

**High Purity Synthetic Process for the Preparation of
Dodecahydro-Naptho-Furanyl-Carbamic Acid Ester Intermediates**

5

Cross Reference to Related Applications

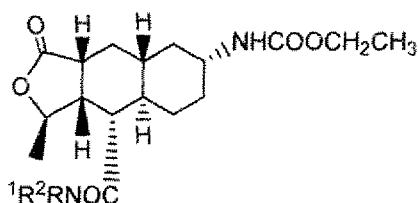
The present application is based on and claims the priority of U.S. Provisional Application 61/000,164 filed October 24, 2007, which application is incorporated herein by reference in its entirety.

10

Field of the Invention

This application discloses a novel process to prepare furanyl carbamic acid ester compounds of Formula Ia in high purity, which have utility, for example, as intermediates in the preparation of pharmaceutically active himbacine analog compounds.

15



Formula Ia

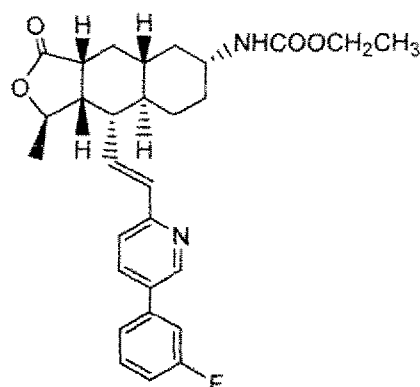
Background of the Invention

20

Identification of any publication in this section or any section of this application is not an admission that such publication is prior art to the present invention.

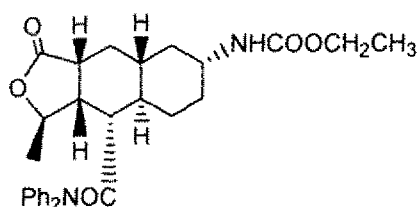
U.S. Patent No. 6,063,847, which is incorporated herein by reference in its entirety, describes himbacine analogs known to act as thrombin receptor antagonists which have useful pharmaceutical activity, for example, the compound of Formula II.

25



Formula II

In some preparation schemes a compound of Formula Ia, for example, the compound of Formula I,



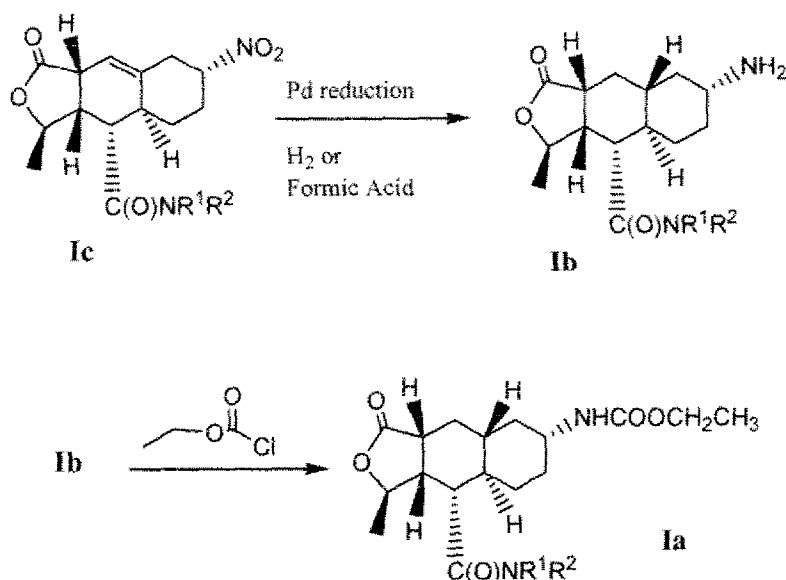
Formula I,

5 is a critical intermediate in the preparation of himbacine analog compounds having desirable pharmaceutical properties, for example, the compound of Formula II. U.S. Patent Application Serial No. 11/331,324, filed January 12, 2006 and published under Publication No. 2006/0247450 (the '450 publication), which is incorporated herein by reference in its entirety, describes in Example 7 the preparation of the compound of

