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(71) Applicant (for all designated States except BB, US):
TEVA GYÓGYSZERGYÁR ZÁRTKÖRÜEN MUKÖDO [HU/HU]; Részvénytársaság, Pallagi ut 13, H-4042 Debrecen (HU).

(71) Applicant (for BB only): **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **HAJKO, Janos** [HU/HU]; Zold Sandor utca 20 4/17, H-4028 Debrecen

(HU). **TAMAS, Tivadar** [HU/HU]; Budai Nagy Antal u. 37, H-4034 Debrecen (HU). **KOVACSNE-MEZEL, Adrienne** [HU/HU]; 252 Karoli Gaspar Street, H-4032 Debrecen (HU). **MOLNARNE, Erika, Magyar** [HU/HU]; Boszormenyi ut 91 IV/13, H-4032 Debrecen (HU). **PETO, Csaba** [HU/HU]; Bercsenyi u. 31, H-Debrecen (HU). **SZABO, Csaba** [HU/HU]; Tozser u. 1, H-4031 Debrecen (HU).

(74) Agent: **BIRDE, Patrick, J.**; KENYON & KENYON LLP, One Broadway, New York, NY 10004-1050 (US).

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(54) Title: PRODUCTION OF DOLASETRON

(57) Abstract: The present invention provides an improved process for the preparation of Dolasetron salts, in particularly Dolasetron mesylate. Also provided are intermediates for the process and methods of preparing the intermediates. Intermediates for preparing Dolasetron according to the invention include 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-trialkylsilyloxy-9-azabicyclo[3.3.1]nonane compounds (SAN compounds) and *endo*-9-alkoxycarbonyl-5-trialkylsilyloxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one compounds (SQO compounds).

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PRODUCTION OF DOLASETRON

CROSS REFERENCE TO RELATED APPLICATIONS

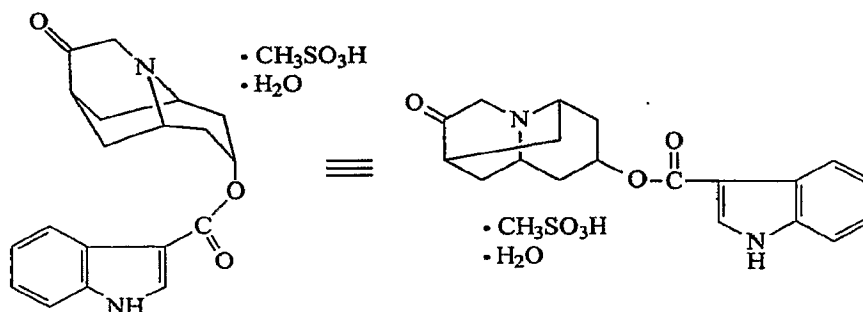
The present application claims the benefit of the following United States Provisional Patent Application Nos.: 60/756,690, filed January 5, 2006; 60/800,884, filed May 15, 2006; 60/838,758, filed August 17, 2006; 60/861,354, filed November 27, 2006; 60/802,842, filed May 22, 2006; 60/818,934, filed July 5, 2006; 60/833,515, filed July 24, 2006; 60/836,432, filed August 7, 2006; 60/763,683, filed January 30, 2006; 60/784,248, filed March 20, 2006; 60/815,199, filed June 19, 2006; 60/852,887, filed October 18, 2006. The contents of these applications are incorporated herein by reference.

FIELD OF THE INVENTION

The present invention relates to an improved process for the preparation of Dolasetron salts, in particularly Dolasetron mesylate, and intermediates thereof.

BACKGROUND OF THE INVENTION

Dolasetron mesylate monohydrate, (2 α ,6 α ,8 α ,9 α) β -octahydro-3-oxo-2,6-methano-2H-quinolizin-8-yl-1H-indole-3-carboxylate monomethanesulfonate monohydrate, (referred to as DLS-MsOH-H₂O) a compound having the chemical structure,

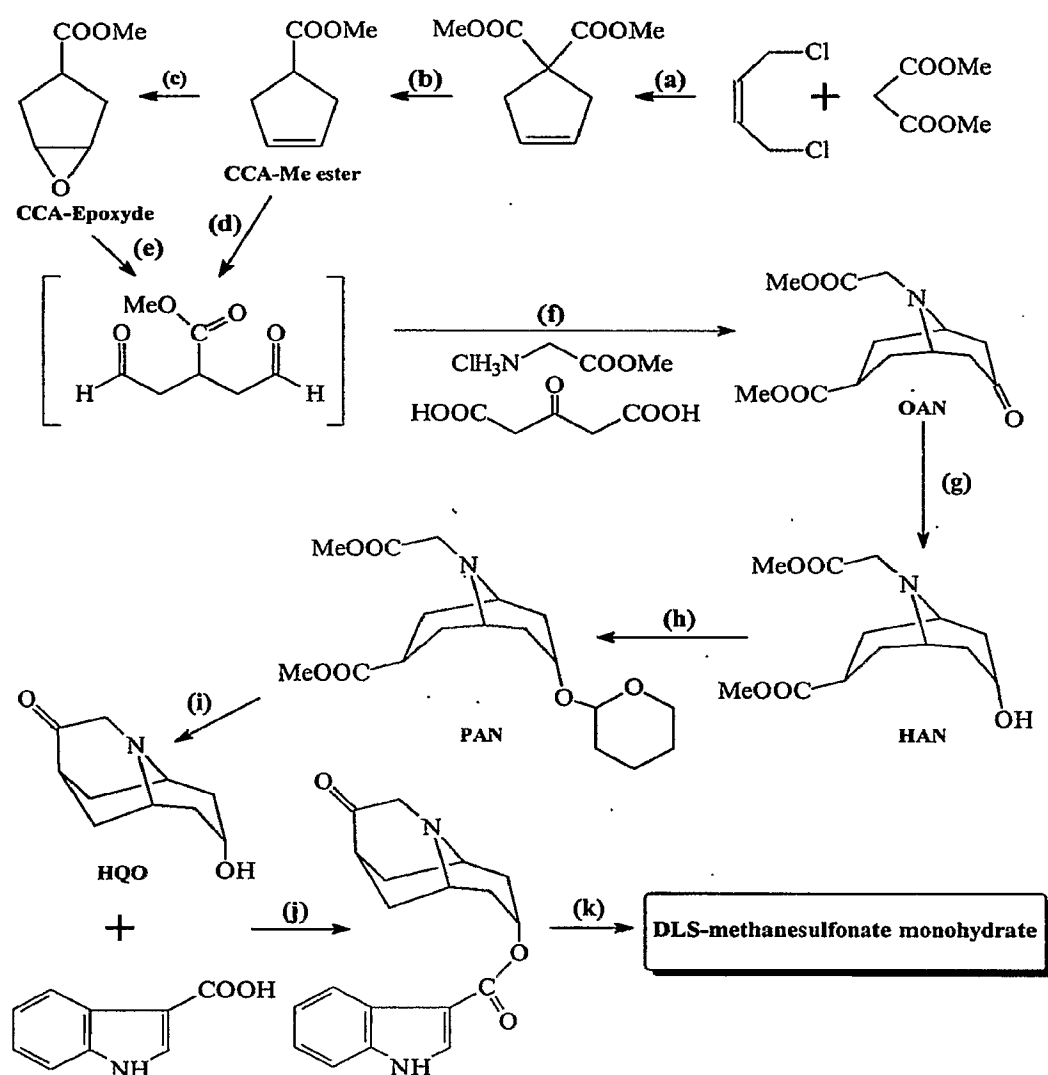


Dolasetron Mesylate monohydrate

is a serotonin receptor (5-HT₃) antagonist used as an antiemetic and antinauseant agent in chemo- and radiotherapies.

DLS-MsOH-H₂O developed by Merrell Dow Pharmaceuticals is marketed as tablets for oral administration and as sterile solution for intravenous administration by Aventis, under the name Anzemet®.

DLS-MSOH and its monohydrate form can be prepared by a multi step synthesis, as described in EP patent No. 0339669 ("the EP '669 patent") as illustrated in the following scheme



Accordingly, step (c) of the reaction involves oxidation with a molar equivalent of an expensive oxidizing reagent, 3-chloroperbenzoic acid (referred to as mCPBA), which transforms to 3-chlorobenzoic acid (referred to as mCBA), waste that is disposed at the end of the reaction. Removal of mCBA is problematic, hence, leading to a contaminated product. CCA-epoxyde is also contaminated by other aromatic impurities, such as $[(3\text{-ClPh})\text{C}(\text{O})\text{O}]_2$ (the corresponding peroxide), in an amount of 5%. Therefore, the oxidation reaction as described above is non-economic for scale-up. Also, the reaction in steps (e) and (f) are done by using periodic acid in

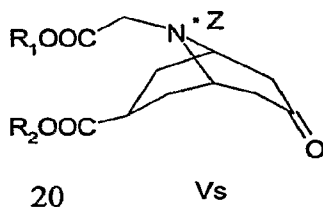
ethyl acetate in step (e), and water as a solvent in step (f). Since, the reagents and the reduction products have low solubility in ethylacetate; the reaction disclosed in the above patent is slower. Also, the reaction in ethylacetate is more dangerous. In addition, since two different solvents are used in steps (e) and (f), a work-up procedure, which can lead to a decomposition of the sensitive 3-methoxycarbonyl-1,5-glutardialdehyde (the product of the oxidation step), is required.

A similar process is apparently described in EP patent No. 0266730, comprising an oxidation reaction, as described in step (c) of the above scheme, to the corresponding diol, instead of to the epoxide, as apparently disclosed in EP patent No. 0339669. The diol is then transformed to DLS-base in a similar way.

Hence, there is a need in the art for an improved process for the preparation of Dolasetron salts, preferably, Dolasetron Mesylate.

SUMMARY OF THE INVENTION

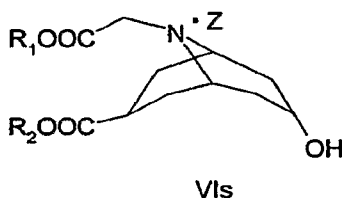
In one embodiment, the present invention provides a quaternary ammonium salt of a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-one compound (referred to as an OAN compound salt) of formula Vs;



wherein R₁ and R₂ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl, preferably, a C₁₋₄ alkyl, more preferably, methyl, and Z is an acid, preferably, methanesulfonic acid.

In another embodiment, the present invention provides crystalline methanesulfonate salt of 7-methoxycarbonyl-9-(methoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-one (referred to as OAN-MsOH).

In yet another embodiment, the present invention provides a quaternary ammonium salt of a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-ol compound (referred to as a HAN compound salt) of formula VIs;



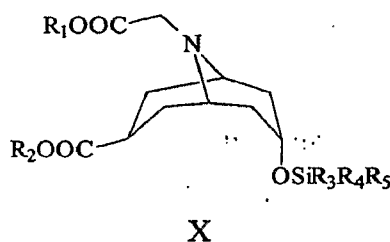
wherein R_1 , R_2 and Z are described before.

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In one embodiment, the present invention provides crystalline methanesulfonate salt of 7-methoxycarbonyl-9-(methoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-ol (referred to as HAN-MsOH).

In yet another embodiment, the present invention provides a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-trialkylsilyloxy-9-azabicyclo[3.3.1]nonane compound (referred to as a SAN compound) of formula X;

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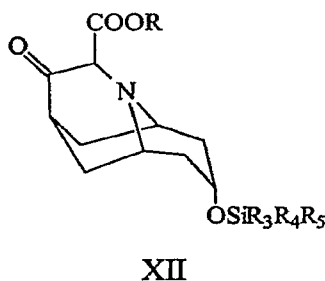


wherein R_1 and R_2 are independently a C_{1-6} alkyl or a C_{6-8} aryl, preferably, a C_{1-4} alkyl, more preferably, methyl, and $R_3R_4R_5$ are independently a C_{1-6} alkyl or a C_{6-8} aryl, or together are a *tert*-butyldialkyl, preferably, *tert*-butyldimethyl.

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In one embodiment, the present invention provides an *endo*-9-alkoxycarbonyl-5-trialkylsilyloxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (*trans*-hexahydro-4-alkoxycarbonyl-8-trialkylsilyloxy-2,6-methano-2H-quinolizin-3(4H)-one) compound (referred to as a SQO compound) of formula XII

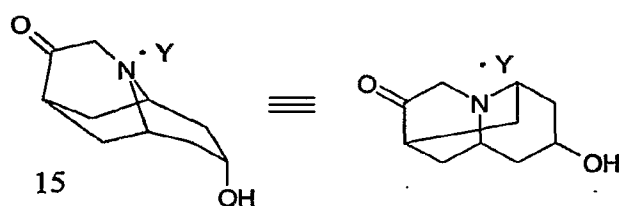
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wherein R is a C₁₋₆ alkyl or a C₆₋₈ aryl, preferably, a C₁₋₄ alkyl, more preferably, methyl, and R₃R₄R₅ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl, or together are a *tert*-butyldialkyl, preferably, *tert*-butyldimethyl.

In another embodiment, the present invention provides crystalline *endo*-9-methoxycarbonyl-5-*tert*-butyldimethylsilyloxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (5 *trans*-hexahydro-4-methoxycarbonyl-8-*tert*-butyldimethylsilyloxy-2,6-methano-2H-quinolizin-3(4H)-one) (referred to as SQO).

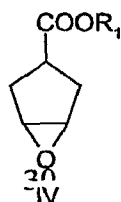
In yet another embodiment, the present invention provides a quaternary ammonium salt of *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (10 *trans*-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one) (referred to as a HQO-salt) of formula IIs;



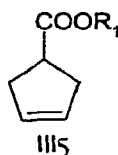
IIs

wherein Y is an acid selected from the group consisting of hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids. 20

In one embodiment, the present invention provides a process for the preparation of a CCA-epoxide of formula IV 25

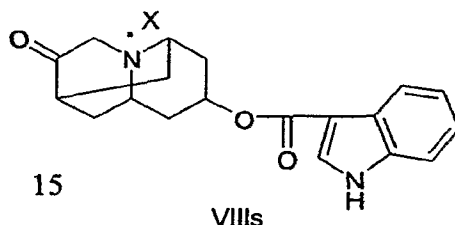


comprising combining a CCA-ester of formula III,



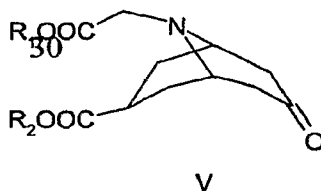
an oxidizing agent selected from a group consisting of hydroperoxide, dialkyl peroxide, peroxyacid, peroxyester, diacyl peroxide, persulphate, perborate, and perphosphate, a catalyst, and a solvent selected from the group consisting of water, a water miscible organic solvent, and mixtures thereof, to obtain a CCA-epoxide of formula IV; wherein, R_1 is C_{1-6} alkyl or C_{6-8} aryl, preferably, C_{1-4} alkyl, more preferably, methyl.

In another embodiment, the present invention provides a process for the preparation of a DLS- salt of formula VIIIs,



comprising preparing a CCA-epoxide of formula IV by the process of the invention; and converting it to a DLS- salt of formula VIIIs, wherein X is an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids, preferably, methane sulfonic acid.

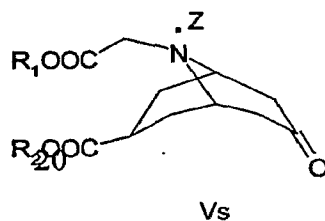
In yet another embodiment, the present invention provides a process for the preparation of an OAN compound of formula V



comprising combining a CCA-epoxide of formula IV, an oxidizing agent, and a solvent selected from the group consisting of water, a water miscible organic solvent, and mixtures thereof, to form a reaction mixture; raising the pH of the reaction mixture; and adding to the resulting product a pH 4 buffer, a glycine C₁₋₄ ester or salts thereof, and a substance comprising a carbonyl moiety selected from the group consisting of 1,3-acetonedicarboxylic acids, acetone and C₁₋₄ esters thereof, to form an OAN compound of formula V, wherein R₁ and R₂ are independently, C₁₋₆ alkyl or C₆₋₈ aryl, preferably, C₁₋₄ alkyl, more preferably, methyl.

In one embodiment, the present invention provides a process for the preparation of a DLS- salt of formula VIIIs, comprising preparing an OAN compound of formula V by the process of the invention; and converting it to a DLS- salt of formula VIIIs.

In another embodiment, the present invention provides a process for the preparation of an OAN compound salt of formula Vs



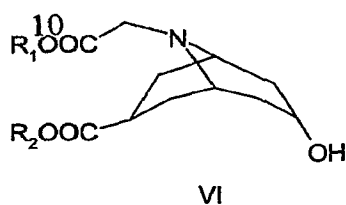
comprising combining an OAN compound of formula V, an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone, a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and mixtures thereof to form an OAN salt; wherein R₁ and R₂ are independently, C₁₋₆ alkyl or C₆₋₈ aryl, preferably, C₁₋₄ alkyl, more preferably, methyl, and Z is an acid, preferably, methanesulfonic acid.

In yet another embodiment, the present invention provides a process for purifying an OAN compound of formula V comprising combining an OAN compound of formula V, an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆

ketone, a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and mixtures thereof; and adding a base to obtain a purified OAN compound.

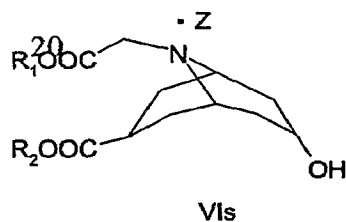
In one embodiment, the present invention provides a process for the preparation of a DLS-salt of formula VIIIa comprising preparing an OAN compound salt of formula Vs by the process of the invention, and converting it to a DLS-salt of formula VIIIa.

In another embodiment, the present invention provides a process for the preparation of a HAN compound of formula VI

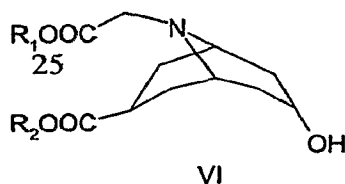


comprising combining an OAN compound salt of formula Vs, a reducing agent, and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof, forming a HAN compound of formula VI.

In yet another embodiment, the present invention provides a process for the preparation of a HAN compound salt of formula VIa



comprising combining a HAN compound of formula VI,



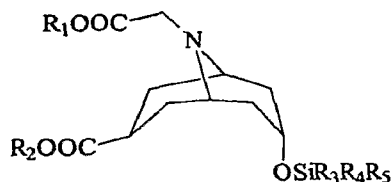
an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone, a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide and mixtures thereof, forming a HAN salt, wherein, Z is an acid, preferably methanesulfonic acid, R₁ and R₂ are independently, C₁₋₆ alkyl or C₆₋₈ aryl, preferably, C₁₋₄ alkyl, more preferably, methyl.

