about 1 ppm, or less than about 0.5 ppm.

202. The composition of any one of claims 193 to 201, wherein the compound of formula IV is oxymorphone or a pharmaceutically acceptable salt or solvate thereof.

203. The composition of any one of claims 193 to 201, wherein the compound of formula IV is oxymorphone sulfate or a solvate thereof.

204. The composition of any one of claims 193 to 201, wherein the compound of formula IV is oxymorphone trifluoroacetate or a solvate thereof.

205. Use of the compound of formula IV or a pharmaceutically acceptable salt or solvate

thereof of any one of claims 190 to 192 as an intermediate or starting material for preparing an opioid or a pharmaceutically acceptable salt or solvate thereof, and/or for preparing a medicament containing the compound of formula IV or the pharmaceutically acceptable salt or solvate thereof, or containing another opioid or a pharmaceutically acceptable salt or solvate thereof.

206. Use of the compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 190 to 192 for preparing a medicament containing the compound of formula IV or the pharmaceutically acceptable salt or solvate thereof, optionally in combination with at least one other opioid or pharmaceutically acceptable salt or solvate thereof.

207. The use of claim 206, wherein the medicament contains oxymorphone hydrochloride as the compound of formula IV according to claim 190.

208. The use of claim 207, wherein the medicament additionally contains naloxone hydrochloride.

209. The compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 190 to 192 for use as a medicament.

210. The compound of formula IV or a pharmaceutically acceptable salt or solvate thereof for use of claim 209, wherein the compound of formula IV or the pharmaceutically acceptable salt or solvate thereof is combined with at least one other opioid or pharmaceutically acceptable salt or solvate thereof in the medicament.

211. The compound of formula IV or a pharmaceutically acceptable salt or solvate thereof for use of claim 209, wherein the medicament contains oxymorphone hydrochloride as the compound of formula IV according to claim 190.

212. The compound of formula IV or a pharmaceutically acceptable salt or solvate thereof for use of claim 211, wherein the medicament additionally contains naloxone hydrochloride.

213. The compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 190 to 192 for use in the treatment or prevention of pain, addiction, cough,

constipation, diarrhea, insomnia associated with and/or caused by pain, cough or addiction, depression associated with and/or resulting from pain, cough or addiction, or a combination of two or more of the foregoing.

214. The compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 190 to 192 for use in the treatment of pain.

215. A method for treating or preventing a medical condition selected from the group consisting of pain, addiction, cough, constipation, diarrhea, insomnia associated with and/or caused by pain, cough or addiction, depression associated with and/or resulting from pain, cough or addiction, and combinations of two or more of the foregoing, in an animal using the compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 190 to 192.

216. A method for treating or preventing pain in an animal using the compound of formula IV or a pharmaceutically acceptable salt or solvate thereof according to any one of claims 190 to 192.

217. A method for treating or preventing a medical condition selected from the group consisting of pain, addiction, cough, constipation, diarrhea, insomnia associated with and/or caused by pain, cough or addiction, depression associated with and/or resulting from pain, cough or addiction, and combinations of two or more of the foregoing in an animal, comprising administering to an animal in need thereof an effective amount of the compound of formula IV or a pharmaceutically acceptable salt or solvate thereof according to any one of claims 190 to 192.

218. A method for treating or preventing pain in an animal, comprising administering to an animal in need thereof an effective amount of the compound of formula IV or a pharmaceutically acceptable salt or solvate thereof according to any one of claims 190 to 192.

219. The method of any one of claims 215 to 218, wherein the animal is a mammal.

220. The method of any one of claims 215 to 218, wherein the animal is a human.

221. Use of a composition comprising the compound of formula IV or a pharmaceutically

acceptable salt or solvate thereof of any one of claims 193 to 204 as an intermediate or starting material for preparing an opioid or a pharmaceutically acceptable salt or solvate thereof, and/or for preparing a medicament containing the compound of formula IV or the pharmaceutically acceptable salt or solvate thereof, or containing another opioid or a pharmaceutically acceptable salt or solvate thereof.