10 Formula II from the compound of Formula I. Preparation of the intermediate compounds of Formula Ia from commercially available starting materials has been accomplished using a multi-step synthesis, for example, as described in the '450 publication, page 13, paragraph [0074] to page 16, paragraph [0078]. For Example, the '450 publication describes on page 8, the preparation of compounds of Formula Ia

15 in accordance with Scheme I,

Scheme I



The purity of compounds of Formula Ia provided by the procedure described in
 5 the '450 publication is highly sensitive to the purity of the precursor compound of
 Formula Ic (referencing Scheme I) used in the preparative process. For an example,
 see the '450 publication at Example 7, starting at paragraph [0098]. When
 synthesized in accordance with the '450 publication, the product comprising the
 compound of Formula I requires a number of recrystallizations to consistently provide
 10 the compound of Formula I having suitable purity for use in the synthesis of
 compounds of Formula II. Without purification, the yield and handling properties of the
 target compound are greatly reduced.

Objectives and Summary of the Invention

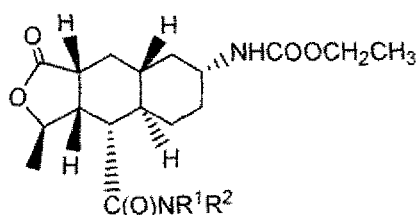
15

In view of the foregoing, what is needed is method for preparing consistently
 high purity quantities of the intermediate compounds of Formula Ia, for example, the
 compound of Formula I. Moreover, what is needed is a process for providing
 compounds of Formula Ia in which product purity is less sensitive to the purity of
 20 precursor materials and which minimizes the need for recrystallization steps to

consistently provide compounds of Formula Ia in high purity. What is needed also is a process for providing the compound of Formula I that can be adapted to a batch size suitable for commercial scale preparation. These and other objectives and/or advantages are provided by the present invention.

5

One preferred aspect of the present invention is a process for providing a purified form of the compound of Formula Ia,



Formula Ia,

10

the process comprising:

- (a) providing a saturated solution comprising the compound of Formula I in a solvent comprising substantially acetone or 2-methyl-tetrahydrofuran (2-Me-THF), at a first temperature, wherein the first temperature is above ambient and is selected to be in a range suitable to form a suspension comprising crystals of the compound of Formula I and maintaining the solution at said first temperature for a period of time sufficient to form a suspension of the compound of Formula I, optionally while agitating the mixture;
- (b) optionally reducing the temperature of the suspension formed in Step "a" to a second temperature, wherein said second temperature is subambient;
- (c) optionally agitating the suspension from step "b" while holding it at said second temperature for a period sufficient to precipitate a crystalline product having less than about 3.0 mole%, preferably less than about 2.0 mole% impurity and comprising at least about 80% of the

25

compound of Formula I initially present in the solution provided in Step "a"; and

(d) optionally isolating the crystalline product precipitated in Step "c".

5 In some embodiments, it is preferred to provide the purified compound of Formula Ia in the form of a solvate. In some embodiments it is preferred to select in step "b" a second temperature of from about (-5) °C to about (+10) °C. In some embodiments it is preferred to reduce the temperature of the suspension in step "b" from said first temperature to said second temperature over a period of up to about 3
10 hours, preferably from about 1 to about 3 hours. In some embodiments employing optional step "c" it is preferred to carry out the agitation over a period of from about 1 to about 2 hours. In some embodiments it is preferred after carrying out optional step "d" to dry the isolated precipitate at a temperature proximal to ambient so as to provide the isolated precipitate in the form of a solvate.

15 In some embodiments it is preferred to carry out this process to provide a purified form of the compound of Formula I using acetone as a purifying solvent, thereby providing a crystalline acetone monosolvate form of the compound of Formula I wherein the crystalline monosolvate product provides an NMR spectrum in
20 deuterochloroform having the following features: ¹HNMR (CDCl₃) δ 7.25 - 7.55 (m, 10 H), 4.89(m, 1H), 4.51 (bs, 1H), 4.09 (d, J = 6.98 Hz, 2H), 3.49 (brs, 1H), 2.41 (m, 2H), 2.25 (m, 1H), 2.19(s, 6 H Acetone), 2.06 (d, J = 10.8 Hz, 2H), 1.96 (d, J = 10.9 Hz, 1H), 1.83 (ddd, J = 13.5, 6.09, 2.51 Hz, 1H), 1.63(m, 1H), 1.52 (d, J = 5.8 Hz, 3H), 1.23 (m, 5H), 1.17 (q, J = 11.5 Hz, 2H), 0.92 (q, J = 11.5 Hz, 1H).