In yet another embodiment, the present invention provides a process for the preparation of a DLS-salt of formula VIII_s comprising preparing a HAN compound of formula VI by the process of the invention, and converting it to a DLS-salt of formula VIII_s.

In one embodiment, the present invention provides a process for purifying a HAN compound of formula VI comprising combining a HAN compound of formula VI, an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone, a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and mixtures thereof; and adding a base to obtain a purified HAN compound.

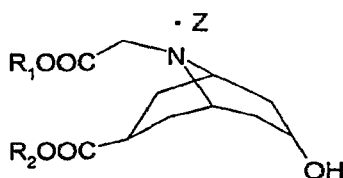
In another embodiment, the present invention provides a process for the preparation of a DLS-salt of formula VIII_s comprising preparing a HAN compound salt of formula VI_s by the process of the invention, and converting it to a DLS-salt of form.

In yet another embodiment, the present invention provides a process for the preparation of a SAN compound of formula X



X

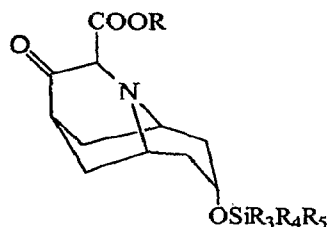
comprising combining a HAN-salt of formula VI_s

VI_s

a silylating agent selected from a group consisting of: silanes, silyl halogenides, silyl cyanides, silyl amines, silyl amides, silyl trifluoromethanesulfonates (silyl triflates), and silazanes, a base, and an aprotic organic solvent to obtain the SAN compound of formula X, wherein R_1 and R_2 are independently, C_{1-6} alkyl or C_{6-8} aryl, preferably, C_{1-4} alkyl, more preferably methyl, $R_3R_4R_5$ are independently a C_{1-6} alkyl or a C_{6-8} aryl, or together are a *tert*-butyldialkyl, preferably *tert*-butyldimethyl, and Z is an acid, preferably methanesulfonic acid.

In one embodiment, the present invention provides a process for the preparation of a DLS-salt of formula VIII, comprising preparing a SAN compound of formula X by the process of the invention, and converting it to a DLS-salt of formula VIII.

In another embodiment, the present invention also provides a process for the preparation a SQO compound of formula XII

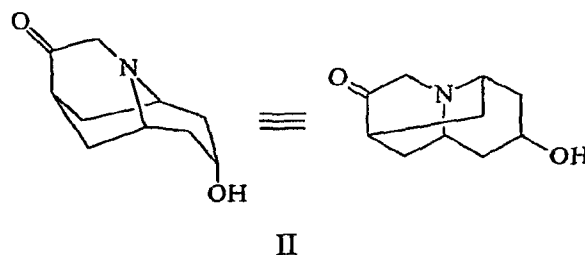


XII

comprising mixing a SAN compound of formula X, a metal alkoxide, and a polar aprotic organic solvent to form a mixture; heating the mixture; and reacting it with a weak acid forming the SQO compound of formula XII, wherein, R is a C_{1-6} alkyl or C_{6-8} aryl, preferably a C_{1-4} alkyl, more preferably methyl, and $R_3R_4R_5$ are independently a C_{1-6} alkyl or a C_{6-8} aryl, or together are a *tert*-butyldialkyl, preferably, *tert*-butyldimethyl.

In yet another embodiment, the present invention provides a process for the preparation of a DLS-salt of formula VIII, comprising preparing a SQO compound of formula XII by the process of the invention, and converting it to a DLS-salt of formula VIII.

In one embodiment, the present invention also provides a process for preparing HQO of formula II



comprising mixing a SQO compound of formula XII, water and an acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids to obtain HQO of formula II.

In another embodiment, the present invention further provides a process for the preparation of a DLS-salt of formula VIIIs, comprising preparing HQO of formula II by the process of the invention, and converting it to a DLS-salt of formula VIIIs.

In yet another embodiment, the present invention provides another process for the preparation of a HQO-salt of formula IIs comprising combining HQO, an alcohol and an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic, and disulfonic acids, forming a HQO salt of formula IIs.

In one embodiment, the present invention provides a process for purifying HQO of formula II comprising a) combining HQO of formula II, an alcohol and an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids,

methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic, and disulfonic acids; and b) adding a base, to obtain a purified HQO of formula II.

In one embodiment, the present invention provides a process for the preparation of a DLS-salt of formula VIIIs, comprising preparing a HQO-salt of formula IIs by the process of the invention, and converting it to a DLS-salt of formula VIIIs.

In yet another embodiment, the present invention provides a process for the preparation of a DLS-salt of formula VIIIs, comprising the steps of a) combining a CCA-ester of formula III, an oxidizing agent selected from the group consisting of: hydroperoxides, dialkyl peroxides, peroxyacids, peroxyesters, diacyl peroxides, persulphate, perborate and perphosphate, a catalyst and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof, to form a first intermediate mixture; b) adding to the first intermediate mixture an oxidizing agent, and a solvent selected from the group consisting of water and a water miscible organic solvent, to form a second intermediate mixture; c) raising the pH of the second intermediate mixture; d) reacting the products in the second reaction mixture with a pH 4 buffer, a glycine C₁₋₄ ester or salts thereof, and a substance comprising a carbonyl moiety selected from the group consisting of 1,3-acetonedicarboxylic acids, acetone and a C₁₋₄ ester thereof, to form a third reaction mixture; e) adding to the third intermediate mixture a reducing agent, and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof, to form a fourth intermediate mixture; f) adding to the fourth intermediate mixture a silylating agent selected from a group consisting of: silanes, silyl halogenides, silyl cyanides, silyl amines, silyl amides, silyl trifluoromethanesulfonates (silyl triflates), and silazanes, a base, and an aprotic organic solvent to form a fifth intermediate mixture; g) adding to the fifth intermediate mixture a metal alkoxide, and a polar aprotic organic solvent to form a sixth intermediate mixture; h) heating the sixth intermediate mixture; i) reacting the products in the sixth intermediate mixture with a weak acid forming a seventh intermediate mixture; j) adding to the seventh intermediate mixture water and an acid to form an eight intermediate mixture; k) mixing the eight intermediate mixture with an anhydride, 3-indole carboxylic acid, a halogenated hydrocarbon, and a catalyst;

and l) reacting the product from step k) with an acid to obtain the DLS-salt of formula VIIIs.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates powder X-ray diffraction pattern for OAN-MsOH.

Figure 2 illustrates powder X-ray diffraction pattern for HAN-MsOH.

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Figure 3 illustrates powder X-ray diffraction pattern for SQO.

Figure 4 illustrates powder X-ray diffraction pattern for HQO-HCl.

Figure 5 illustrates powder X-ray diffraction pattern for HQO-CSA.

Figure 6 illustrates powder X-ray diffraction pattern for HQO-base.

DETAILED DESCRIPTION OF THE INVENTION

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The present invention offers novel intermediates in the syntheses of Dolasetron salts, and processes for preparing them. The invention also offers the use of these intermediates in novel processes for preparing Dolasetron salts, especially, the mesylate salt.

The present invention provides a process for the preparation of a DLS-salt of formula VIIIs, comprising the steps of a) combining a CCA-ester of formula III, an oxidizing agent selected from the group consisting of: hydroperoxides, dialkyl peroxides, peroxyacids, peroxyesters, diacyl peroxides, persulphate, perborate and perphosphate, a catalyst and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof, to form CCA-epoxide of formula IV; b) admixing CCA-epoxide with an oxidizing agent, and a solvent selected from the group consisting of water and a water miscible organic solvent; c) raising the pH of the mixture; d) admixing the mixture with a pH 4 buffer, a glycine C₁₋₄ ester or salts thereof, and a substance comprising a carbonyl moiety selected from the group consisting of 1,3 acetonedicarboxylic acids, acetone and a C₁₋₄ ester thereof, to form OAN of formula V; e) admixing the material of the previous step with a reducing agent, and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof, to form HAN of formula VI; f) admixing the material of the previous step with a silylating agent selected from a group consisting of: silanes, silyl halogenides, silyl cyanides, silyl amines, silyl amides, silyl trifluoromethanesulfonates (silyl triflates), and silazanes, a base, and an aprotic organic solvent to form SAN of formula X; g) admixing the material of the previous step with a metal alkoxide, and a polar a-protic organic solvent to form a reaction

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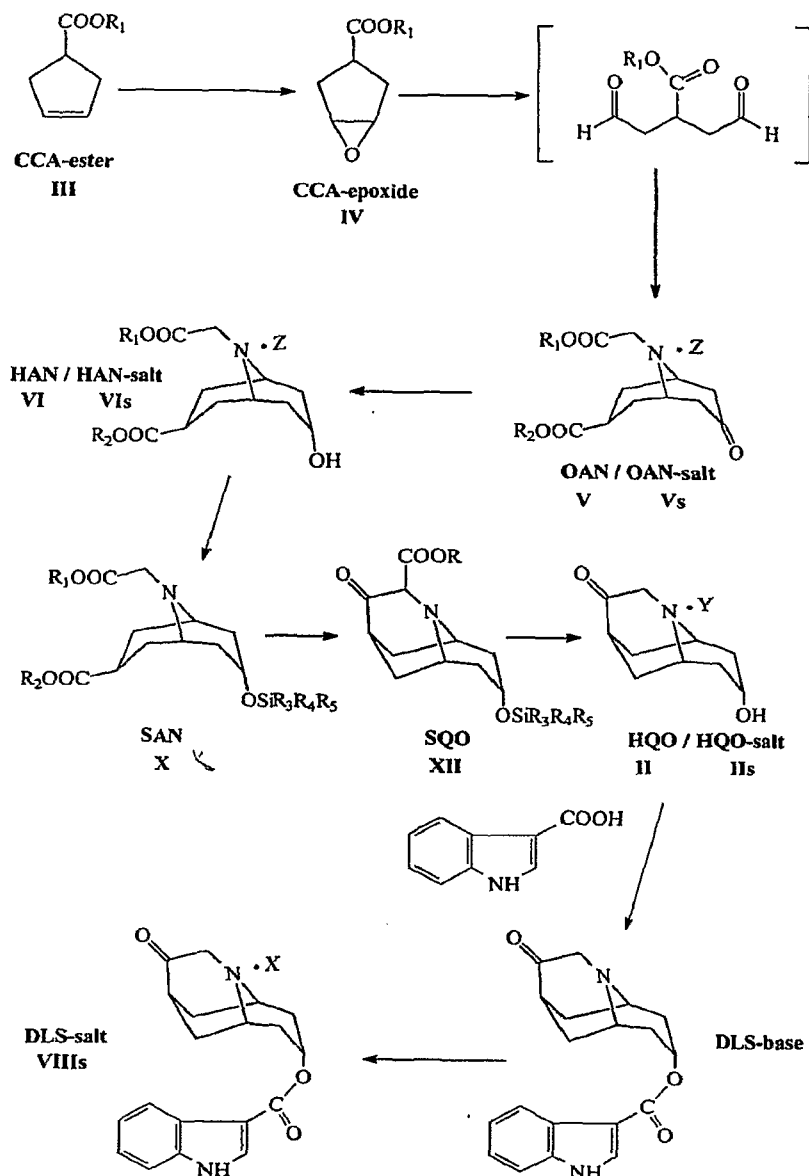
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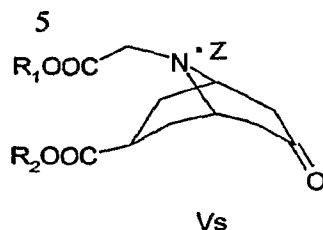
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mixture; h) heating the reaction mixture; i) quenching the reaction mixture with a weak acid forming SQO of formula XII; j) admixing the material of the previous step with a solvent selected from a group consisting of: water, and water-immiscible organic solvent, and an acid to form HQO of formula II; k) admixing the material of the previous step with an anhydride, 3-indole carboxylic acid, a halogenated hydrocarbon, and a catalyst to obtain Dolasetron base; and l) reacting Dolasetron base with an acid to obtain the DLS-salt of formula VIIIs. Preferably, the weak acid in step i) is selected from the group consisting of acetic acid, formic acid, acetic acid, propionic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, and salicylic acid. Preferably, the acid in step j) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids. Preferably, the acid in step l) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids, preferably, methane sulfonic acid. In the alternative, the weak acid in step i) can be a (strong) acid as in step j), in which instant the step j) of this process may be omitted.

The process can be illustrated by the following scheme:

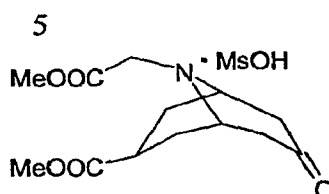


The present invention provides a quaternary ammonium salt of a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-one compound (referred to as an OAN-salt) of formula Vs;



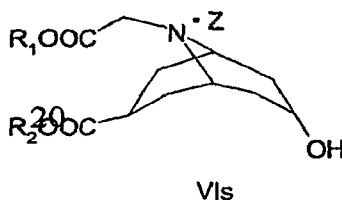
wherein R_1 and R_2 are independently a C_{1-6} alkyl or a C_{6-8} aryl, preferably, a C_{1-4} alkyl, more preferably, methyl, and Z is an acid, preferably, methanesulfonic acid.

When R_1 and R_2 are methyl, and Z is methanesulfonic acid, said compound of formula Vs refers to the methanesulfonate salt of 7-methoxycarbonyl-9-(methoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-one (referred to as OAN-MsOH) of the following formula.



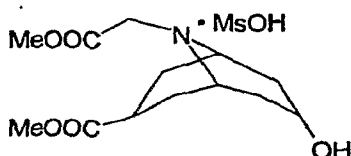
The present invention further provides crystalline OAN-MsOH. The crystalline OAN-MsOH of the present invention may be characterized by a powder XRD diffraction pattern having peaks at about 8.5, 18.0, and 20.9 degrees two-theta, ± 0.2 degrees two-theta. Crystalline OAN-MsOH may be further characterized by a powder XRD diffraction pattern having peaks at about 14.7, 22.7, 24.3, 25.0, 26.3 and 27.9 degrees two-theta, ± 0.2 degrees two-theta. Crystalline OAN-MsOH may be also substantially identified by the PXRD pattern as depicted in Figure 1.

The present invention also provides a quaternary ammonium salt of a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-ol compound (referred to as a HAN-salt) of formula VIs;



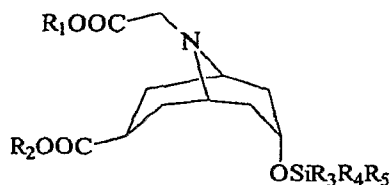
wherein R_1 , R_2 and Z are described before.

When R_1 and R_2 are methyl, and Z is methanesulfonic acid, said compound of formula VIs refers to the methanesulfonate salt of 7-methoxycarbonyl-9-(methoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-ol (referred to as HAN-MsOH) of the following formula.



The present invention provides crystalline HAN-MsOH. The crystalline HAN-MsOH of the present invention may be characterized by a powder XRD diffraction pattern having peaks at about 7.3, 11.6, and 14.6 degrees two-theta, ± 0.2 degrees two-theta. The crystalline HAN-MsOH may be further characterized by a powder XRD diffraction pattern having peaks at about 15.9, 17.9, 19.0, 20.4, 21.9, 29.0 and 29.4 degrees two-theta, ± 0.2 degrees two-theta. The crystalline HAN-MsOH may be also substantially identified by the PXRD pattern as depicted in Figure 2.

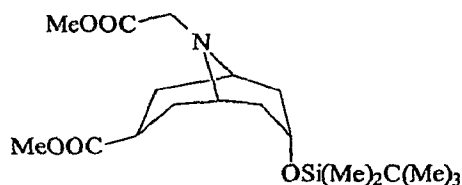
The present invention further provides a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-trialkylsilyloxy-9-azabicyclo[3.3.1]nonane compound (referred to as a SAN compound) of formula X;



X

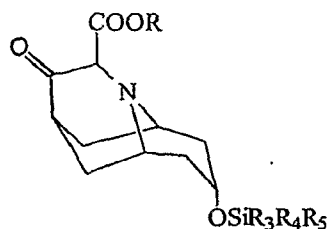
wherein R_1 and R_2 are described before.

When R_1 and R_2 are methyl, and $R_3R_4R_5$ is *tert*-butyldimethyl, said compound of formula X refers to 7-methoxycarbonyl-9-(methoxycarbonylmethyl)-3-*tert*-butyldimethylsilyloxy-9-azabicyclo[3.3.1]nonane (referred to as SAN) of the following formula.



XI

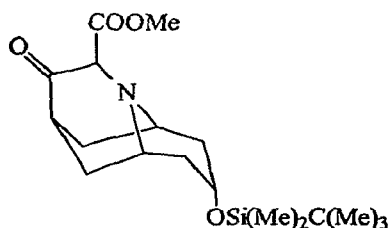
The present invention also provides an *endo*-9-alkoxycarbonyl-5-trialkylsilyloxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (*trans*-hexahydro-4-alkoxycarbonyl-8-trialkylsilyloxy-2,6-methano-2H-quinolizin-3(4H)-one) compound (referred to as a SQO compound) of formula XII



XII

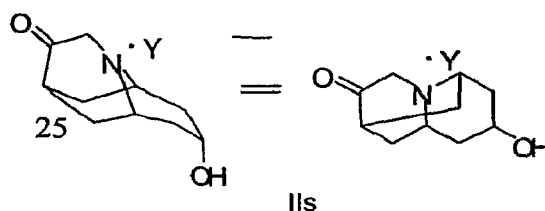
wherein R is a C₁₋₆ alkyl or a C₆₋₈ aryl, preferably, a C₁₋₄ alkyl, more preferably, methyl, and R₃R₄R₅ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl, preferably, *tert*-butyldialkyl, more preferably, *tert*-butyldimethyl.

Preferably, when R is methyl and R₃R₄R₅ is *tert*-butyldimethyl, said compound of formula XII refers to *endo*-9-methoxycarbonyl-5-*tert*-butyldimethylsilyloxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (*trans*-hexahydro-4-methoxycarbonyl-8-*tert*-butyldimethylsilyloxy-2,6-methano-2H-quinolizin-3(4H)-one) (referred to as SQO) of the following formula.