222. Use of the composition comprising the compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 193 to 204 for preparing a medicament containing the compound of formula IV or the pharmaceutically acceptable salt or solvate thereof, optionally in combination with at least one other opioid or pharmaceutically acceptable salt or solvate thereof.

223. The use of claim 222, wherein the medicament contains oxymorphone hydrochloride as the compound of formula IV comprised in the composition according to any one of claims 193 to 204.

224. The use of claim 222, wherein the medicament additionally contains naloxone hydrochloride.

225. The composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 193 to 204 for use as a medicament.

226. The composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof for use of claim 225, wherein the compound of formula IV or the pharmaceutically acceptable salt or solvate thereof is combined with at least one other opioid or pharmaceutically acceptable salt or solvate thereof in the medicament.

227. The composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof for use of claim 225, wherein the medicament contains oxymorphone hydrochloride as the compound of formula IV comprised in the composition according to any one of claims 193 to 204.

228. The composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof for use of claim 225, wherein the medicament additionally

contains naloxone hydrochloride.

229. The composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 193 to 204 for use in the treatment or prevention of pain, addiction, cough, constipation, diarrhea, insomnia associated with and/or caused by pain, cough or addiction, depression associated with and/or resulting from pain, cough or addiction, or a combination of two or more of the foregoing.

230. The composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof of any one of claims 193 to 204 for use in the treatment of pain.

231. A method for treating or preventing a medical condition selected from the group consisting of pain, addiction, cough, constipation, diarrhea, insomnia associated with and/or caused by pain, cough or addiction, depression associated with and/or resulting from pain, cough or addiction, and combinations of two or more of the foregoing, in an animal using the composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof according to any one claims 193 to 204.

232. A method for treating or preventing pain in an animal using the composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof according to any one claims 193 to 204.

233. A method for treating or preventing a medical condition selected from the group consisting of pain, addiction, cough, constipation, diarrhea, insomnia associated with and/or caused by pain, cough or addiction, depression associated with and/or resulting from pain, cough or addiction, and combinations of two or more of the foregoing in an animal, comprising administering to an animal in need thereof an effective amount of the composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof according to any one of claims 193 to 204.

234. A method for treating or preventing pain in an animal, comprising administering to an animal in need thereof an effective amount of the composition comprising a compound of formula IV or a pharmaceutically acceptable salt or solvate thereof according to any one of

claims 193 to 204.

235. The method of any one of claims 231 to 234, wherein the animal is a mammal.

236. The method of any one of claims 231 to 234, wherein the animal is a human.

237. The process, compound, composition or use of any one of the preceding claims, wherein the solvate is a hydrate.

238. The process, compound, composition or use of claim 237, wherein the hydrate is a hydrate containing from 0.5 to 10.0 water molecules per molecule of the compound.

239. The process, compound, composition or use of claim 237, wherein the hydrate is a hydrate containing from 0.1 to 6.9 water molecules per molecule of the compound.

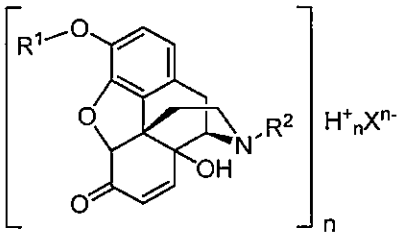
240. The process, compound, composition or use of claim 237, wherein the solvate is a monohydrate, dihydrate, trihydrate, tetrahydrate, pentahydrate, or hexahydrate.