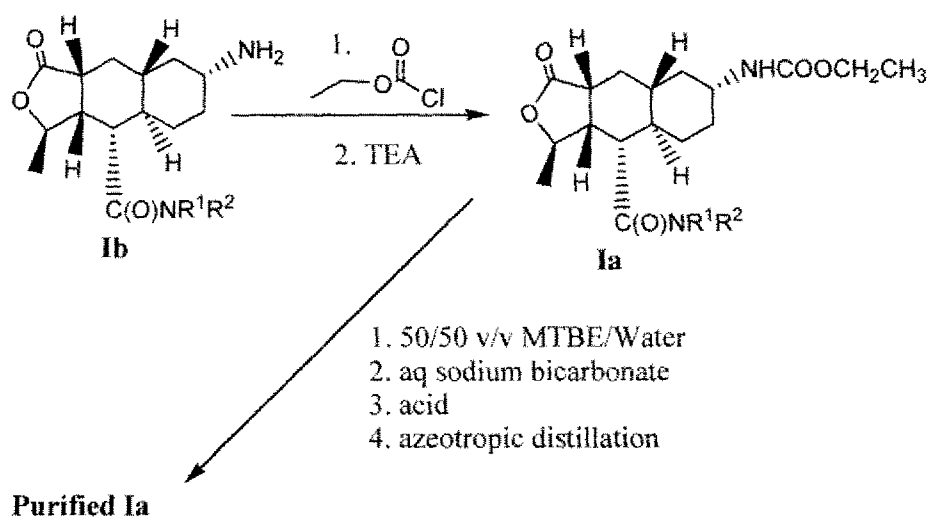
25 In some embodiments it is preferred to carry out this process to provide a purified form of the compound of Formula I using 2-methyl-tetrahydrofuran (2-Me-THF) as a purifying solvent, thereby providing a crystalline 2-Me-THF monosolvate form of the compound of Formula I wherein the crystalline monosolvate product provides an
30 NMR spectrum in deuterochloroform having the following features: ¹HNMR (CDCl₃) δ

7.25 - 7.55 (m, 10 H), 4.89(m, 1H), 4.51 (bs, 1H), 4.09 (d, J = 6.98 Hz, 2H), 3.98-3.86 (m, 2H, 2-Me-THF), 3.73-3.68 (m, 1H, 2-Me-THF), 3.49 (brs, 1H), 2.41 (m, 2H), 2.25 (m, 1H), 2.06 (d, J = 10.8 Hz, 2H), 1.96 (d, J = 10.9 Hz, 1H), 1.92-1.79(m, 3H, 2-Me-THF), 1.83 (ddd, J = 13.5, 6.09, 2.51 Hz, 1H), 1.63(m, 1H), 1.52 (d, J = 5.8 Hz, 3H),
 5 1.45-1.36(m, 1H, 2-methyl-THF) 1.23 (m, 5H), 1.22 (d, 3H, 2-Me-THF) 1.17 (q, J = 11.5 Hz, 2H), 0.92 (q, J = 11.5 Hz, 1H).

In one embodiment, the precipitation process is incorporated into a process for synthesis of the compound of Formula Ia in accordance with Scheme II,

10

SCHEME II



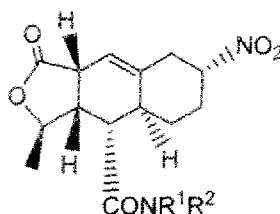
15 the process comprising;

- providing a THF solution of the compound of Formula Ib;
- forming the amide of Formula Ia in a reaction mixture provided by treating the THF solution from step "i" first with ethylchloroformate and adding thereafter triethyl amine;