The present invention provides crystalline SQO. The crystalline SQO of the present invention may be characterized by an XRD diffraction pattern having peaks at about 5.1, 10.1, 12.7, and 20.3 degrees two-theta, ± 0.2 degrees two-theta. The crystalline SQO may be further characterized by an XRD diffraction pattern having peaks at about 15.2, 17.0, 17.6, 18.3, 19.1, and 19.8 degrees two-theta, ± 0.2 degrees two-theta. The crystalline SQO may be also substantially identified by the PXRD pattern as depicted in Figure 3.

The present invention further provides a quaternary ammonium salt of *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (*trans*-hexahydro-8-hydroxy-2,6-methano-2H-quinolizin-3(4H)-one) (referred to as a HQO-salt) of formula IIs;

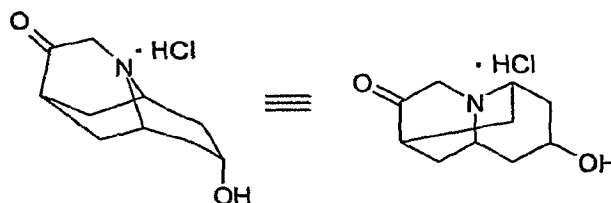


wherein Y is an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids, preferably, methanesulfonic acid.

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Preferably, when Y is HCl, said HQO-salt of formula IIa corresponds to HQO-HCl of the following formula.

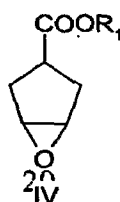
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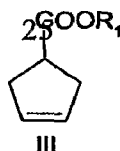
The present invention provides crystalline HQO-HCl salt. The crystalline HQO-HCl salt of the present invention may be characterized by a powder XRD diffraction pattern as depicted in Figure 4.

The present invention also provides a process for the preparation of a CCA-epoxide of formula IV

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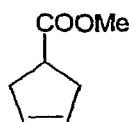
comprising combining a CCA-ester of formula III,



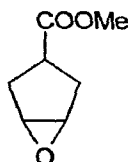
an oxidizing agent selected from the group consisting of: a hydroperoxide, a dialkyl peroxide, a peroxyacid, a peroxyester, a diacyl peroxide, a persulphate, a perborate, a

perphosphate, and a dimethyldioxiran, a catalyst, and a solvent selected from the group consisting of water, water miscible organic solvents, and mixtures thereof, to obtain the CCA-epoxide of formula IV, wherein R_1 is a C_{1-6} alkyl or a C_{6-8} aryl, preferably, a C_{1-4} alkyl, more preferably, methyl.

When R_1 is methyl, said CCA-ester of formula III corresponds to CCA-methylester of the following formula,



and said CCA-epoxide of formula IV corresponds to CCA-epoxide of the following formula.



Preferably, the CCA-ester of formula III is combined with a solvent selected from the group consisting of water, water miscible organic solvents, and mixtures thereof, to obtain a solution.

Preferably, the water miscible organic solvent is selected from the group consisting of linear or branched C_{1-4} alcohols. Preferably, the C_{1-4} alcohol is a C_{1-3} alcohol, more preferably, a C_{1-2} alcohol, most preferably, methanol. In the alternative, a mixture of water and a water immiscible organic solvent may be used in the presence of a phase transfer catalyst. Preferably, the water immiscible organic solvent is selected from the group consisting of a C_{1-8} halogenated hydrocarbon, a C_{2-8} ester, a C_{2-8} ether and a C_{3-6} ketone. A preferred C_{1-8} halogenated hydrocarbon is a C_{1-4} halogenated hydrocarbon, more preferably a C_{1-2} halogenated hydrocarbon. Preferably, the C_{1-2} halogenated hydrocarbon is dichloromethane, 1,2-dichloroethane or chloroform, more preferably dichloromethane. A preferred C_{2-8} ester is a C_{2-6} ester, more preferably, a C_{4-6} ester. Preferably, the C_{4-6} ester is ethyl acetate, *n*-butyl acetate or isobutyl acetate, more preferably ethyl acetate. A preferred C_{2-8} ether is a C_{2-6} ether, more preferably, a C_{4-6} ether. Preferably, the C_{4-6} ether is diethyl ether, diisopropyl ether or *tert*-butyl methyl ether, more preferably *tert*-butyl methyl ether. A preferred C_{3-6} ketone is a C_{4-6} ketone. Preferably, the C_{4-6} ketone is methyl ethyl ketone (2-butanone), 2-pentanone, 3-pentanone or 3,3-dimethyl-2-butanone, more

preferably 2-pentanone. The most preferred solvent is dichloromethane. Further, the phase transfer catalyst is preferably a quaternary ammonium salt, more preferably the phase transfer catalyst is tetrabutyl ammonium bromide.

Preferably, the solution is combined with an oxidizing agent selected from the group consisting of: a hydroperoxide, a dialkyl peroxide, a peroxyacid, a peroxyester, a diacyl peroxide, a persulphate, a perborate, a perphosphate, and a dimethyldioxiran, and a catalyst, to obtain a mixture.

Preferably, the hydroperoxide is RO-OH, wherein R is either H or an alkyl group. Preferably, the alkyl group is a C₁₋₆ alkyl, more preferably *t*-butyl. A preferred dialkyl peroxide is RO-OR, wherein R is a C₁₋₆ alkyl, preferably *t*-butyl. Preferably, the peroxyacid is RCO-O-OH. More preferably, the RCO-O-OH is selected from the group consisting of: peracetic acid, trifluoroperacetic acid, perlauroic acid, perbenzoic acid, and 3,5-dinitroperbenzoic acid. Preferably, the peroxyester is RCO-O-OR', wherein R is phenyl or methyl, and R' is an C₁₋₆ alkyl, preferably *t*-butyl. A preferred diacyl peroxide is RCO-O-O-COR, wherein R is phenyl or methyl. A preferred persulphate is peroxydisulphuric acid (M₂S₂O₈) in the form of a potassium, sodium or ammonium (M=K, Na, NH₄) salt, peroxymonosulfuric acid (Caro's acid), and Oxone® (potassium monopersulfate triple salt: KHSO₅-KHSO₄-K₂SO₄ (2:1:1)). The more preferred oxidizing agent is hydroperoxide, most preferably, hydrogen peroxide. Preferably, an aqueous solution of hydrogen peroxide is used. A preferred concentration of the solution is of about 3% to about 50%, more preferably of about 20% to about 40%, most preferably of about 30% to about 35%.

Preferably, the catalyst is selected from the group consisting of Zeolites and polyoxometalates. Preferably, the metal moiety of the polyoxometalates is selected from the group consisting of tungsten, molybdenum, rhenium, vanadium and niobium. More preferably, the catalyst is either sodium tungstate dihydrate or sodium molybdenate dihydrate.

A preferred amount of the catalyst is about 0.01 mole% to about 50 mole% per mole of the CCA-ester, more preferably about 1 mole% to about 10 mole% per mole of the CCA-ester, most preferably about 2 mole% per mole of the CCA-ester.

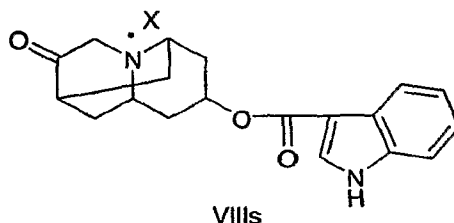
In preparing the CCA epoxide of formula IV, the reaction mixture is maintained at a temperature of about 0°C to about 80°C, preferably about 30°C to about 80°C, more preferably, at a temperature of about 15°C to about 65°C, most

preferably at a temperature of about 60°C to about 65°C. The reaction mixture is preferably, maintained at such temperature for a period of about 0.5 hours to about 24 hours, more preferably for about 1 to about 10 hours, most preferably for about 2 hours to about 4 hours.

The progress of the reaction may be monitored by gas-chromatography (referred to as GC) or by thin-layer chromatography (referred to as TLC). When monitored by TLC, an eluent of *n*-hexane and ethylacetate in a ratio of 1:1 may be used.

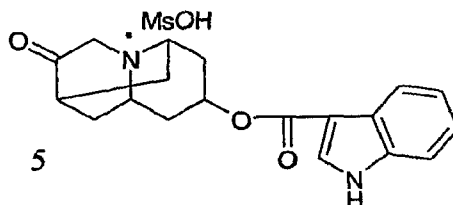
The process for preparing a CCA-ester of formula IV may further comprise a recovery step. The CCA-epoxide of formula IV may be recovered comprising the steps of adjusting the temperature of the reaction mixture to a temperature of about 20°C to about 30°C; extracting the product with a water immiscible organic solvent, preferably, dichloromethane; and evaporating the solvent.

The process for preparing a CCA-ester of formula IV may further comprise a process for converting it to a DLS- salt of formula VIIIs,



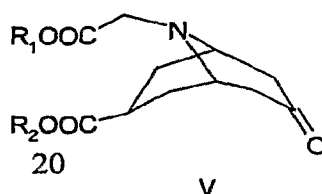
wherein, X is an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids, preferably, methane sulfonic acid. This conversion to a DLS salt of formula VIIIs may be carried out by the process of the invention or any other known process converting the CCA epoxide of formula IV to a DLS salt of formula VIIIs as described for example in EP 0339699, example 9.

When X is methane sulfonic acid, said DLS- salt of formula VIIIa corresponds to DLS-MsOH of the following formula.



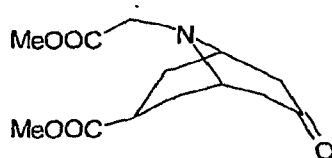
The process of the present invention provides an OAN compound of formula V prepared by a process comprising an oxidation reaction followed by Robinson-Schöpf reaction, wherein both reactions are done in water, and therefore can be done concurrently, i.e., without isolation of the oxidation product, prior to the Robinson-Schöpf reaction. The oxidation applies the use of periodic acid in water, in which the reagents and the reduction products have high solubility; hence, the reaction is fast. Also, using water allows controlling the exothermic nature of the reaction, thus, reducing the danger.

The present invention further provides a process for the preparation of an OAN compound of formula V



comprising combining a) a CCA-epoxide of formula IV, an oxidizing agent, and a solvent selected from the group consisting of water, water miscible organic solvents, and mixtures thereof, to form a reaction mixture; b) raising the pH of the reaction mixture; c) and adding to the reaction mixture of step b) a pH 4 buffer, glycine C₁₋₄ ester or salts thereof, and a substance comprising carbonyl moiety selected from the group consisting of 1,3-acetonedicarboxylic acid, acetone and a C₁₋₄ ester thereof, to form the OAN compound of formula V, wherein R₁ and R₂ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl, preferably, a C₁₋₄ alkyl, more preferably, methyl.

When R₁ and R₂ are methyl, said OAN compound of formula V corresponds to OAN of the following formula.



Combining a CCA-epoxide of formula IV, an oxidizing agent, and a solvent selected from the group consisting of water, water miscible organic solvents, and mixtures thereof, to form a reaction mixture; and raising the pH of the reaction mixture, may be designated as an oxidation reaction.

Preferably, combining a CCA-epoxide of formula IV with an oxidizing agent, and a solvent selected from the group consisting of water, water miscible organic solvent and mixtures thereof provides a first reaction mixture.

Preferably, the water miscible organic solvent is selected from the group consisting of: a nitrile, a ketone and an ether. A preferred nitrile is a C₂₋₄ nitrile. Preferably, the C₂₋₄ nitrile is acetonitrile, propionitrile or butyronitrile. A preferred ketone is a C₃₋₆ ketone. Preferably, the C₃₋₆ ketone is acetone, methyl ethyl ketone or diethyl ketone. Preferably, the ether is a cyclic ether. A preferred cyclic ether is THF, 1,4-dioxane or 1,3-dioxolane. The preferred solvent is water.

Preferably, the oxidizing agent is selected from the group consisting of: periodic acid and salts thereof, lead tetraacetate, cerium and ammonium nitrate (Ce(NH₄)₂(NO₃)₆). More preferably, the oxidizing agent is periodic acid. Preferably, the oxidizing agent is added in the form of a solution when the solvent is water.

Preferably, the first reaction mixture is maintained at a temperature of about 10°C to about 60°C, more preferably at a temperature of about 10°C to about 15°C. Preferably, the first mixture is maintained for a period of about 0.5 hours to about 24 hours, and more preferably for about 1 to about 3 hours. Maintaining the first reaction mixture is preferably done while stirring.

The first reaction mixture is, preferably, acidic. Preferably, the pH of the acidic first reaction mixture is of about 0.5 to about 7, more preferably of about 0.5 to about 2.

Preferably, the pH of the maintained first reaction mixture is increased to about 2 to about 7. The pH is raised, preferably to about 3.5 to about 4.5. Preferably,

the pH is raised by using a water immiscible base, more preferably either poly(4-vinylpyridine) or OH resins, and even more preferably, OH resins. The water immiscible base is, preferably, filtered off, more preferably through Celite, providing an aqueous solution of the product of the oxidation reaction. Preferably, adjusting the pH is performed at a temperature of about 15°C to about 35°C, more preferably at about room temperature. 5

The reaction may be run stepwise or concurrently, *i.e.*, without isolation of the oxidation product prior to the Robinson-Schöpf reaction. Preferably, the process is run concurrently.

Preferably, after adjusting the pH, a pH 4 buffer, a glycine C₁₋₄ ester or salts thereof, and a substance comprising carbonyl moiety selected from the group consisting of a 1,3-acetonedicarboxylic acids, acetone and C₁₋₄ esters thereof, are added to obtain a second reaction mixture. 10

Preferably, the pH 4 buffer is an amine-free buffer. Preferably, the amine-free buffer is selected from the group consisting of: a citric acid-sodium hydroxide-hydrochloric acid buffer, a citric acid-disodium hydrogenphosphate buffer, a sodium acetate-acetic acid buffer, a potassium diphthalate-sodium hydroxide buffer, sodium dihydrogen phosphate and potassium hydrogen phthalate. More preferably, the amine-free buffer is potassium hydrogen phthalate. Preferably, the buffer is used in an amount of about 1 to about 10 mole equivalents, more preferably about 2 to 5 mole equivalents, most preferably about 3 mole equivalents, per mole equivalent of the CCA-epoxide. 15 20

Preferably, the glycine C₁₋₄ ester is a methyl ester. A preferred salt of the glycine C₁₋₄ ester is glycine hydrochloride. More preferably, the glycine C₁₋₄ ester or salts thereof, is glycin methylester hydrochloride. 25

Preferably, the C₁₋₄ ester of 1,3-acetonedicarboxylic acid is selected from the group consisting of symmetrical and mixed C₁₋₄ ester derivatives. The preferred substance comprising a carbonyl moiety is 1,3-acetonedicarboxylic acid.

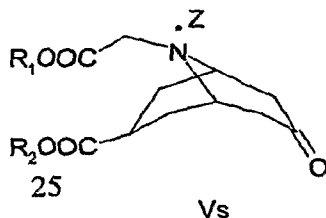
Preferably, the second reaction mixture is maintained at a temperature of about 0°C to about 60°C, more preferably, at about 10°C to about 40°C, most preferably at about room temperature. The second mixture is maintained, preferably for about 10 to about 72 hours, and more preferably for about 12 to about 24 hours, most preferably 30

for about 18 hours. Maintaining the second reaction mixture is preferably done while stirring.

The process for preparing the OAN compound of formula V may further comprise a recovery step. The recovery may be done by any known process. The OAN compound of formula V may be recovered by filtering off the undissolved solid particles from the second reaction mixture, preferably, through Celite, followed by washing with water, and combining the filtrate with an inorganic base to obtain a pH of about 7 to about 9, more preferably, of about 7.5 to about 8. Preferably, the inorganic base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate, more preferably is sodium bicarbonate. The basic filtrate is then extracted with a water immiscible organic solvent, preferably a C₂₋₅ acetate, more preferably isobutylacetate, and the solvent is evaporated.

The present invention also provides a process for the preparation of a DLS-salt of formula VIIIs comprising preparing the OAN compound of formula V by the process of the invention, and converting it to a DLS-salt of formula VIIIs. This conversion to a DLS salt of formula VIIIs may be carried out by the process of the invention or any other known process converting an OAN compound of formula V to a DLS salt of formula VIIIs as described for example in EP 0339699, examples 4 and 9.

The present invention provides a process for the preparation of an OAN-salt of formula Vs



comprising reacting the OAN compound of formula V, an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone and a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide and mixtures thereof, wherein, R₁ and R₂ are described before, and Z is an acid, preferably, methanesulfonic acid.

The present invention further provides a process for purifying the OAN compound of formula V comprising reacting the OAN compound of formula V, an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone and a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide and mixtures thereof; and adding a base. 5

The OAN compound of formula V used as a starting material may be a crude OAN compound or a concentrated solution of a crude OAN compound, obtained in the recovery process of the OAN compound.

Preferably, the OAN compound of formula V is dissolved in an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone and a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide and mixtures thereof, prior to adding the acid. 10

Preferably, the C₁₋₄ alcohol is a C₁₋₃ alcohol. Preferably, the C₁₋₃ alcohol is methanol, *n*-propanol, isopropanol or ethanol. A preferred C₂₋₈ ester is a C₂₋₆ ester, more preferably, a C₂₋₄ ester. A preferred C₂₋₄ ester is ethyl acetate, propylacetate, *n*-butyl acetate, or isobutylacetate. A preferred linear, branched or cyclic C₂₋₈ ether is a C₂₋₇ ether, more preferably, a C₂₋₅ ether. A preferred C₂₋₅ ether is 1,4-dioxane, diisopropyl ether, *t*-butyl methyl ether or tetrahydrofuran. Preferably, the C₃₋₆ ketone is a C₃₋₅ ketone. Preferably, the C₃₋₅ ketone is methyl ethyl ketone (2-butanone), 2-pentanone, 3-pentanone, 3,3-dimethyl-2-butanone or acetone. Preferably, the C₅₋₈ aliphatic hydrocarbon is a C₅₋₇ aliphatic hydrocarbon, more preferably, a C₆₋₇ aliphatic hydrocarbon. A preferred C₆₋₇ aliphatic hydrocarbon is either *n*-hexane, or *n*-heptane. A preferred C₁₋₈ halogenated hydrocarbon is a C₁₋₆ halogenated hydrocarbon, more preferably a C₁₋₄ halogenated hydrocarbon, most preferably a C₁₋₂ halogenated hydrocarbon. A preferred C₁₋₂ halogenated hydrocarbon is dichloroethane, chloroform or dichloromethane. A preferred C₁₋₄ nitroalkane is a C₁₋₂ nitroalkane. Preferably, the C₁₋₂ nitroalkane is nitromethane or nitroethane. Preferably, the C₁₋₄ alkylcyanide is a C₁₋₃ alkylcyanide. A preferred C₁₋₃ alkylcyanide is either propionitrile or acetonitrile. A preferred C₆₋₈ aromatic hydrocarbon is a C₆₋₇ aromatic hydrocarbon. Preferably, the C₆₋₇ aromatic hydrocarbon is toluene. A preferred C₃₋₁₀ amide is a C₃₋₆ amide. Preferably, the C₃₋₆ amide is dimethylformamide. The more preferred solvent is a 15 20 25 30

mixture of a C₂₋₄ ester and a C₁₋₃ alcohol, more preferably, of isobutylacetate and ethanol. Preferably, the mixture contains isobutylacetate and ethanol in a ratio of about 1:1, respectively.