241. The process, compound, composition or use of claim 237, wherein the solvate is a monohydrate.

242. The process, compound, composition or use of claim 237, wherein the solvate is a pentahydrate.

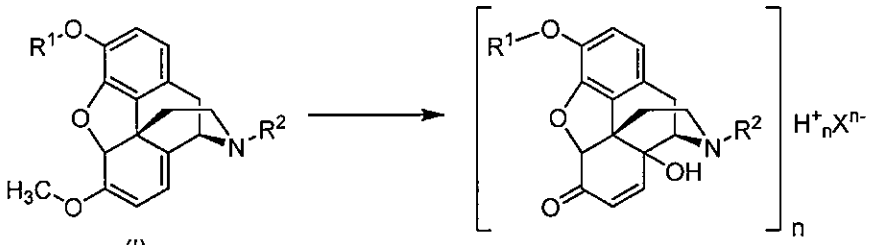
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A process for preparing a compound of formula V or a solvate thereof



(V)

from a compound of formula I or a salt or solvate thereof, the process comprising:



(I) (V)

(a) oxidizing the compound of formula I;

(b) adding an acid $H^+_nX^{n-}$ to the reaction mixture before and/or during the oxidation reaction;

(c) precipitating the compound of formula V; and

(d) isolating the precipitate from the reaction mixture,

wherein,

R^1 is -H, -(C_1-C_7)alkyl, aralkyl, -(C_2-C_6)alkenyl, -SiR^3_3, -(C_3-C_7)cycloalkyl, -(C_1-C_7)alkyl-(C_3-C_7)cycloalkyl, -(C_3-C_7)cycloalkenyl, -(C_1-C_7)alkyl-(C_3-C_7)cycloalkenyl, -CR^4_2-O-(C_1-C_6)alkyl, -C(halo)$_3$, -CH_2(halo), -CH(halo)$_2$,-SO_2R^5, or an O-protecting group;

R^2 is -H, -CH_3, -(C_2-C_7)alkyl, -(C_2-C_4)alkenyl, benzyl, -(C_1-C_7)alkyl-(C_3-C_7)cycloalkyl, -CN, or an N-protecting group;

each R^3 is independently selected from aryl, –(C_1-C_6)alkyl and –(C_1-C_6)alkoxy;

each R^4 is independently selected from –H and –(C_1-C_6)alkyl;

R^5 is -(C_6-C_{14})aryl or –(C_1-C_6)alkyl;

X^{n-} is SO_4^{2-};

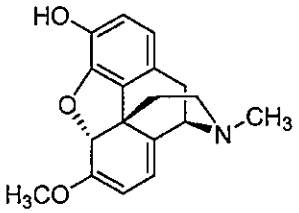
n is 2; and

the acid $H^+_nX^{n-}$ is H_2SO_4.

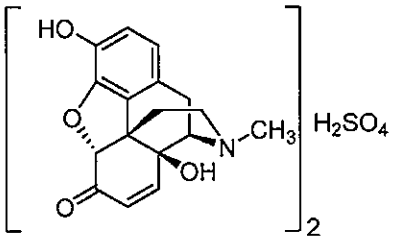
2. The process of claim 1, wherein R^2 is $–CH_3$ or –H.

3. The process of any one of the preceding claims, wherein R^1 is –H.

4. The process of any one of the preceding claims, wherein the compound of formula I is



and the compound of formula V is



or a solvate thereof.

5. The process of any one of the preceding claims, wherein the H_2SO_4 is added to the reaction mixture in an amount of from 0.4 to 0.6 molar equivalents per molar equivalent of the compound of formula I in step (b).

6. The process of claim 5, wherein the H_2SO_4 is added to the reaction mixture in an

amount of from 0.45 to 0.55 molar equivalents per molar equivalent of the compound of formula I in step (b).

7. The process of claim 6, wherein the H_2SO_4 is added to the reaction mixture in an amount of from 0.51 to 0.55 molar equivalents per molar equivalent of the compound of formula I in step (b).

8. The process of any one of the preceding claims, wherein the reaction mixture is maintained at a temperature of from about 30 °C to about 38 °C during the oxidation reaction.