Preferably, the acid is either an organic acid or an inorganic acid. The organic acid is selected from the group consisting of carboxylic acids and sulfonic acids. 5
Preferably, the carboxylic acid is selected from the group consisting of: formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids. More preferably, the carboxylic acid is tartaric acid. A preferred sulfonic acid is selected 10
from the group consisting of: methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids. More preferably, the sulfonic acid is either methane sulfonic acid or camphorsulfonic acid. Preferably, the inorganic acid is selected from the group consisting of: hydrochloric acid, 15
hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, and fluoroboric acid. The more preferred inorganic acid is hydrochloric acid. The more preferred acid is methane sulfonic acid.

Combining the OAN compound of formula V, the solvent and the acid provides a mixture. Preferably, the mixture is maintained at a temperature of about 20
10°C to about 60°C, more preferably, at a temperature of about 20°C to about 50°C, most preferably at a temperature of about 30°C to about 40°C. The mixture is preferably maintained at such temperature for about 1 hour to about 24 hours, and more preferably, for about 2 to about 12 hours. Maintaining the reaction mixture is preferably done while stirring. 25

Preferably, reacting the OAN compound with an acid provides the corresponding OAN-salt of formula Vs. Preferably, the OAN-salt of formula Vs precipitates from the reaction mixture. Preferably, in the process of purifying the OAN compound of formula V, the precipitate is reacted with a base providing the OAN compound of formula V back again. Preferably, the precipitate is recovered 30
prior to reacting with a base.

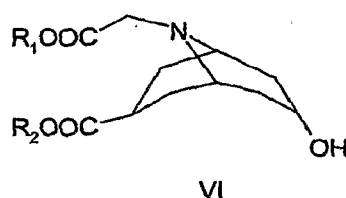
Preferably, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. More preferably, the base is sodium

bicarbonate.

The process for preparing an OAN-salt of formula Vs may further comprise a process for converting it to a DLS- salt of formula VIIIs.

The present invention provides a process for the preparation of a HAN compound of formula VI

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comprising combining an OAN salt of formula Vs, a reducing agent, and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof to obtain the HAN compound of formula VI.

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Preferably, the OAN-salt of formula Vs is OAN-MsOH. When the OAN-salt is used as a starting material, it is combined with a water miscible organic solvent, providing a suspension. Preferably, the suspension is prepared at a temperature of about 15°C to about 35°C, preferably of about 20°C to about 25°C. Optionally, the OAN compound of formula V may be used as a starting material. When, the OAN compound of formula V is used as a starting material, it is combined with a water miscible organic solvent, providing a solution. Preferably, the water miscible organic solvent is a C₁₋₄ alcohol, more preferably, a C₁₋₃ alcohol, most preferably, a C₁₋₂ alcohol. A preferred C₁₋₂ alcohol is methanol.

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Preferably, the reducing reagent is a metal hydride complex, preferably lithium borohydride, selectricde or sodium borohydride, more preferably, sodium borohydride. The reducing agent may be used in a basic aqueous solution or as a solid. When the OAN compound of formula V is the starting material, a basic aqueous solution of the reducing agent may be used. Preferably, the basic aqueous solution is an aqueous solution of an alkali hydroxide, more preferably an aqueous solution of sodium hydroxide. Preferably, the basic aqueous solution contains about 30% to about 50% by weight, preferably about 30%, of sodium hydroxide.

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Preferably, the solution of the OAN compound of formula V in a C₁₋₄ alcohol and the basic aqueous solution of the reducing agent are combined at a temperature of

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about 0°C to about 10°C, preferably about 0°C to about 5°C. Preferably, the solution of the reducing reagent is added drop-wise to the solution of the OAN compound in a C₁₋₄ alcohol.

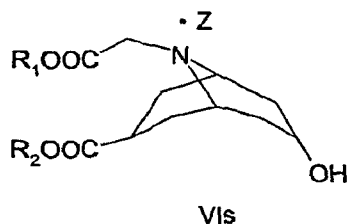
When the OAN-salt of formula Vs is the starting material, a solid reducing agent may be used. Preferably, the suspension of the OAN-salt of formula Vs in a C₁₋₄ alcohol and the reducing agent are combined at a temperature of about 15°C to about 35°C, preferably about 20°C to about 25°C. Preferably, the reducing reagent is added portion-wise to the suspension of the OAN-salt in a C₁₋₄ alcohol. Preferably, the portion-wise addition of the reducing agent is done while maintaining the temperature at about 15°C to about 35°C, preferably about 25°C to about 35°C.

Combining the above substances leads to a mixture. Preferably, the mixture is maintained for about a half hour to about 2 hours, preferably for about a half hour to about an hour at such temperature, prior to recovering the HAN compound of formula VI.

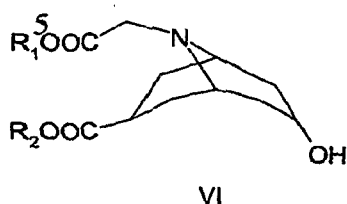
When the OAN compound of formula V is used as a starting material, the mixture is maintained at a temperature of about 0°C to about 5°C, for about an hour, and when the starting material is OAN-salt of formula Vs, the mixture is maintained at a temperature of about 25°C to about 35°C, for about a half an hour. The reaction may be monitored by TLC using ethylacetate as an eluent.

The process for preparing the HAN compound of formula VI may further comprise a recovery step. The recovery may be carried out by any known method. The HAN compound of formula VI may be recovered by a process comprising adding an acid, preferably a water miscible organic acid, more preferably acetic acid, to the reaction mixture, to give a precipitate. The precipitate is then combined with water and with a halogenated hydrocarbon, preferably a C₁₋₂ halogenated hydrocarbon, to give a solution, optionally followed by filtration. The aqueous phase is then extracted, and the solvent is evaporated from the combined organic phase, providing a crude HAN compound. Optionally, after adding acetic acid, the mixture is evaporated and the residue is combined with ethylacetate. The undissolved particles are then, filtered off, and the filtrate is concentrated, providing a crude HAN compound.

The present invention further provides a process for the preparation of a HAN-salt of formula VIs,

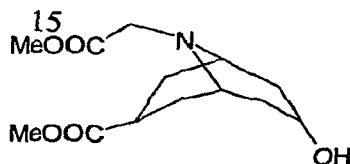


comprising reacting the HAN compound of formula VI,

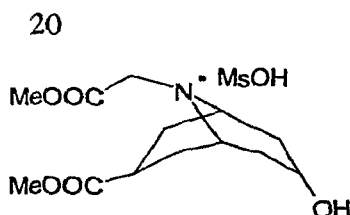


an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone and a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and mixtures thereof, wherein, Z, R₁ and R₂ are described before. 10

When R₁ and R₂ are methyl, said HAN compound of formula VI corresponds to HAN of the following formula,



and when R₁ and R₂ are methyl Z is methane sulfonic acid, said HAN-salt of formula VI corresponds to HAN-MsOH of the following formula.



The process for preparing the HAN compound of formula VI may further comprise a process for converting it to a DLS-salt of formula VIII. 25

The present invention also provides a process for purifying the HAN compound of formula VI comprising combining the HAN compound of formula VI,

an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone and a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and mixtures thereof; and adding a base.

The HAN compound of formula VI used as a starting material may be a crude HAN compound. 5

Preferably, the HAN compound of formula VI is dissolved in an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, linear, branched or cyclic C₂₋₈ ethers, a C₃₋₆ ketone and a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and mixtures thereof, prior to adding the acid. 10

Preferably, the C₁₋₄ alcohol is a C₁₋₃ alcohol. Preferably, the C₁₋₃ alcohol is methanol, ethanol, *n*-propanol, or isopropanol. A preferred C₂₋₈ ester is a C₂₋₆ ester, more preferably a C₄₋₆ ester. A preferred C₄₋₆ ester is ethyl acetate, propyl acetate, butyl acetate, or isobutyl acetate. A preferred linear, branched or cyclic C₂₋₈ ether is a C₂₋₇ ether, more preferably a C₂₋₆ ether. A preferred C₂₋₆ ether is tetrahydrofuran, 1,4-dioxane, diisopropyl ether, or *t*-butyl methyl ether. Preferably, the C₃₋₆ ketone is a C₃₋₅ ketone. Preferably, the C₃₋₅ ketone is acetone, methyl ethyl ketone (2-butanone), 2-pentanone, 3-pentanone, or 3,3-dimethyl-2-butanone. Preferably, the C₅₋₈ aliphatic hydrocarbon is a C₅₋₇ aliphatic hydrocarbon, more preferably a C₆₋₇ aliphatic hydrocarbon. A preferred C₆₋₇ aliphatic hydrocarbon is either *n*-hexane, or *n*-heptane. A preferred C₁₋₈ halogenated hydrocarbon is a C₁₋₆ halogenated hydrocarbon, more preferably a C₁₋₄ halogenated hydrocarbon, most preferably a C₁₋₂ halogenated hydrocarbon. A preferred C₁₋₂ halogenated hydrocarbon is dichloromethane, dichloroethane, or chloroform. A preferred C₁₋₄ nitroalkane is a C₁₋₂ nitroalkane. Preferably, the C₁₋₂ nitroalkane is nitromethane or nitroethane. Preferably, the C₁₋₄ alkylcyanide is a C₁₋₃ alkylcyanide. A preferred C₁₋₃ alkylcyanide is either acetonitrile or propionitrile. A preferred C₆₋₈ aromatic hydrocarbon is a C₆₋₇ aromatic hydrocarbon. Preferably, the C₆₋₇ aromatic hydrocarbon is toluene. A preferred C₃₋₁₀ amide is a C₃₋₆ amide. Preferably, the C₃₋₆ amide is dimethylformamide. The more preferred solvent for dissolving the HAN compound of formula VI is a C₂₋₄ ester, most preferably, ethylacetate. 20 25 30

Preferably, the acid is the same as the acid in the process for preparing the purified OAN compound of formula V. The more preferred acid is methane sulfonic acid.

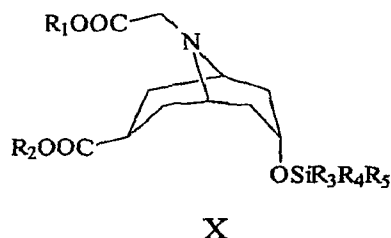
Combining the HAN compound of formula VI, the solvent and the acid provides a mixture. Preferably, the mixture is maintained at a temperature of about 10°C to about 60°C, more preferably, at a temperature of about 20°C to about 50°C, most preferably at a temperature of about 30°C to about 40°C. The mixture is preferably maintained at such temperature for about 0.5 hours to about 24 hours, and more preferably for about 1 hour to about 3 hours, most preferably for about 2 hours. Maintaining the reaction mixture is preferably done while stirring.

Preferably, reacting the HAN compound with an acid provides a corresponding HAN-salt of formula VI_s. Preferably, the HAN-salt of formula VI_s precipitates from the reaction mixture. Preferably, in a process for purifying the HAN compound of formula VI, the HAN-salt of formula VI_s is reacted with a base, providing the HAN compound of formula VI back again. Preferably, the precipitate is recovered prior to reacting with a base.

Preferably, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. More preferably, the base is sodium bicarbonate.

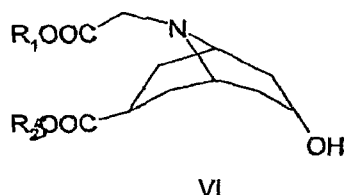
The process for preparing a HAN-salt of formula VI_s may further comprise a process for converting it to a DLS-salt of formula VIII_s.

The present invention further provides a process for the preparation of a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-trialkylsilyloxy-9-azabicyclo[3.3.1]-nonane compound (referred to as a SAN compound) of formula X



wherein R₁ and R₂ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl, preferably, a C₁₋₄ alkyl, more preferably, methyl, and R₃R₄R₅ are independently a C₁₋₆ alkyl or a C₆₋₈

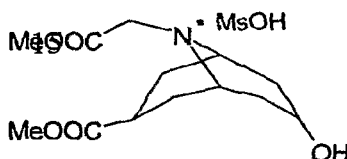
aryl, preferably, *tert*-butyldialkyl, more preferably, *tert*-butyldimethyl comprising combining a HAN compound of formula VI or a salt thereof



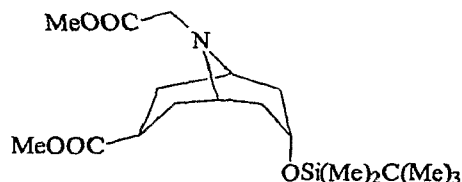
a silylating agent selected from the group consisting of: silanes, silyl halogenides, silyl cyanides, silyl amines, silyl amides, silyl trifluoromethanesulfonates (silyl triflates), silazanes, a base, and an a-protic organic solvent forming a mixture to obtain the SAN compound of formula X, wherein, R₁ and R₂ and Z are described before.

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When R₁ and R₂ are methyl, and Z is MsOH, said compound of formula VI corresponds to HAN-MsOH of the following formula,



and said compound of formula X corresponds to SAN of the following formula.



Preferably, the HAN-salt of formula VI is combined with an a-protic organic solvent. Preferably, the a-protic organic solvent is selected from a group consisting of a C₁₋₈ halogenated hydrocarbon, a C₂₋₈ ester, a C₂₋₈ ether, C₆₋₈ aromatic hydrocarbon, C₃₋₁₀ amide, and a C₃₋₆ ketone to obtain a suspension. A preferred C₁₋₈ halogenated hydrocarbon is a C₁₋₅ halogenated hydrocarbon, more preferably, a C₁₋₃ halogenated hydrocarbon. Preferably, the a C₁₋₃ halogenated hydrocarbon is dichloromethane, 1,2-dichloroethane or chloroform. A preferred C₂₋₈ ester is a C₄₋₆ ester. Preferably, the C₄₋₆ ester is ethyl acetate, *n*-butyl acetate or isobutyl acetate. A preferred C₂₋₈ ether is a C₄₋₆ ether. Preferably, the C₄₋₆ ether is diethyl ether, diisopropyl ether or *tert*-butyl methyl ether. A preferred C₆₋₈ aromatic hydrocarbon is a C₆₋₇ aromatic hydrocarbon.

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Preferably, the C₆₋₇ aromatic hydrocarbon is toluene. A preferred C₃₋₁₀ amide is a C₃₋₆ amide. Preferably, the C₃₋₆ amide is dimethylformamide. A preferred C₃₋₆ ketone is a C₄₋₆ ketone. Preferably, the C₄₋₆ ketone is methyl ethyl ketone (2-butanone), 2-pentanone, 3-pentanone or 3,3-dimethyl-2-butanone. The preferred solvent is dichloromethane.

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The base is added to the suspension, providing a solution. Preferably, about 2 to about 10 mole equivalent of base per mole equivalent of the HAN-salt is used. More preferably, about 3 to about 6 mole equivalent of base per mole equivalent of the HAN-salt is used. Preferably, the base is selected from the group consisting of: sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate, potassium bicarbonate, trialkyl amines, and N-containing heterocycles. Preferably, the trialkylamine is triethylamine, diisopropylethyl amine or tributyl amine. A preferred N-containing heterocycle is piperidine, pyridine, pyrimidine, piperazine, triazine, pyrrolidine, imidazole, or triazole. The preferred base is an N-containing heterocycle, more preferably, imidazole.

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Preferably, the base is added at a temperature of about 15°C to about 55°C, more preferably, at 20°C to about 25°C.

Preferably the silane is selected from the groups consisting of triethylsilane, triisopropylsilane, and triphenylsilane. Preferably the silyl halogenide is selected from the group consisting of trimethylsilyl chloride, *tert*-butyldimethylsilyl chloride, and *tert*-butyldiphenylsilyl chloride. Preferably the silyl cyanide is selected from the group consisting of trimethylsilyl cyanide, triethylsilyl cyanide, and *tert*-butyldimethylsilyl cyanide. Preferably the silyl amine is trimethylsilyldiethylamine or triethylsilyldiethylamine. Preferably the silyl amide is selected from the group consisting of *N*-methyl-*N*-trimethylsilylacetamide, *N*-methyl-*N*-triethylsilylacetamide, and *tert*-butyldimethylsilyl-*N*-methyltrifluoroacetamide. Preferably the silyl triflate is selected from the group consisting of trimethylsilyl trifluoromethanesulfonate, triethylsilyl trifluoromethanesulfonate, and *tert*-butyldimethylsilyl trifluoromethanesulfonate. Preferably the silazane is hexamethyldisilazane or hexaethyldisilazane. Preferably, the silylating agent is trialkylsilyl halogenide. Preferably, the alkyl group is *t*-butyldimethyl. The preferred silylating agent is *tert*-butyldimethylsilyl chloride. Preferably, the silylating agent is added to the solution, providing a reaction mixture.

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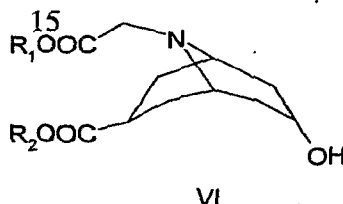
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Preferably, about 1 to about 4 mole equivalent of silylating agent per mole equivalent of the HAN-salt is used. More preferably, about 1.5 to about 2.5 mole equivalent of silylating agent per mole equivalent of the HAN-salt is used. Preferably, the mixture is maintained at a temperature of about 0°C to about 80°C, more preferably, more preferably at a temperature of about 20°C to about 60°C, most preferably, at about 40°C to about 60°C. Preferably, the mixture is maintained for about 0.5 hours to about 24 hours, and more preferably, for about 4 to about 12 hours.