9. The process of any one of the preceding claims, wherein the precipitation is caused by the presence of the acid $H^+_nX^{n-}$ in the reaction mixture.

10. The process of claim 9, wherein the precipitation is initiated and/or enhanced by adding an antisolvent.

11. The process of claim 10, wherein the antisolvent is selected from the group consisting of: *tert*-butyl methyl ether, diethyl ether, hexane(s), *tert*-amyl alcohol, methanol, ethanol, isopropanol, 2-butanol, heptanes, xylenes, toluene, acetone, 2-butanone, ethyl acetate, tetrahydrofuran, 1,2-dichloroethane, chloroform, dichloromethane, 1-methoxy-2-propanol, 2-ethoxyethanol, n-propanol, 1-butanol, *tert*-butanol, isobutanol, isopropyl acetate, 1,4-dioxane, 2-methyl-tetrahydrofuran, methyl formate, methyl acetate, and any mixtures of two or more of any of the foregoing.

12. The process of any one of the preceding claims, wherein the oxidation in step (a) is performed in the presence of an oxidizing agent, wherein the oxidizing agent comprises or is at least one peracid.

13. The process of claim 12, wherein the at least one peracid is generated in situ in the reaction mixture of step (a) from hydrogen peroxide and at least one acid.

14. The process of any one of claims 12 to 13, wherein the at least one peracid is selected from the group consisting of: performic acid, peracetic acid, 3-chloroperoxybenzoic acid, potassium peroxymonosulfate, trifluoro peracetic acid, persulfuric acid, and any combinations of the foregoing.

15. The process of claim 14, wherein the at least one peracid is selected from the group consisting of performic acid, persulfuric acid, and a combination thereof.

16. The process of claim 15, wherein the at least one peracid is performic acid, which is generated in situ in step (a) from hydrogen peroxide and formic acid, or wherein the at least one peracid is a combination of performic acid and persulfuric acid, which is generated in situ in step (a) from hydrogen peroxide, sulfuric acid and formic acid.

17. The process of any one of claims 12 to 16, wherein the total amount of acid in the reaction mixture, including the acid $H^+_nX^{n-}$ and the at least one acid used for generating the peracid, is from about 0.6 to about 14.0 molar equivalents of total acid per molar equivalent of the compound of formula I.

18. The process of claim 17, wherein the total amount of acid is from about 1.5 to about 4.5 molar equivalents of total acid per molar equivalent of the compound of formula I.

19. The process of claim 17, wherein the total amount of acid is from about 2.5 to about 5.5 molar equivalents of total acid per molar equivalent of the compound of formula I.

20. The process of any one of claims 12 to 19, wherein the molar amount of the acid used for generating the peracid is from about 2.5 to about 4.5 molar equivalents per molar equivalent of the compound of formula I, and wherein the acid used for generating the peracid is formic acid.

21. The process of any one of the preceding claims, wherein the precipitation temperature is in a range of from about 5 °C to about 22 °C, and the total amount of acid present in the reaction mixture is from about 1 to about 7 molar equivalents of total acid per molar equivalent of the compound of formula I.

22. The process of any one of the preceding claims, wherein the compound of formula V is 14-hydroxymorphinone sulfate or a hydrate thereof.

23. The process of claim 22, wherein the compound of formula V is 14-hydroxymorphinone sulfate hydrate.

24. The process of claim 23, wherein the hydrate is a monohydrate, dihydrate, trihydrate, tetrahydrate, pentahydrate, or hexahydrate.

25. The process of any one of the preceding claims, wherein:

the compound of formula (I) is oripavine or a salt or solvate thereof;

the oxidation agent comprises or is performic acid formed from hydrogen peroxide and formic acid;

the acid $H^+_nX^{n-}$ in step (b) is sulfuric acid which is added to the reaction mixture; and

the compound of formula V is 14-hydroxymorphinone sulfate or a solvate thereof.