The progress of the reaction may be monitored by HPLC or by TLC. When monitored by TLC, an eluent of ethyl acetate is used

The process for preparing the SAN compound of formula X may further comprise a recovery step. The SAN compound of formula X may be recovered by extracting the product with water, and evaporating the solvent.

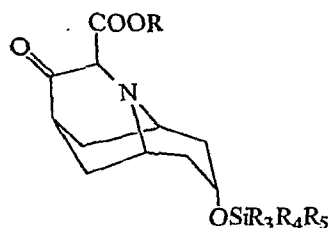
The SAN compound of formula X may also be prepared from the HAN compound of formula VI



using similar conditions as used when the HAN-salt of formula VI is the starting material, however, a smaller amount of base and of a silylated agent may be used and the most preferred solvent is dichloromethane. Preferably, when the HAN compound of formula VI is the starting material, about 1 to about 5 mole equivalent of base per mole equivalent of the HAN compound is used, more preferably, about 1 to about 3 mole equivalent of base per mole equivalent of the HAN compound is used. Preferably, about 1 to about 3 mole equivalent of silylating agent per mole equivalent of the HAN compound is used. More preferably, about 1 to about 2 mole equivalent of silylating agent per mole equivalent of the HAN compound is used.

The process for preparing the SAN compound of formula X may further comprise a process for converting it to a DLS-salt of formula VIIIs.

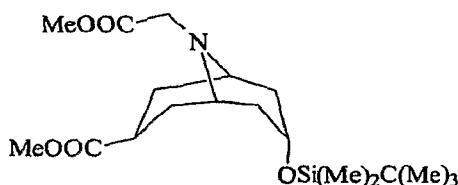
The present invention provides a process for the preparation of a SQO compound of formula XII



XII

comprising mixing a SAN compound of formula X, a metal alkoxide, and a polar aprotic organic solvent to form a mixture; heating the mixture; and reacting this mixture with a weak acid, forming the SQO compound of formula XII, wherein, R, R₃R₄ and R₅ are described before.

When R is methyl, and R₃R₄R₅ are *tert*-butyldimethyl said compound of formula XII corresponds to SQO of the following formula.



A preferred polar aprotic organic solvent is selected from the group consisting of a C₂₋₈ ether having a boiling point of about 60°C to about 100°C. Preferably, the C₂₋₈ ether having a boiling point of about 60°C to about 100°C is tetrahydrofuran (referred to as THF), 2-methyltetrahydrofuran, tetrahydropyran, monoglyme, diisopropyl ether, or methyl *t*-butyl ether. The more preferred polar aprotic organic solvent is THF.

Preferably, the SAN compound of formula X is dissolved in a polar aprotic organic solvent, prior to adding the metal alkoxide.

Preferably, the metal alkoxide is selected from the group consisting of lithium alcoholates, sodium alcoholates and potassium alcoholates; wherein the alcoholate moiety contains 1 to 4 carbons. More preferably, the metal alkoxide is potassium *tert*-butoxide.

Combining the SAN compound of formula X, the polar aprotic organic solvent and the metal alkoxide provides a solution. Preferably, the solution is heated to a temperature of about 40°C to about 120°C, more preferably, to a temperature of about 60°C to about 80°C. The solution is heated, preferably, for about 0.5 hours to

about 8 hours, and more preferably, for about 1 hour to about 3 hours. Heating the solution is preferably done under stirring.

While heating, the solution is concentrated, preferably, by distillation of the polar a-protic organic solvent, providing a mixture. The mixture is, preferably, cooled to a temperature of about 0°C to about 30°C, more preferably, to a temperature of about 15°C to about 25°C, prior to reacting with the acid. 5

Preferably, the weak acid is selected from the group consisting of acetic acid, formic acid, propionic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids. Preferably, the acid is a water miscible organic acid, preferably acetic acid, more preferably acetic acid combined with water, providing a diluted aqueous solution of acetic acid. Preferably, the acid is added to the cooled mixture, providing an acidic mixture, prior to recovering the SQO compound of formula XII. Preferably, the pH of the acidic mixture is of about 4 to about 6, more preferably, of about 5 to about 6. 10 15

The process for preparing the SQO compound of formula XII may further comprise a step of recovering it. The recovery may be carried out by any known method. The SQO compound of formula XII may be recovered by a process comprising combining the acidic mixture with a base, providing a slight basic mixture; concentrating the slight basic mixture; precipitating the SQO compound of formula XII; and recovering it. 20

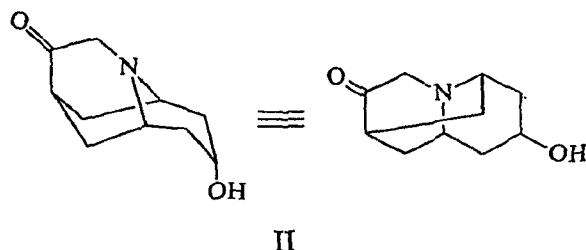
Preferably, the pH of the slightly basic mixture is of about 7 to about 8. Preferably, the base is selected from a group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. The more preferred base is sodium bicarbonate. 25

Preferably, the basic mixture is concentrated by removing the polar a-protic organic solvent. Preferably, removal of the polar a-protic organic solvent is done by distillation. The removal of the polar a-protic organic solvent provides a concentrated aqueous mixture. Preferably, the precipitation of the SQO compound of formula XII is done by cooling the concentrated aqueous mixture to about 0°C to about 10°C, preferably about 2°C to about 8°C. The cooled concentrated aqueous mixture is maintained, preferably, for about 3 hours to about 24 hours, and more preferably, for 30

about 8 hours to about 18 hours, prior to filtering the precipitate. The filtered SQO compound of formula XII is washed with water, and dried.

The process for preparing the SQO compound of formula XII may further comprise a process for converting it to a DLS-salt of formula VIII.

The present invention also provides a process for preparing HQO of formula II 5



comprising mixing a SQO compound of formula XII, a solvent selected from the group consisting of water and a water-miscible organic solvent, and an acid to obtain HQO. 10

Preferably, the acid is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids. 15

Preferably, the SQO compound of formula XII is combined with water or a water-miscible organic solvent to obtain a suspension. Preferably, the water-miscible organic solvent is dimethylformamide, dimethylacetamide, dimethyl sulfoxide, or diglyme, more preferably dimethylformamide. Preferably, the SQO compound of formula XII is combined with water at a temperature of about 10°C to about 50°C, more preferably, at 20°C to about 25°C. 20

Preferably, the acid is added to the suspension providing a solution. Preferably, the addition of the acid provides an acidic solution. Preferably, the acidic solution has a pH of about 0.5 to about 3, more preferably, of about 1 to about 2.

The acidic solution is heated, preferably, to a temperature of about 80°C to about 100°C. The heated solution is maintained, preferably, for about 3 hours to about 24 hours, and more preferably, for about 6 hours to about 10 hours. Heating the solution is preferably done while stirring. 25

The progress of the reaction may be monitored by HPLC or by TLC. When monitored by TLC, an eluent of methylene chloride and methanol in a ratio of 1:1 is used.

The process for preparing HQO of formula II may further comprise a recovery step. The recovery may be carried out by any known method. HQO of formula II may be recovered by cooling the heated acidic solution, adding a base to the cooled acidic mixture, extracting the product with a water immiscible organic solvent, and evaporating the water immiscible organic solvent to obtain HQO of formula II.

Preferably, the heated solution is cooled to a temperature of about 0°C to about 30°C, more preferably, to a temperature of about 15°C to about 25°C.

Preferably, a base is added to the cooled solution. Preferably, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. The more preferred base is sodium hydroxide. Preferably, the addition of the base provides a basic mixture. Preferably, the basic mixture has a pH of about 8 to about 13, more preferably, of about 11 to about 12.

The preferred water immiscible organic solvent is selected from the group consisting of a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone and a C₅₋₈ aliphatic hydrocarbon, and a C₁₋₈ halogenated hydrocarbon. The most preferred water immiscible organic solvent is methylene chloride. A preferred C₂₋₈ ester is a C₄₋₆ ester. Preferably, the C₄₋₆ ester is ethyl acetate, *n*-butyl acetate or isobutyl acetate. A preferred C₂₋₈ ether is a C₄₋₆ ether. Preferably, the C₄₋₆ ether is diethyl ether, diisopropyl ether or *tert*-butyl methyl ether. A preferred C₃₋₆ ketone is a C₄₋₆ ketone. Preferably, the C₄₋₆ ketone is methyl ethyl ketone (2-butanone), 2-pentanone, 3-pentanone or 3,3-dimethyl-2-butanone. A preferred C₅₋₈ aliphatic hydrocarbon is a C₆₋₇ aliphatic hydrocarbon. Preferably, the C₆₋₇ aliphatic hydrocarbon is *n*-hexane or *n*-heptane. A preferred C₁₋₈ halogenated hydrocarbon is a C₁₋₂ halogenated hydrocarbon. Preferably, the C₁₋₂ halogenated hydrocarbon is dichloromethane, 1,2-dichloroethane or chloroform.

Optionally, HQO of formula II may be prepared directly from the SAN compound of formula X, i.e., without isolating the SQO compound of formula XII. Preferably, the reaction may include the same steps as described in the process for preparing the SQO compound of formula XII, but using a strong acid instead of a weak acid, and heating. Preferably, the strong acid is selected from the group

consisting of methanesulfonic acid, sulfuric acid, phosphoric acid, hydrochloric acid, hydrobromic acid, and triflic acid.

This process for preparing HQO of formula II from the SQO compound of formula XII or directly from the SAN compound of formula X may further comprise a process for converting it to a DLS-salt of formula VIIIs.

Preferably, reacting SAN with an acid provides the corresponding salt of HQO, a HQO-salt of formula IIs. Preferably, the HQO-salt of formula IIs precipitates in the reaction mixture. Preferably, the HQO-salt of formula IIs is reacted with a base, providing HQO of formula II back again. Preferably, the precipitate is recovered prior to reacting with a base.

Preferably, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate, and potassium bicarbonate, more preferably sodium bicarbonate.

The present invention also provides another process for the preparation of a HQO-salt of formula IIs comprising combining HQO, an alcohol and an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic, and disulfonic acid to obtain a HQO salt of formula IIs.

The present invention provides a process for purifying HQO of formula II by a process comprising combining HQO of formula II, an alcohol and an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic, and disulfonic acid forming a mixture, and adding a base to obtain purified HQO.

Preferably, the alcohol is a C₁₋₄ alcohol, more preferably, ethanol.

Preferably, the acid is an organic acid, more preferably, a sulfonic acid, most preferably, methanesulfonic acid.

The process for preparing a HQO-salt of formula IIs can further comprise a process for converting it to a DLS-salt of formula IIIs.

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HQO-salt of formula IIs may be converted to a DLS-salt of formula IIIs comprising converting it to the free base, HQO of formula II; reacting HQO with a base to form a reaction mixture; mixing the reaction mixture with an anhydride, indole-3-carboxylic acid, an organic solvent, and a catalyst to form a mixture; and reacting the mixture with an acid, to obtain the DLS-salt of formula IIIs.

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Preferably, the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate. The more preferred base is sodium bicarbonate.

Preferably, the organic solvent is selected from the group consisting of a C₁₋₂ halogenated hydrocarbon, a C₆₋₈ aromatic hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkyl cyanide, trifluoroacetic acid and mixtures thereof. A preferred C₁₋₂ halogenated hydrocarbon is dichloromethane, 1,2-dichloroethane or chloroform, more preferably dichloromethane. A preferred C₆₋₈ aromatic hydrocarbon is benzene, toluene or xylol, more preferably toluene. Preferably, the C₁₋₄ nitroalkane is a C₁₋₂ nitroalkane, either nitromethane or nitroethane, more preferably nitromethane. Preferably, the C₁₋₄ alkyl cyanide is a C₁₋₂ alkyl cyanide, either acetonitrile or propionitrile, more preferably acetonitrile.

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Preferably, the anhydride is either trifluoroacetic anhydride or methyl chlorocarbonate, more preferably, trifluoroacetic anhydride.

Preferably, indole-3-carboxylic acid is added drop-wise, more preferably, over a period of about 10 minutes to about 30 minutes, preferably about 15 minutes.

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Preferably, the catalyst is either a saturated trisubstituted amine or an aromatic amine. Preferably, the saturated trisubstituted amine is either a trialkyl amine or 4-dialkylaminopyridine amine. Preferably, the trisubstituted amine is 4-dimethylaminopyridine or diisopropylethylamine, more preferably, 4-dimethylaminopyridine.

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Preferably, HQO and the catalyst are added at the same time to a solution of the anhydride, the organic solvent and the 3-indole-carboxylic acid, providing a reaction mixture. Preferably, the reaction mixture is heated to a temperature of about 25°C to about 40°C, more preferably to about 30°C to about 35°C, for about 2 to about 18 hours, more preferably for about 2 hours, and preferably while stirring, providing Dolasetron base. 5

Dolasetron base may be recovered by removing the solvent to obtain a precipitate and filtering off the precipitate.

Dolasetron may be converted to Dolasetron salt by combining Dolasetron with an acid. Preferably, Dolasetron may be converted to Dolasetron mesylate monohydrate by combining Dolasetron, a mixture of acetone and water, and methane sulfonic acid. 10

Combining Dolasetron and the mixture of acetone and water provides a suspension, in which the solid dissolves when adding methane sulfonic acid. After complete dissolution, a precipitate of DLS-MsOH is obtained. The precipitate may be maintained in a fridge, and recovered by filtration, washing and drying. 15

Having thus described the invention with reference to particular preferred embodiments and illustrative examples, those in the art can appreciate modifications to the invention as described and illustrated that do not depart from the spirit and scope of the invention as disclosed in the specification. The Examples are set forth to aid in understanding the invention but are not intended to, and should not be construed to limit its scope in any way. 20

EXAMPLES

Example 1: Preparation of CCA-epoxide of formula IV 25

CCA-Me ester (37.8 g, 0.3 mol) was dissolved in 60 ml of methanol followed by the addition of hydrogen peroxide (30-35%, 43 ml, 1.3 equiv.) and sodium tungstate dihydrate (2 g, 2 mol%). The yellow reaction mixture was refluxed slightly (at 60-65°C) for 2-4 hours until the reaction was completed (GC or TLC: eluent *n*-hexane-ethyl acetate 1:1, visualized by iodine). After cooling it was extracted with methylene 30

chloride (3×100 ml). The combined organic phases were dried on sodium sulfate and evaporated to dryness. The product was 40.5 g colorless oil (95% yield).

Example 2: Preparation of OAN of formula V

To a well-stirred solution of periodic acid (32 g, 0.14 mol) in water (200 ml) was added CCA-epoxide (19 g, 0.14 mol), and the reaction mixture was stirred at 10-15°C for 1 hour. After completion, the reaction mixture having a pH of 1, was cooled and the pH was adjusted to 3.5-4 by the addition of OH-resin (or poly(4-vinylpyridine)), followed by stirring the mixture for 10-15 min at room temperature. The solid material was filtered through a layer of Celite and washed with water (2×150 ml). To the aqueous solution were added sequentially at room temperature (86 g, 0.42 mol, 3 equiv) potassium hydrogen phthalate, (21 g, 0.17 mol, 1.2 equiv) glycine methyl ester hydrochloride and (25 g, 0.17 mol, 1.2 equiv) 1,3-acetonedicarboxylic acid. The dark red reaction mixture was stirred at room temperature for 18 h (overnight). The undissolved solid was filtered through a layer of Celite, washed with a small volume of water (2×50 ml). To the solution was added, in portions, solid sodium hydrogen carbonate (until pH 7.5-8), then the solution was extracted with isobutyl acetate (5×200 ml). The combined organic phases were dried on sodium sulfate and evaporated to dryness or to a reduced volume of about 40 ml.

TLC: *n*-hexane- ethyl acetate 1:1, visualized by UV-light and/or iodine.

Example 3: Preparation of OAN-MsOH salt of formula Vs

Crude OAN (600 g) was dissolved in isopropanol (3 L) at room temperature followed by the addition of (144 ml, 1 equiv) methanesulfonic acid, under stirring. The mixture was warmed to 30-40°C, and stirred for overnight. The precipitated oil solidified. The salt was filtered at room temperature, washed with isopropanol (600+2×300 ml) and dried.

The overall yield (from CCA-epoxyde): 35-40% (purity: <90%).

Example 4: Preparation of OAN-MsOH salt of formula Vs

OAN solution in isobutyl acetate (1.2 L, containing 600 g of OAN) was combined with ethanol (1.2 L) at room temperature followed by the addition of (144 ml, 1 equiv) methanesulfonic acid, under stirring. The mixture was stirred for 3 hours. The salt was filtered, washed with a mixture of isobutyl acetate-ethanol 1:1 (12×300 ml) and dried.

The overall yield (from CCA-epoxyde): 35-40%.

Example 5: Preparation of HAN of formula VI

Sodium borohydride (71 g, 1.4 equiv.) was dissolved in a mixture of water (500 ml) and aqueous solution of sodium hydroxide (30%, 14 ml). OAN (361 g, 1.34 mol) was dissolved in methanol (3.6 L), and the solution was cooled to 0-5°C. The solution of sodium borohydride was added drop-wise to the solution of OAN in methanol, and the mixture was stirred at 0-5°C for about 1 hour. The reaction was monitored by TLC (eluent: ethyl acetate). After completion of reaction acetic acid (80 ml) was added under stirring while cooling (foaming, warming and precipitating). Water (0.5 L) and methylene chloride (1 L) were added (filtration can be necessary). The aqueous phase was extracted with (2×1 L) of methylene chloride. The combined organic phases were dried on sodium sulfate and evaporated to dryness. The yield was 70%. 5 10

Example 6: Preparation of HAN of formula VI

(14.6 g, 40 mmol) OAN-MsOH was suspended at 20-25°C in (300 ml) ethanol, then to this suspension (4.2 g, 2.8 equiv) sodium borohydride was added in portions in order to keep the inner temperature between 25-35°C. After addition of the reducing agent the reaction mixture was stirred for additional 30 minutes. The conversion was monitored by TLC (eluent: ethyl acetate), when it was complete (4.5 ml) acetic acid was added (pH 6-7) and the mixture was evaporated to dryness on rotavapor at 35-40°C. The residue was mixed with ethyl acetate (60 ml), the unsolved material was filtered off and the filtered material was washed with ethyl acetate (2×20 ml). The filtrate was concentrated on rotavapor at 35-40°C, to obtain 10.2 g (94%) of crude HAN. 15 20

Example 7: Preparation of HAN-MsOH salt of formula VI

Crude HAN (17 g) was dissolved in ethyl acetate (100 ml) at room temperature and (3.6 ml, 1.1 equiv) of methanesulfonic acid was added under stirring. The mixture was heated to 30-40°C, and was stirred for 2 hours. The precipitated oil solidified. The salt was filtered at room temperature, washed with ethyl acetate (2×30 ml) and dried. Yield was 80%. 25 30

Example 8: Preparation of HQO-CSA salt of formula IIs

To a solution of HQO (0.18 g, 1 mmol) in (3 ml) ethanol was added camphorsulfonic acid (0.23 g) in (2.5 ml) ethanol. The mixture was stirred for 20 minutes, filtered, then the solid material was washed with ethyl acetate and dried.

Example 9: Example 13: Preparation of DLS-base with catalyst

To a solution of 52.9 ml (1.3 equiv) trifluoroacetic anhydride in 1.0 L of dry
dichloromethane 47.5 g (1.3 equiv) indole-3-carboxylic acid was added in portions
within 15 minutes. The reaction mixture was cooled to 20-25°C and after 5 minutes
48.5 g (0.27 mol) HQO and 0.33 g (1 mol%) 4-dimethylaminopyridine were added in
one portion. The reaction mixture was heated to 30-35°C and stirred for 2 hours, then
26.5 ml (0.7 equiv) trifluoroacetic anhydride was added. The reaction mixture was
stirred for additional 2 hours, then diluted with 800 ml of 10% sodium carbonate.
From the mixture dichloromethane was distilled off. The precipitated solid was
filtered, washed with water (3×100 ml) and dried. Yield is 97%.
Crude Dolasetron base (84 g) was dissolved in isobutyl acetate (2.6 L) at 95-100°C.
Charcoal (4.2 g) was added to the solution, and after 10 minutes of stirring it was
filtered off, and washed with isobutyl acetate (0.26 L). The solution was evaporated
under reduced pressure to obtain a residue weighing 0.5-0.6 kg, which allowed to cool
to room temperature, and then further cooled in a fridge overnight. The precipitated
crystals were filtered off, washed with isobutyl acetate (2×50 ml), and dried overnight
at 40-45°C under reduced pressure. Yield was 88%.

Example 10: Preparation of DLS-base without catalyst

Indole-3-carboxylic acid (17.7 g, 1.1 equiv.) was added in portions to a solution of
trifluoroacetic anhydride (20 ml, 1.4 equiv.) in a mixture toluene (360 ml) and
trifluoroacetic acid (90 ml), at room temperature (20-25°C), during 15 minutes. After
5-minutes of stirring, *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]-undecan-10-one (18.12
g, 0.1 mol), was added in one portion. The reaction mixture heated to 30-35°C, the
solid phase dissolved. The solution was stirred for 2 hours without external heating.
The trifluoroacetic acid was removed by evaporation under reduced pressure until
starting of crystallization. 10% of an aqueous solution of sodium carbonate (360 ml)
was added, then toluene was removed by evaporation under reduced pressure. The
precipitated Dolasetron base monohydrate was collected by filtration, washed with

water (3×60 ml), and dried overnight at 40°C under reduced pressure. The dry product was weighed as 33.63 g (98%).

The dried crude Dolasetron base was dissolved in isobutyl acetate (1 L) at 95-100°C. Charcoal (1.7 g) was added to the solution, and after 10 minutes of stirring it was filtered off, and washed with isobutyl acetate (0.1 L). The solution was evaporated under reduced pressure to obtain a residue weighing 0.20-0.25 kg, which allowed to cool to room temperature, and then further cooled in a fridge overnight. The precipitated crystals were filtered off, washed with isobutyl acetate (2×20 ml), and dried overnight at 40-45°C under reduced pressure. Yield was 88%. 5

Example 11: Preparation of DLS-MsOH of formula VIII 10

Methanesulfonic acid (2.85 ml, 1 equiv) was added to a stirred suspension of Dolasetron base (14.24 g, 43.9 mmol) in a mixture of acetone-water 95:5 (100 ml). The solid dissolved immediately, after some minutes the salt precipitated in crystalline form. The mixture was put into fridge, after 4 hours the salt was filtered off, washed with same solvent mixture (2×15 ml), dried overnight in an air-ventilated oven at 40°C. The yield was 15.63 g (81%). 15

Example 12: Preparation of SAN from HAN

In a 250-ml flask HAN (41 mmol) was dissolved in methylene chloride (120 ml). The solution was mixed with 1.5 equiv (7 g) of imidazole at 20-25°C. After complete dissolution, to this solution 1.3 equiv (12.4 g) of *tert*-butyldimethylsilyl chloride was added and the reaction mixture was stirred for 6 hours. The conversion was monitored by TLC (eluent: ethyl acetate). The reaction mixture was washed with water (2×40 ml). The combined aqueous layer was washed with methylene chloride (120 ml). The combined organic phase was dried on sodium sulfate, evaporated to dryness on rotavapor at 40-45°C. The product was about 19 g of oil. 20 25

Example 13: Preparation of SAN from HAN-mesylate

In a 500-ml flask HAN-mesylate (70 mmol) was mixed with methylene chloride (260 ml). To the suspension 4.5 equiv (21 g) of imidazole was added at 20-25°C. After complete dissolution, to this solution 2 equiv (21 g) of *tert*-butyldimethylsilyl chloride was added and the reaction mixture was stirred for 2 days at 40-45°C. The conversion was monitored by TLC (eluent: ethyl acetate). The reaction mixture was diluted with methylene chloride (260 ml), washed with water (2×130 ml). The combined organic 30

phase was dried on sodium sulfate, evaporated to dryness on rotavapor at 40-45°C. The product is about 32 g of oil.

Example 14: Preparation of SQO

In a 250-ml flask the crude SAN (ca 19 g, theoretically 41 mmol) was dissolved in THF (190 ml) and potassium *tert*-butoxide (9.2 g, 2 equiv) was added under stirring. 5
The solution was heated to reflux for 2 hours, and 95 ml of THF was distilled off during this reflux period. The mixture was cooled to 20-25°C and aqueous acetic acid (5.4 ml /94 mmol/ of acetic acid in 80 ml of water) was added, then the pH is adjusted to 7-8 by addition of solid sodium hydrogencarbonate (6-7 g). The rest of THF was distilled off, then the aqueous mixture was cooled to 20-25°C, and stored in the fridge 10
(2-8 °C) overnight. The precipitated material was filtered off, washed with water, and dried in vacuum. The product was 7.5 g of white solid.

Example 15: Preparation of HQO from SQO

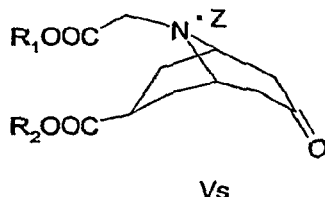
In a 250-ml flask SQO (10.6 g) was suspended in 22 ml of water at 20-25°C and 3 equiv (4.5 ml) cc HCl was added. The obtained clear solution (pH 1) was stirred for 6 15
hours at reflux temperature. The conversion was monitored by TLC (eluent: 1:1 methylene chloride-methanol). The reaction mixture was cooled to 20-25°C and the pH of the solution was adjusted to 12 by addition of solid sodium hydroxide under cooling. The solution was extracted with methylene chloride (5×50 ml). The combined organic phase was dried on sodium sulfate, and evaporated to dryness on 20
rotavapor at 30-35°C. The residue was 4.7 g of white solid.

Example 16: Preparation of HQO from SAN

In a 250-ml flask the crude SAN (ca 4 g, theoretically 10 mmol) was dissolved in THF (50 ml) and potassium *tert*-butoxide (1.6 g, 1.4 equiv) was added under stirring. 25
The solution was heated to reflux for 2 hours, and 25 ml of THF was distilled off during this reflux period. The mixture was cooled to 20-25°C, diluted with water (15 ml), and the pH was adjusted to 1 with concentrated HCl. The rest of THF was distilled out, and the mixture was refluxed for 6 hours, then cooled to 20-25°C. The pH of the solution was adjusted to 12 by addition of solid sodium hydroxide under cooling. The basic solution was extracted with methylene chloride (5×30 ml). The 30
combined organic phase was dried on sodium sulfate, and evaporated to dryness. The residue was 0.82 g of brownish solid.

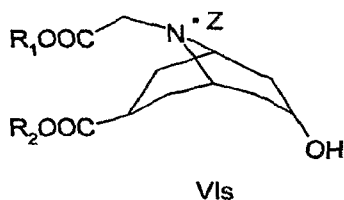
Claims

1. A quaternary ammonium salt of a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-one compound (an OAN salt) of formula Vs,



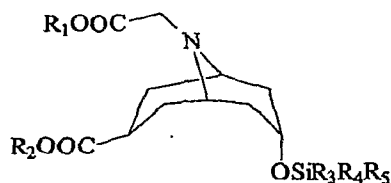
wherein R_1 and R_2 are independently a C_{1-6} alkyl or a C_{6-8} aryl, and Z is an acid.

2. The quaternary ammonium salt of claim 1, wherein R_1 and R_2 are a C_{1-4} alkyl.
3. The quaternary ammonium salt of claim 2, wherein R_1 and R_2 are methyl and Z is methanesulfonic acid (OAN-MsOH).
4. The quaternary ammonium salt of claim 3, wherein the quaternary ammonium salt is crystalline.
5. The quaternary ammonium salt of claim 4, wherein the quaternary ammonium salt is crystalline OAN-MsOH is characterized by an XRD diffraction pattern having peaks at about 8.5, 18.0, and 20.9 degrees two-theta, ± 0.2 degrees two-theta.
6. The quaternary ammonium salt of claim 5, wherein crystalline OAN-MsOH is further characterized by the XRD diffraction pattern having peaks at about 14.7, 22.7, 24.3, 25.0, 26.3 and 27.9 degrees two-theta, ± 0.2 degrees two-theta.
7. The quaternary ammonium salt of claim 6, wherein the crystalline OAN-MsOH is characterized having a PXRD pattern as depicted in Figure 1.
8. A quaternary ammonium salt of 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-ol (a HAN salt) of formula VIs,



wherein R_1 and R_2 are independently a C_{1-6} alkyl or a C_{6-8} aryl, and Z is an acid.

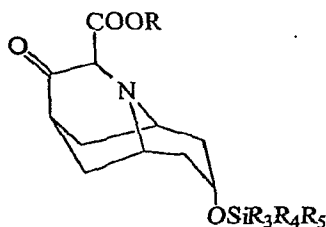
9. The quaternary ammonium salt of claim 8, wherein R_1 and R_2 are C_{1-4} alkyl.
10. The quaternary ammonium salt of claim 9, wherein R_1 and R_2 are methyl and Z is methanesulfonic acid (HAN-MsOH).
11. The quaternary ammonium salt of claim 10, wherein the quaternary ammonium salt is crystalline.
12. The quaternary ammonium salt of claim 11, wherein the quaternary ammonium salt is crystalline HAN-MsOH characterized by an XRD diffraction pattern having peaks at about 7.3, 11.6, and 14.6 degrees two-theta, ± 0.2 degrees two-theta.
13. The quaternary ammonium salt of claim 12, wherein crystalline HAN-MsOH is further characterized by the XRD diffraction pattern having peaks at about 15.9, 17.9, 19.0, 20.4, 21.9, 29.0 and 29.4 degrees two-theta, ± 0.2 degrees two-theta.
14. The quaternary ammonium salt of claim 13, wherein the crystalline HAN-MsOH is characterized having a PXRD pattern as depicted in Figure 2.
15. A 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-trialkylsilyloxy-9-azabicyclo[3.3.1]nonane compound (a SAN compound) of formula X



X

wherein R_1 and R_2 are independently C_{1-6} alkyl or C_{6-8} aryl, and $R_3R_4R_5$ are independently a C_{1-6} alkyl or a C_{6-8} aryl, or $R_3R_4R_5$ together are a *tert*-butyldialkyl.

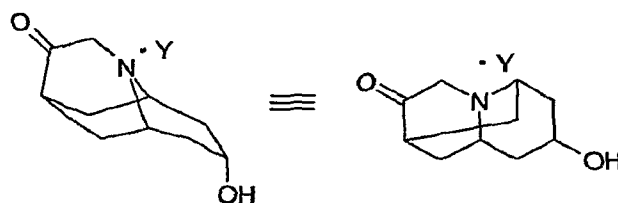
16. The compound of claim 15, wherein R_1 and R_2 are C_{1-4} alkyl.
17. The compound of claim 16, wherein R_1 and R_2 are methyl and $R_3R_4R_5$ is *tert*-butyldimethyl (SAN).
18. An *endo*-9-alkoxycarbonyl-5-trialkylsilyloxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one compound (a SQO compound) of formula XII



XII

wherein R is a C₁₋₆ alkyl or a C₆₋₈ aryl, and R₃R₄R₅ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl, or R₃R₄R₅ together are a *tert*-butyldialkyl.

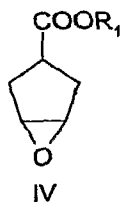
19. The compound of claim 18, wherein R is C₁₋₄ alkyl.
20. The compound of claim 19, wherein R is methyl, and R₃R₄R₅ are together *tert*-butyldimethyl (SQO).
21. The compound of claim 20, wherein the compound is crystalline.
22. The compound of claim 21, wherein the compound is crystalline SQO, characterized by an XRD diffraction pattern having peaks at about 5.1, 10.1, 12.7, and 20.3 degrees two-theta, ± 0.2 degrees two-theta.
23. The quaternary ammonium salt of claim 22, wherein the crystalline SQO is further characterized by the XRD diffraction pattern having peaks at about 15.2, 17.0, 17.6, 18.3, 19.1, and 19.8 degrees two-theta, ± 0.2 degrees two-theta.
24. The quaternary ammonium salt of claim 23, wherein the crystalline SQO is characterized having a PXRD pattern depicted in Figure 3.
25. A quaternary ammonium salt of *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one (a HQO salt) of formula IIs,



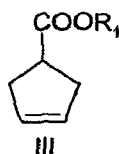
wherein Y an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid,

naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acid.

26. The quaternary ammonium salt of claim 25, wherein Y is Hydrochloric acid (HCl).
27. The quaternary ammonium salt of claim 26, wherein the salt is crystalline.
28. The quaternary ammonium salt of claim 27, wherein the HCl is crystalline characterized by a PXRD pattern as depicted in Figure 4.
29. The quaternary ammonium salt of claim 25, wherein Y is Camphorsulfonic acid (CSA).
30. The quaternary ammonium salt of claim 29, wherein the salt is crystalline.
31. The quaternary ammonium salt of claim 30, wherein the CSA is crystalline characterized by a PXRD pattern as depicted in Figure 5.
32. A method for the preparation of a CCA-epoxide of formula IV



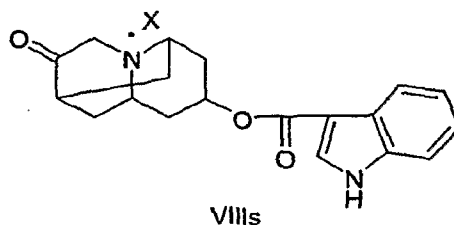
comprising combining a CCA-ester of formula III,



an oxidizing agent, a catalyst, and a solvent selected from the group consisting of water, a water miscible organic solvent, and mixtures thereof forming a mixture, to obtain the CCA-epoxide of formula IV, wherein, R₁ is a C₁₋₆ alkyl or C₆₋₈ aryl.

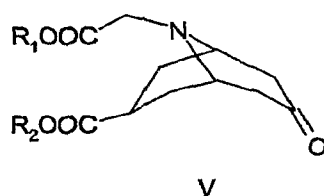
33. The method of claim 32, wherein R₁ is methyl.
34. The method of any one of claims 32 and 33, wherein the oxidizing agent is selected from the group consisting of: hydroxyperoxide, dialkyl peroxide, peroxyacid, peroxyester, diacyl peroxide, persulphate, perborate, and perphosphate.
35. The method of claim 34, wherein the oxidizing agent is a hydroperoxide.

36. The method of claim 35, wherein the hydroperoxide is hydrogen peroxide.
37. The method of any one of claims 32 to 36, wherein the water miscible organic solvent is selected from the group consisting of linear or branched C₁₋₄ alcohols.
38. The method of claim 37, wherein the C₁₋₄ alcohol is methanol.
39. The method of any one of claims 32 to 38, wherein the solvent is a mixture of water and a water immiscible organic solvent in the presence of a phase transfer catalyst.
40. The method of claim 39, wherein the water immiscible organic solvent is selected from the group consisting of a C₁₋₈ halogenated hydrocarbon, a C₂₋₈ ester, a C₂₋₈ ether and a C₃₋₆ ketone.
41. The method of any one of claims 32 to 40, wherein the catalyst is selected from the group consisting of Zeolites and polyoxometalates.
42. The method of claim 41, wherein the metal moiety of the polyoxometalates is selected from the group consisting of tungsten, molybdenum, rhenium, vanadium and niobium.
43. The method of claim 42, wherein the catalyst is either sodium tungstate dihydrate or sodium molybdenate dihydrate.
44. The method of any one of claims 41 and 42, wherein the amount of the catalyst used is about 0.01 mole% to about 50 mole% per mole of the CCA-ester.
45. The method of any one of claims 32 to 44, wherein the reaction mixture is maintained at a temperature of about 0°C to about 80°C.
46. The method of any one of claims 32 to 45, further comprising recovering the CCA-epoxide of formula IV.
47. The method of any one of claims 32 to 46, further comprising converting the CCA-epoxide of formula IV to a Dolasetron (DLS) salt of formula VIIIs,



wherein, X is an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids.

48. The method of claim 47, wherein X is methane sulfonic acid.
49. The method of claim 46, wherein the recovery comprises adding an organic solvent is selected from the group consisting of a C₁₋₂ halogenated hydrocarbon, a C₆₋₈ aromatic hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkyl cyanide, trifluoroacetic acid and mixtures thereof to the mixture.
50. A method for the preparation of a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-one compound (an OAN compound) of formula V

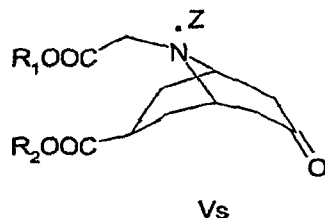


comprising

- a) combining a CCA-epoxide of formula IV, an oxidizing agent, and a solvent selected from the group consisting of water, water miscible organic solvent, and mixtures thereof to form a reaction mixture;
- b) raising the pH of the reaction mixture; and
- c) reacting the reaction mixture of step b) with a pH 4 buffer, a glycine C₁₋₄ ester or salts thereof, and a substance containing a carbonyl moiety selected from the group consisting of 1,3-acetonedicarboxylic acids, acetone and C₁₋₄ esters thereof to form an OAN compound of formula V, wherein R₁ and R₂ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl.
51. The method of claim 50, wherein R₁ and R₂ are methyl.