26. The process of claim 25, which is performed by:

(i) forming a solution or a suspension comprising the compound of formula I, from about 1.5 to about 2.0 ml water per g compound of formula I, and from about 2.5 to about 4.5 molar equivalents of formic acid per molar equivalent of compound of formula I;

(ii) adding from about 0.5 to about 0.6 molar equivalents of sulfuric acid per molar equivalent of the compound of formula I to the solution or the suspension;

(iii) adding from about 1.0 to about 1.4 molar equivalents of hydrogen peroxide to the solution or the suspension from (ii), then incubating the mixture at a temperature of from about 30 °C to about 38 °C until the conversion is complete; and

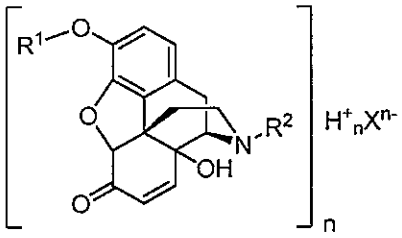
(iv) precipitating the compound of formula V from the resulting solution or suspension.

27. The process of claim 26, wherein step (iv) is performed by adding an antisolvent to the solution.

28. The process of claim 27, wherein the antisolvent is: methanol, isopropanol, 2-butanol, *tert*-butyl methyl ether and/or tetrahydrofuran.

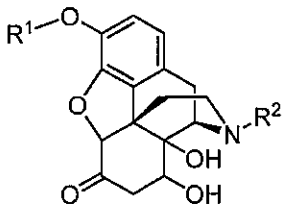
29. The process of any one of claims 26 to 28, wherein in step (iii) from about 1.2 to about 1.3 molar equivalents of hydrogen peroxide are added to the solution or the suspension from (ii) and the mixture is then incubated at a temperature of from about 32 °C to about 36 °C until the conversion is complete.

30. A composition comprising a compound of formula V or a solvate thereof



(V)

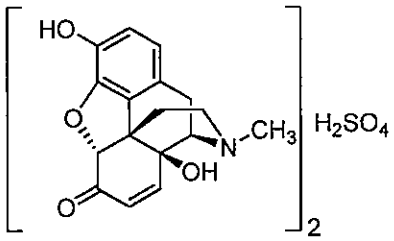
wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 3, which additionally comprises a compound of formula III



(III)

wherein R^1 and R^2 are defined as in the compound of formula V,
or a salt or solvate thereof.

31. The composition of claim 30, wherein the compound of formula V is

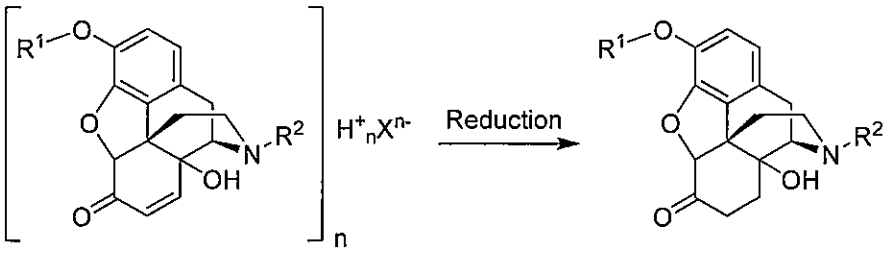


or a solvate thereof.

32. The composition of claim 30 or 31, wherein the amount of the compound of formula III in the composition is less than about 2500 ppm, less than about 2250 ppm, less than about 2000 ppm, less than about 1750 ppm, less than about 1500 ppm, or less than about 1250 ppm of the compound of formula V (HPLC peak area ratio).

33. The composition of any one of claims 30 to 32, which is obtained by the process according to any one of claims 1 to 24.