52. The method of any one of claims 50 and 51, wherein the water miscible organic solvent is selected from the group consisting of: a nitrile, a ketone and an ether.
53. The method of claim 52, wherein the nitrile is a C₂₋₄ nitrile, the ketone is a C₃₋₆ ketone, and the ether is a cyclic ether.
54. The method of any one of claims 50 to 53, wherein the solvent is water.
55. The method of any one of claims 50 to 54, wherein the oxidizing agent is selected from the group consisting of: periodic acid and salts thereof, lead tetraacetate, cerium and ammonium nitrate (Ce(NH₄)₂(NO₃)₆).
56. The method of claim 55, wherein the oxidizing agent is periodic acid.
57. The method of any one of claims 50 to 56, wherein the reaction mixture is maintained at a temperature of about 10°C to about 60°C.
58. The method of claim 57, wherein the pH of the first reaction mixture is of about 0.5 to about 7.
59. The method of claim 58, wherein the pH of the reaction mixture is increased to about 2 to about 7.
60. The method of claim 59, wherein the pH is raised by using a water immiscible base selected from poly(4-vinylpyridine) and OH resins.
61. The method of any one of claims 50 to 60, wherein the pH 4 buffer is an amine-free buffer selected from the group consisting of: citric acid-sodium hydroxide-hydrochloric acid, citric acid-disodium hydrogenphosphate, sodium acetate-acetic acid, potassium diphthalate-sodium hydroxide, sodium dihydrogen phosphate and potassium hydrogen phthalate.
62. The method of claim 61, wherein the amine-free buffer is potassium hydrogen phthalate.
63. The method of any one of claims 61 and 62, wherein the buffer is used in an amount of about 1 to about 10 mole equivalents per mole equivalent of the CCA-epoxide.
64. The method of any one of claims 50 to 63, wherein the glycine C₁₋₄ ester is a methyl ester.
65. The method of claim 64, wherein the glycine C₁₋₄ ester is glycine methylester hydrochloride.
66. The method of any one of claims 50 to 65, wherein the substance comprising a carbonyl moiety is 1,3-acetonedicarboxylic acid.

67. The method of any one of claims 50 to 66, wherein the reaction mixture in step c) is maintained at a temperature of about 0°C to about 60°C.
68. The method of any one of claims 50 to 67, further comprising recovering the OAN compound of formula V.
69. The method of any one of claims 50 to 68, further comprising converting the OAN compound of formula V to a Dolasetron (DLS) salt of formula V_s.
70. The method of claim 69, wherein Dolasetron (DLS) salt is Dolasetron mesylate.
71. The method of any one of claims 50 to 68, further comprising; combining the OAN compound of formula V, an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone, a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and mixtures thereof, forming a mixture to obtain an OAN-salt of formula V_s

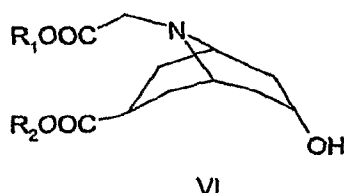


wherein, R₁ and R₂ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl, and Z is an acid.

72. The method of claim 71, wherein Z is methanesulfonic acid.
73. The method of any one of claims 71 and 72, wherein the acid is an organic acid selected from the group consisting of carboxylic acid and sulfonic acid, or an inorganic acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, and fluoroboric acid.
74. The method of claim 73, wherein the acid is selected from the group consisting of: formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid,

naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids.

75. The method of claim 74, wherein the acid is either methane sulfonic acid or camphorsulfonic acid.
76. The method of any one of claims 71 to 75, wherein the mixture of the OAN compound of formula V, the solvent and the acid form is maintained at a temperature of about 10°C to about 60°C.
77. The method of any one of claims 71 to 76, further comprising adding a base, wherein the OAN compound of formula V is obtained as a purified compound.
78. The method of claim 77, wherein the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate.
79. The method of any one of claims 71 to 78, further comprising converting the OAN salt of formula Vs to a Dolasetron (DLS) salt of formula VIIIs.
80. A method of preparing a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-9-azabicyclo[3.3.1]nonane-3-ol compound (a HAN compound) of formula VI

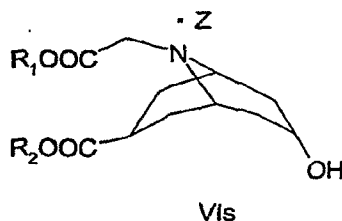


comprising combining an OAN salt of formula Vs, a reducing agent, and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof to form mixture, to obtain an HAN compound of formula VI,

wherein R_1 and R_2 are independently a C_{1-6} alkyl or a C_{6-8} aryl.

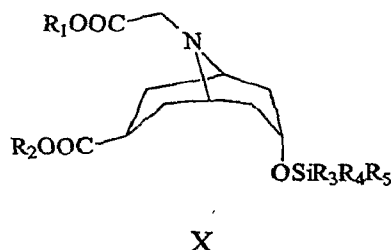
81. The method of claim 80, wherein R_1 and R_2 are methyl.
82. The method of any one of claims 80 and 81, wherein the OAN salt is OAN-MsOH.

83. The method of any one of claims 80 to 82, wherein the water miscible organic solvent is a C₁₋₄ alcohol.
84. The method of claim 83, wherein the C₁₋₄ alcohol is ethanol.
85. The method of any one of claims 80 to 84, wherein the reducing reagent is a metal hydride complex.
86. The method of claim 85, wherein the metal hydride complex is sodium borohydride.
87. The method of any one of claims 80 to 86, wherein the mixture comprising the OAN salt, the water miscible organic solvent, and the reducing agent is maintained at a temperature of about 25°C to about 35°C.
88. The method of any one of claims 80 to 87, further comprising recovering the HAN compound of formula VI.
89. The method of any one of claims 80 to 88, further comprising converting the HAN compound of formula VI to a Dolasetron (DLS) salt of formula VIIIs.
90. The method of claim 89, wherein Dolasetron (DLS) salt is dolasetron mesylate.
91. The method of any one of claims 80 to 88, further comprising combining the HAN compound of formula VI, an acid, and an organic solvent selected from the group consisting of a C₁₋₄ alcohol, a C₂₋₈ ester, a linear, branched or cyclic C₂₋₈ ether, a C₃₋₆ ketone, a C₅₋₈ aliphatic hydrocarbon, a C₁₋₈ halogenated hydrocarbon, a C₁₋₄ nitroalkane, a C₁₋₄ alkylcyanide, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and mixtures thereof, forming a mixture to obtain a HAN-salt of formula VIIs

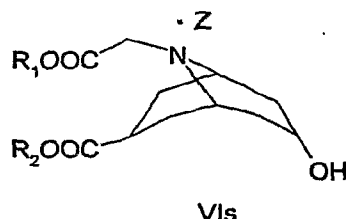


wherein R₁ and R₂ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl and Z is an acid.

92. The method of claim 91, wherein R_1 and R_2 are methyl and Z is methane sulfonic acid.
93. The method of any one of claims 91 and 92, further comprising adding a base, wherein the HAN compound of formula V is obtained as a purified compound.
94. The method of claim 93, wherein the base is selected from the group consisting of sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate and potassium bicarbonate.
95. The method of any one of claims 91 to 94, wherein the organic solvent is ethylacetate
96. The method of any one of claims 91 to 95, further comprising converting the HAN salt of formula VI to a Dolasetron (DLS) salt of formula VIIIs.
97. The method of claim 96, wherein the Dolasetron (DLS) salt is Dolasetron mesylate.
98. A method of preparing a 7-alkoxycarbonyl-9-(alkoxycarbonylmethyl)-3-trialkylsilyloxy-9-azabicyclo[3.3.1]nonane compound (a SAN compound) of formula X



comprising combining a HAN-salt of formula VI



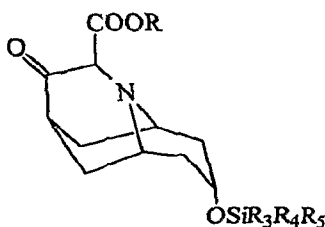
a silylating agent selected from a group consisting of: silanes, silyl halogenides, silyl cyanides, silyl amines, silyl amides, silyl trifluoromethanesulfonates (silyl triflates), and silazanes, a base, and an

aprotic organic solvent, forming a mixture to obtain the SAN compound of formula X,

wherein, R₁ and R₂ are independently C₁₋₆ alkyl or C₆₋₈ aryl, and R₃R₄R₅ are independently C₁₋₆ alkyl or C₆₋₈ aryl, or R₃R₄R₅ together are a *tert*-butyldialkyl, and Z is an acid.

99. The method of claim 98, wherein R₁ and R₂ are methyl, R₃R₄R₅ together are *tert*-butyldimethyl.
100. The method of any one of claims 98 and 99, wherein the a-protic organic solvent is selected from the group consisting of a C₁₋₈ halogenated hydrocarbon, a C₂₋₈ ester, a C₂₋₈ ether, a C₆₋₈ aromatic hydrocarbon, a C₃₋₁₀ amide, and a C₃₋₆ ketone.
101. The method of claim 100, wherein the C₁₋₈ halogenated hydrocarbon is methylene chloride.
102. The method of any one of claims 98 to 101, wherein the amount of base is about 2 to about 10 mole equivalent of base per mole equivalent of the HAN-salt.
103. The method of any one of claims 98 to 102, wherein the base is selected from the group consisting of: sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, potassium carbonate potassium bicarbonate, trialkyl amines, and N-containing heterocycles.
104. The method of claim 103, wherein the base imidazole.
105. The method of any one of claims 103 and 104, wherein about 2 to about 10 mole of base per mole equivalent of the HAN-salt is used
106. The method of any one of claims 98 to 105, wherein the base is added at a temperature of about 15°C to about 55°C.
107. The method of any one of claims 98 to 106, wherein the silylating agent is selected from the group consisting of triethylsilane, triisopropylsilane, and triphenylsilane.
108. The method of any one of claims 98 to 106, wherein the silylating agent is trialkylsilyl halogenide.

109. The method of claim 108, wherein the silylating agent is *tert*-butyldimethylsilyl chloride.
110. The method of any one of claims 108 and 109, wherein the silylating agent is added in an amount of about 1 to about 4 mole equivalent of silylating agent per mole equivalent of the HAN-salt.
111. The method of any one of claims 98 to 110, wherein the mixture is maintained at a temperature of about 20°C to about 60°C.
112. The method of any one of claim 98 to 111, further comprising recovering SAN of formula X.
113. The method of any one of claims 98 to 112 further comprising converting SAN of formula X to Dolasetron salt of formula VIIIs.
114. The method of claim 113, wherein the Dolasetron salt is Dolasetron mesylate.
115. A method of preparing an *endo*-9-alkoxycarbonyl-5-trialkylsilyloxy-8-azatricyclo[5.3.1.0^{3,8}]undecan-10-one compound (a SQO compound) of formula XII



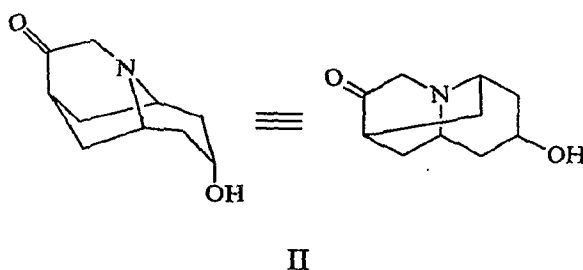
XII

comprising

- a) mixing a SAN compound of formula X, a metal alkoxide, and a polar aprotic organic solvent to form a mixture;
 - b) heating the mixture; and
 - c) reacting the heated mixture of step b) with a weak acid, forming the SQO compound of formula XII,
- wherein, R is a C₁₋₆ alkyl or a C₆₋₈ aryl, and R₃R₄R₅ are independently a C₁₋₆ alkyl or a C₆₋₈ aryl, or R₃R₄R₅ together are a *tert*-butyldialkyl.
116. The method of claim 115, wherein R is methyl and R₃R₄R₅ together are *tert*-butyldimethyl.

117. The method of any one of claims 115 and 116, wherein the polar a-protic organic solvent is selected from a group consisting of C₂₋₈ ethers having a boiling point of about 60°C to about 100°C.
118. The method of claim 117, wherein the polar a-protic organic solvent is THF.
119. The method of any one of claims 115 to 118, wherein the metal alkoxide is selected from the group consisting of lithium alcoholates, sodium alcoholates and potassium alcoholates; wherein the alcoholate moiety contains 1 to 4 carbons.
120. The method of claim 119, wherein the metal alkoxide is potassium *tert*-butoxide.
121. The method of any one of claims 115 to 120, wherein the mixture is heated to a temperature of about 40°C to about 120°C.
122. The method of claim 121, wherein the heated mixture is cooled to a temperature of about 0°C to about 30°C.
123. The method of any one of claims 115 to 122, wherein the weak acid is selected from the group consisting of acetic acid, formic acid, propionic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids
124. The method of claim 123, wherein the acid is acetic acid.
125. The method of any one of claims 123 and 124, wherein the mixture after addition of the acid has a pH of about 4 to about 6.
126. The method of any one of claims 115 to 125, further comprising recovering the SQO compound of formula XII.
127. The method of any one of claims 115 to 126, further comprising converting the SQO compound of formula XII to a Dolasetron (DLS) salt of formula VIII.

128. The method of claim 127, wherein the Dolasetron (DLS) salt of formula VIII is Dolasetron mesylate.
129. A method of preparing *endo*-5-hydroxy-8-azatricyclo[5.3.1.0^{3,8}] undecan-10-one (HQO) of formula II



comprising mixing a SQO compound of formula XII, water or a water-miscible organic solvent, and an acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids, to obtain the HQO compound.

130. The method of claim 129, wherein the water-miscible organic solvent is dimethylformamide, dimethylacetamide, dimethyl sulfoxide, or diglyme.
131. The method of any one of claims 129 and 130, wherein the solvent is water.
132. The method of any one of claims 129 to 131, wherein the SQO compound of formula XII is combined with the solvent at a temperature of about 10°C to about 50°C.
133. The method of any one of claims 129 to 132, wherein the mixture after adding the acid has a pH of about 0.5 to about 3.
134. The method of claim 133, wherein the mixture is heated to a temperature of about 80°C to about 100°C.
135. The method of any one of claims 129 to 134, further comprising recovering HQO of formula II.
136. The method of claim 129, wherein HQO is prepared comprising combining a SAN compound of formula X, in stead of the SQO compound of formula XII.

137. The method of claim 136, further comprising converting the HQO compound of formula II to a Dolasetron (DLS) salt of formula VIIIs.
138. The method of any one of claims 129 to 136, further comprising combining HQO, an alcohol and an acid selected from the group consisting of: hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, salicylic acid, naphthalene carboxylic and dicarboxylic acids, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, benzenesulfonic acid, naphthalene sulfonic, and disulfonic acid to obtain a HQO salt of formula IIs.
139. The method of claim 138, further comprising the step of adding a base to obtain purified HQO.
140. The method of any one of claims 138 and 139, wherein the alcohol is a C₁₋₄ alcohol.
141. The method of any one of claims 129 to 136, further comprising mixing a reaction mixture containing HQO with an anhydride, indole-3-carboxylic acid, an organic solvent, and a catalyst to form a mixture; and reacting the mixture with an acid, to obtain a DLS-salt of formula VIIIs.
142. The method of claim 141, wherein the anhydride is either trifluoroacetic anhydride or methyl chlorocarbonate.
143. The method of any one of claims 141 and 142, wherein the organic solvent is selected from the group consisting of C₁₋₂ halogenated hydrocarbon, C₆₋₈ aromatic hydrocarbon, C₁₋₄ nitroalkane, C₁₋₄ alkyl cyanide, trifluoroacetic acid and mixtures thereof.
144. The method of any one of claims 141 to 143, wherein the catalyst is either a saturated trisubstituted amine or an aromatic amine.
145. The method of any one of claims 141 to 144, wherein the catalyst is absent.
146. The method of any one of claims 141 to 143, wherein HQO and the catalyst are added at the same time to a solution of the anhydride, the organic solvent

and the 3-indole-carboxylic acid, providing a reaction mixture, which is maintained for about 2 to about 18 hours to obtain Dolasetron base.

147. The method of claim 146, wherein Dolasetron is converted to a Dolasetron salt by a process comprising combining Dolasetron, a mixture of acetone and water, and an acid.
148. The method of claim 147, wherein the acid is methane sulfonic acid.
149. The method of any one of claims 147 and 148, wherein combining Dolasetron and the mixture of acetone and water provides a suspension, in which the solid dissolves when adding methane sulfonic acid, and wherein after complete dissolution, a precipitate of DLS-MsOH is obtained.
150. A method of preparing a Dolasetron salt of formula VIII, comprising
 - a) combining a CCA-ester of formula III, an oxidizing agent selected from the group consisting of: hydroperoxides, dialkyl peroxides, peroxyacids, peroxyesters, diacyl peroxides, persulphate, perborate and perphosphate, a catalyst and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof, to form CCA-epoxide of formula IV;
 - b) admixing CCA-epoxide with an oxidizing agent, and a solvent selected from the group consisting of water and a water miscible organic solvent;
 - c) raising the pH;
 - d) admixing with a pH 4 buffer, a glycine C₁₋₄ ester or salts thereof, and a substance comprising a carbonyl moiety selected from the group consisting of 1,3 acetonedicarboxylic acids, acetone and a C₁₋₄ ester thereof, to form OAN of formula V;
 - e) admixing with a reducing agent, and a solvent selected from the group consisting of water, water miscible organic solvents and mixtures thereof, to form HAN of formula VI;
 - f) admixing with a silylating agent selected from a group consisting of: silanes, silyl halogenides, silyl cyanides, silyl amines, silyl amides, silyl trifluoromethanesulfonates (silyl triflates), and silazanes, a base, and an aprotic organic solvent to form SAN of formula X;

- g) admixing with a metal alkoxide, and a polar a-protic organic solvent to form a reaction mixture;
- h) heating the reaction mixture;
- i) quenching with a weak acid selected from the group consisting of acetic acid, formic acid, propionic acid, maleic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, citric acid, mandelic acid, benzoic acid, and salicylic acid forming SQO of formula XII;
- j) admixing with a solvent selected from a group consisting of: water, and water-immiscible organic solvent, and an acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, perchloric acid, fluoroboric acid, methanesulfonic acid, ethanesulfonic acid, trifluoromethanesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, benzenesulfonic acid, naphthalene sulfonic and disulfonic acids to form HQO of formula II;
- k) admixing with an anhydride, 3-indole carboxylic acid, a halogenated hydrocarbon, and a catalyst to obtain Dolasetron abse; and
- l) reacting Dolasetron base with an acid to obtain the DLS-salt of formula VIIIs.

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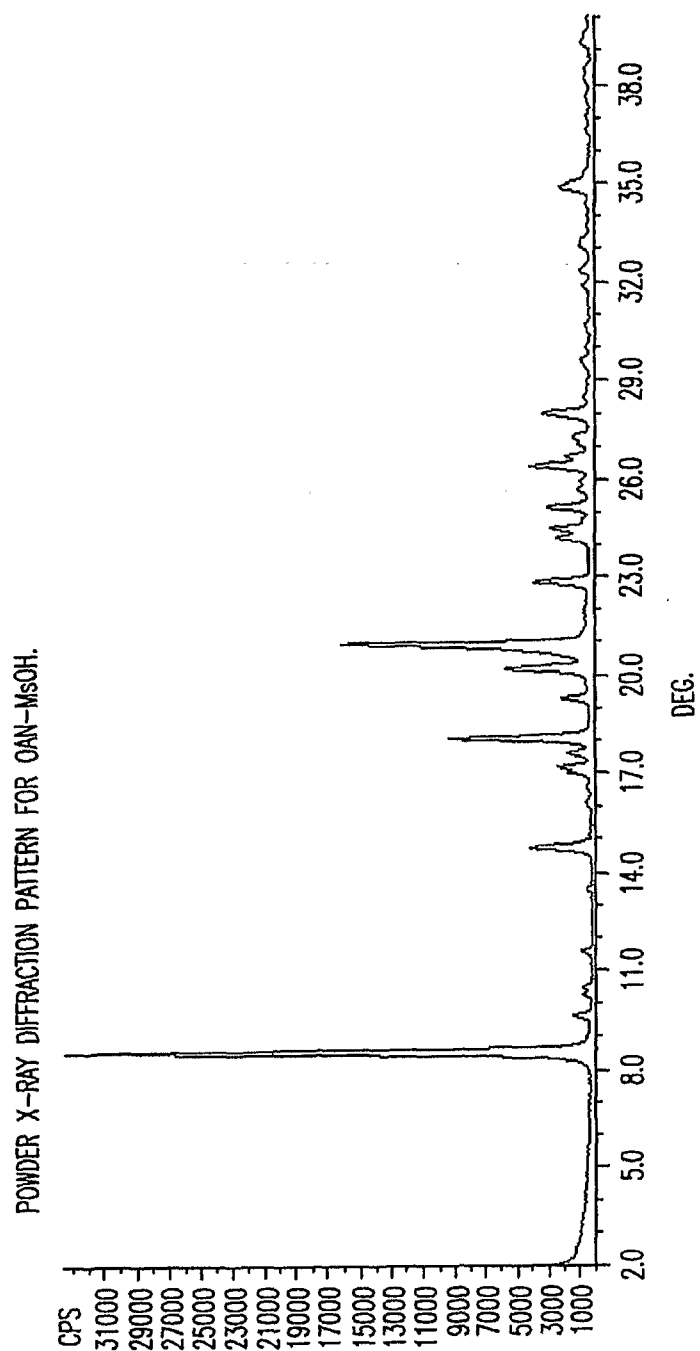


FIG. 1

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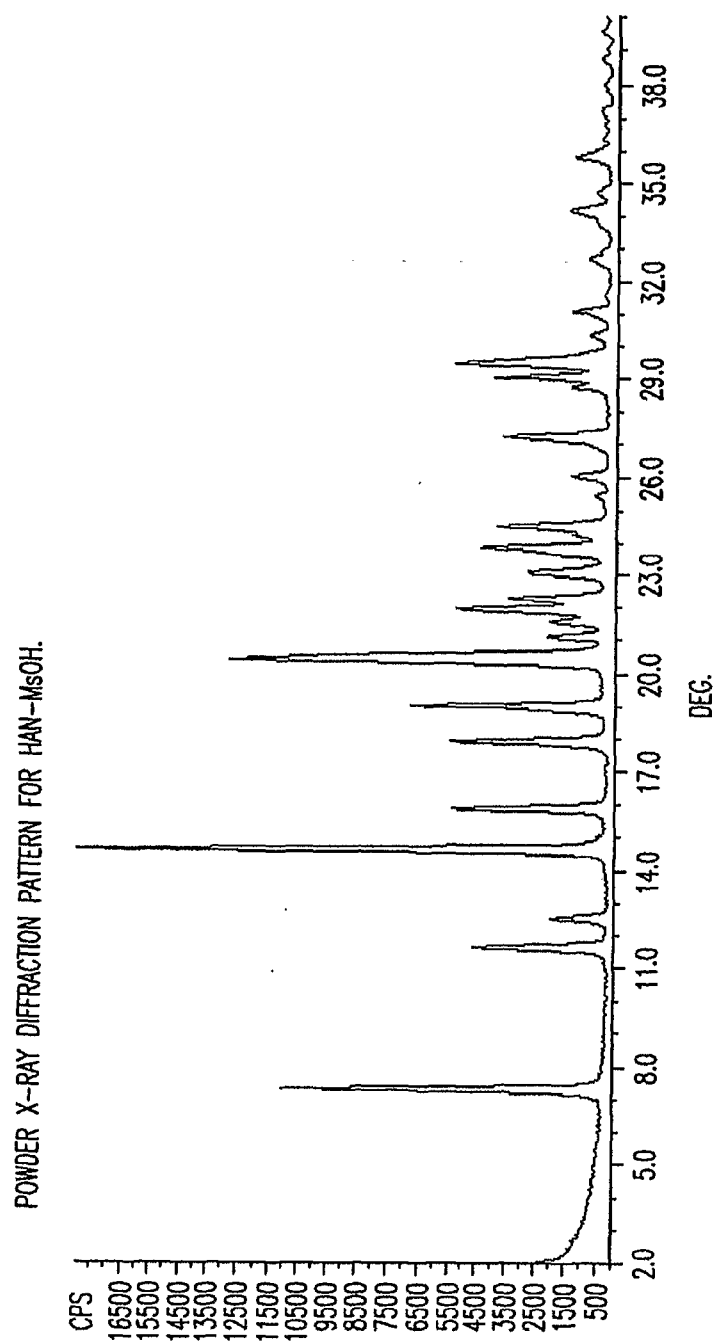


FIG. 2

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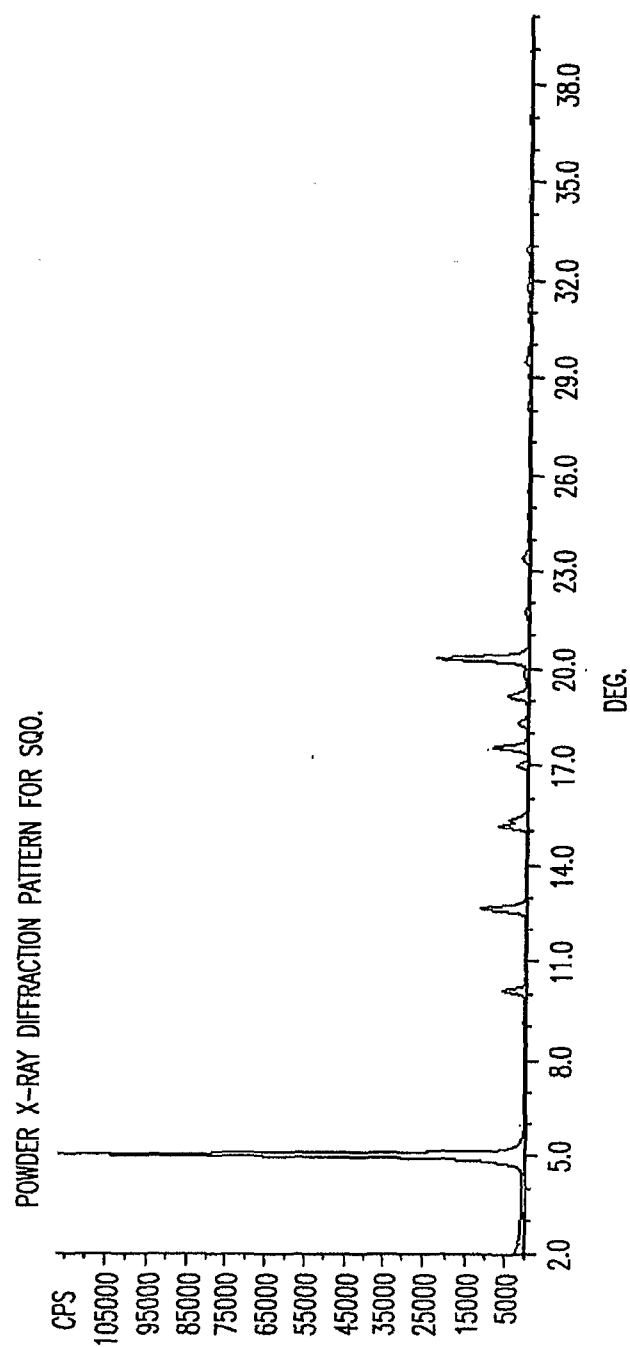


FIG.3

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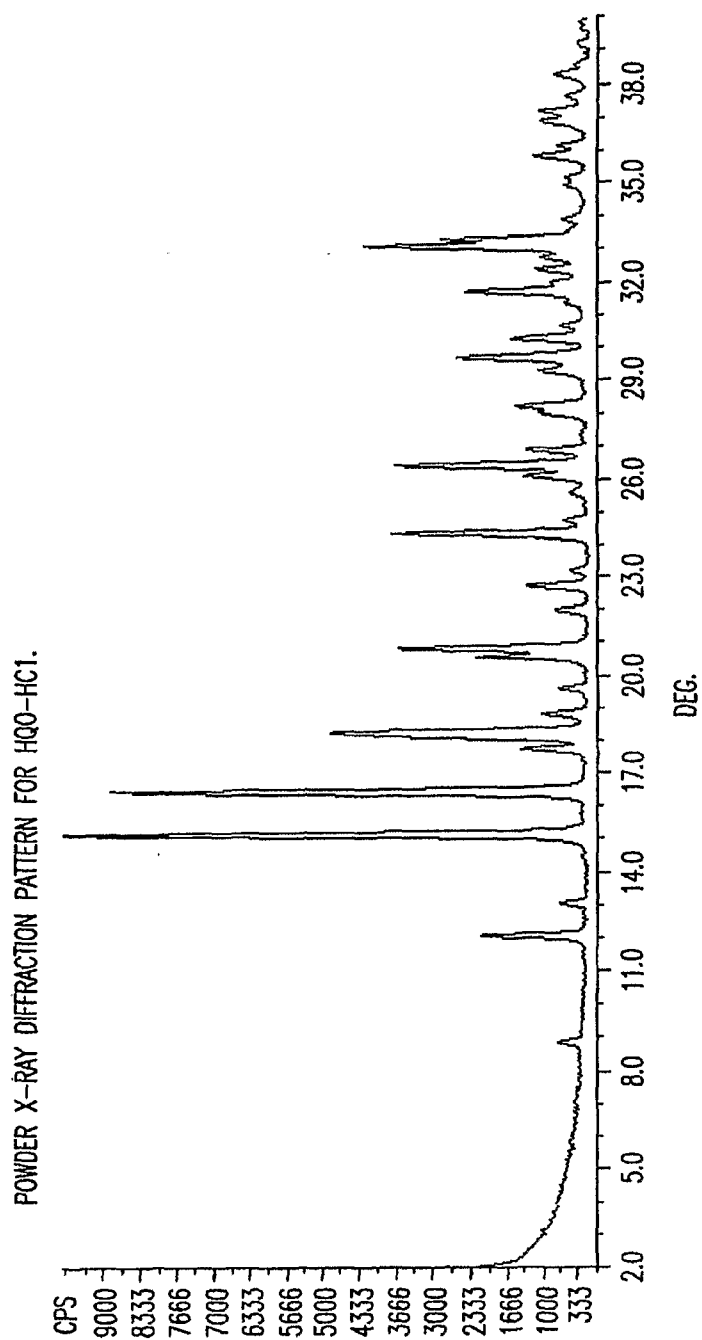


FIG.4

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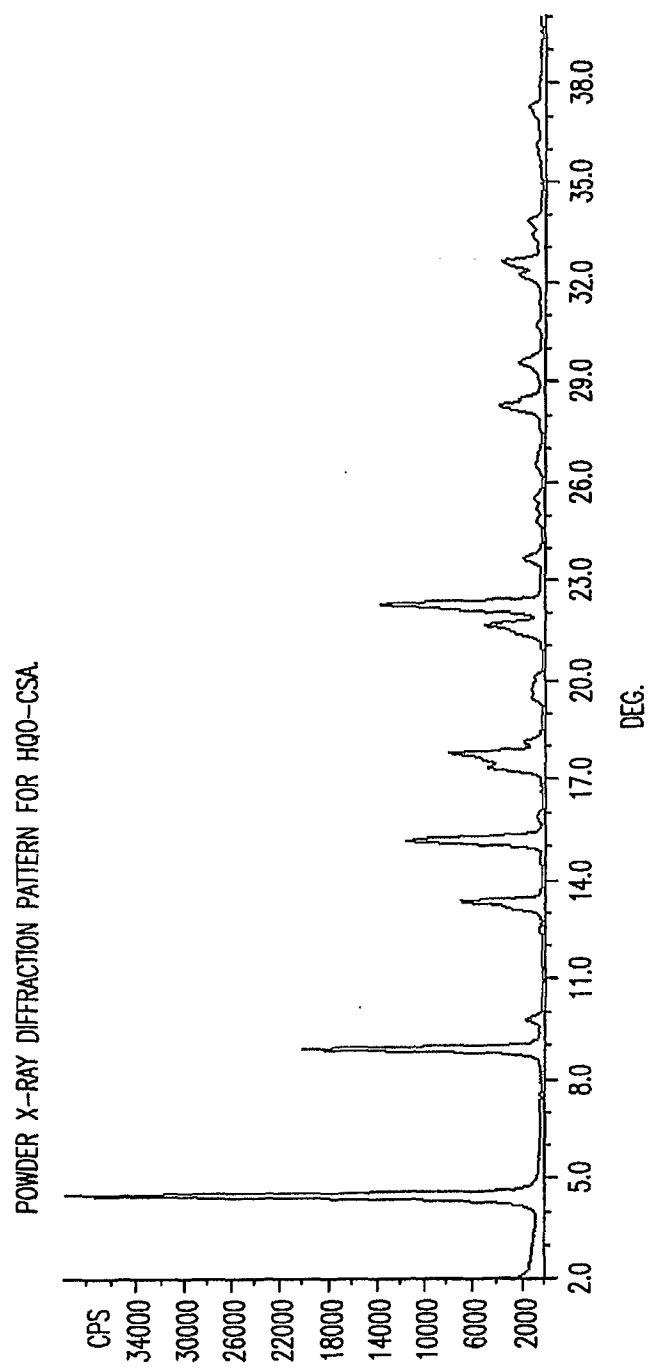


FIG.5

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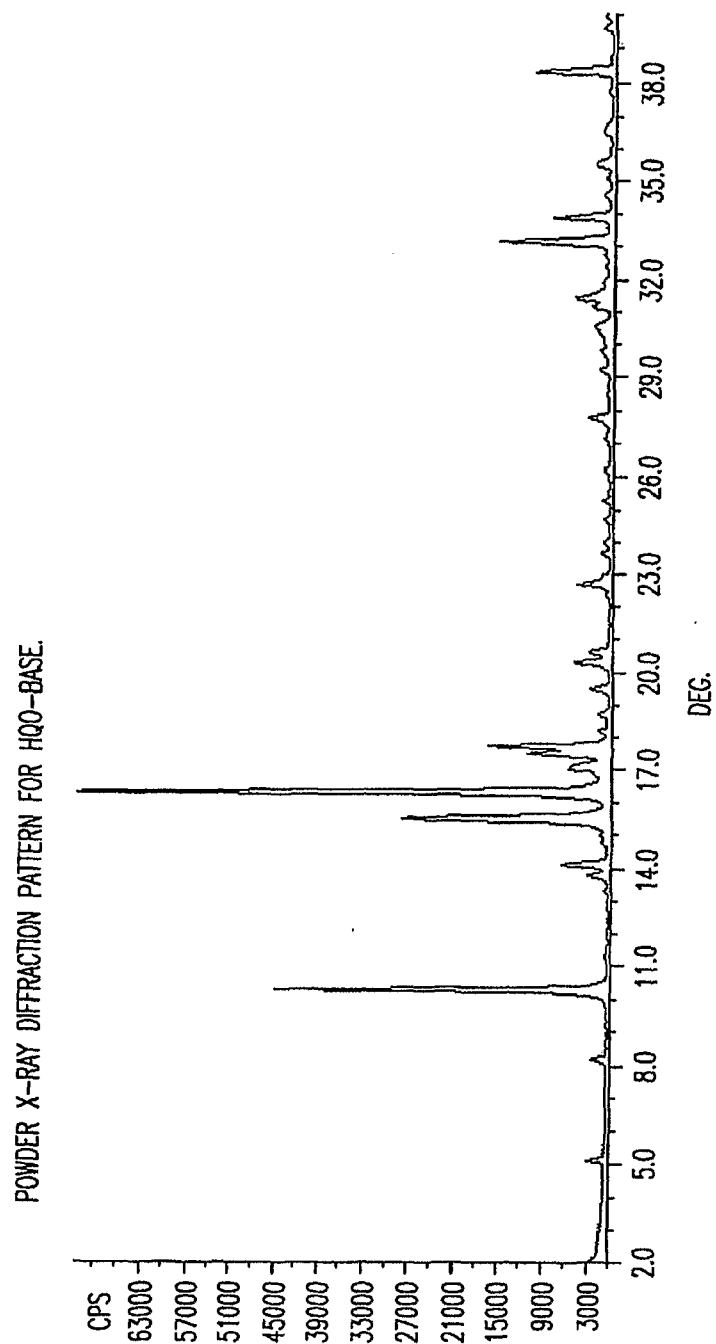


FIG. 6