34. A process for preparing a compound of formula IV or a salt or solvate thereof from a compound having formula V or a solvate thereof



(V) (IV)

the process comprising the steps of

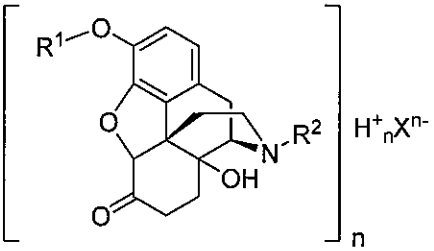
(a) to (d) preparing and isolating the compound having formula V or a solvate thereof according to the process of any one of claims 1 to 29;

(e) providing a solution or suspension of the compound having formula V or a solvate thereof isolated in step (d); and

(f) reducing the compound of formula V to the compound of formula IV,

wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 3.

35. The process of claims 34, wherein the compound of formula IV is prepared in the form of its salt



wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 3,

or a solvate thereof.

36. The process of any one of claims 34 to 35, wherein:

the compound of formula (I) is oripavine or a salt or solvate thereof;

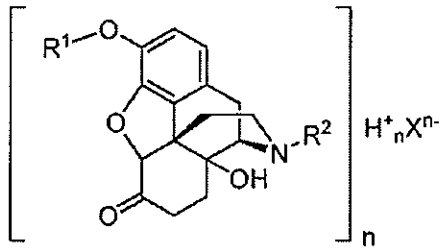
the oxidation agent comprises or is performic acid formed in situ from hydrogen peroxide and formic acid;

the acid $H^+_nX^{n-}$ in step (b) is sulfuric acid which is added to the reaction mixture;

the compound having formula V is 14-hydroxymorphinone sulfate or a solvate thereof; and

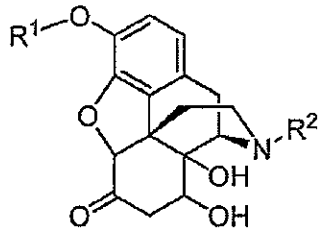
the compound of formula IV is oxymorphone or a salt or solvate thereof.

37. A composition comprising a compound of formula IV in the form of its salt



wherein R^1, R^2, X^{n-} and n are defined as in any one of claims 1 to 3,

which additionally comprises an amount of a compound of formula III

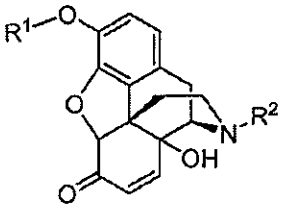


(III)

wherein R^1 and R^2 are defined as in any one of claims 1 to 3,

or a salt or solvate thereof, and

which additionally comprises an amount of a compound of formula II



(II)

wherein R^1 and R^2 are defined as in any one of claims 1 to 3,

or a pharmaceutically acceptable salt or solvate thereof, wherein the combined amount of the compound of formula II and III in the composition is less than about 3000 ppm, less than about

2500 ppm, less than about 2000 ppm, less than about 1500 ppm, less than about 1000 ppm, less than about 500 ppm, less than about 400 ppm, or less than about 300 ppm in relation to the amount of the compound of formula IV (HPLC peak area ratio).

38. The composition of claim 37,

wherein the amount of the compound of formula III in relation to the amount of the compound of formula IV is less than about 1000 ppm, less than about 500 ppm, less than about 300 ppm, less than about 250 ppm, less than about 200 ppm, less than about 150 ppm, less than about 100 ppm, less than about 50 ppm, less than about 20 ppm, or less than about 10 ppm of the compound of formula IV (HPLC peak area ratio), and

wherein the amount of the compound of formula II in relation to the amount of the compound of formula IV is less than about 200 ppm, less than about 100 ppm, less than about 50 ppm, less than about 25 ppm, less than about 20 ppm, less than about 15 ppm, less than about 10 ppm, less than about 5 ppm, less than about 2.5 ppm, or less than about 1 ppm of the compound of formula IV (HPLC peak area ratio).

39. The composition of any one of claims 37 to 38, wherein the compound of formula IV is oxymorphone sulfate or a solvate thereof.

40. The composition of any one of claims 37 to 39, which is obtained by the process according to any one of claims 34 to 36.