- (iii) working up the reaction mixture from step "ii" by adding equal volumes of water and methyl tert-butyl ether (MTBE) and then separating the resulting organic and aqueous phases;
- (iv) mixing the separated organic phase from step "iii" with an equal volume of water and an aliquot of a carbonate base solution;
- (v) adjusting the pH of the mixture provided in Step "iv" with an aqueous acid to a pH of from about pH 6 to about pH 7.5 and separating the aqueous and organic phases of the mixture;
- (vi) modifying the solvent in the separated organic phase obtained in Step "v" by a process comprising:
- mixing a purifying solvent with the separated organic phase obtained in Step "v", wherein the purifying solvent is acetone or 2-Me-THF;
 - azotropically distilling the mixture until it is concentrated; and
 - repeating steps "a" and "b" until the solvent in the mixture is substantially the purifying solvent; and
- (vii) cooling the phase provided in Step "vii", thereby precipitating a substantially pure solvate form of the compound of Formula Ia.

In some embodiments of the process it is preferred for the compound of Formula Ia to be the compound of Formula I, thus, R^1 and R^2 in each occurrence in the compounds of Formulae Ic, Ib, and Ia is phenyl.

In some embodiments it is preferred to provide the compound of Formula Ib by hydrogenating the compound of Formula Ic,



Formula Ic

using a palladium catalyst and a mixed water/THF reaction medium.

In some embodiments of the inventive process it is preferred in Step "iv" to employ an aqueous 5% sodium bicarbonate solution as the carbonate base solution. In some embodiments of the inventive process it is preferred to employ in Step "v" an aqueous sulfuric acid solution to adjust the pH of the mixture. In some embodiments of the inventive process it is preferred to concentrate the separated organic phase by
5 distilling off solvent prior to carrying out solvent modification in Step "vi".

In some embodiments of the inventive process, in the synthesis process of Scheme I, step "vii" comprises holding a saturated solution of the compound of
10 Formula Ia at a first temperature, wherein, nucleation of crystals of the compound of Formula Ia are formed, producing a suspension of the compound of Formula Ia, followed by a reduction in temperature to a second temperature at which a crystalline form, preferably a crystalline solvate form, of the compound of Formula Ia is precipitated from the modified organic phase, preferably holding the phase at a second
15 temperature, preferable a subambient temperature, at which precipitation of a crystalline form of the compound of Formula Ia is maximized. In some embodiments wherein the solvate form of the compound of Formula Ia precipitated in Step "vii" is a 2-methyl-tetrahydrofuran mono-solvate form or an acetone mono-solvate form of the compound of Formula I, preferably said first temperature is a temperature of from
20 about 45 °C to about 60 °C, and said second temperature is preferably a temperature of from about (-5 °C) to about (+10 °C).

These and other aspects of the invention are further described in the following description.

25 **Detailed Description of the invention**

A process for providing the compound of Formula I is described in the '450 publication in Example 7, which is incorporated herein by reference. With reference to Scheme I, above, the '450 publication describes preparing the compound of Formula
30 Ib from the compound of Formula Ic (wherein, in each instance, R¹ and R² are each

phenyl) by hydrogenation over palladium catalyst, and subsequently reacting the amine intermediate thereby formed with a chloroformate to provide the carbamic acid ester compound of Formula I. As mentioned above, the process described in the '450 publication provides high impurity levels in the intermediate compound of Formula I
5 when the chloroformate reaction is worked up with subsequent precipitation of the compound of Formula I from the mixture resulting from treating the reaction mixture with an ethanol/water mixture followed by azeotropic distillation of the mixture in accordance with the teaching of Example 7 in the '450 publication.

10 Attempts to use various solvents, for example, Methyl-tert.-Butyl Ether (MTBE); and various solvent/antisolvent systems, for example, ethylacetate/heptane and toluene/heptane, to recrystallize aliquots of the precipitate comprising the compound of Formula I made in accordance with the process described in the '450 publication resulted in the formation of oils. These oils did not yield a reduced impurity profile in
15 synthesis of the compound of Formula I, nor provide an improvement in the quality of the product compound of Formula II provided from the process described in the '450 publication.

Accordingly, in one aspect, the process of the present invention provides
20 improvements in the synthetic process as described in the '450 publication by adapting the present invention to that process to reduce the level of impurities present in the precipitation product comprising the compound of Formula Ia made in accordance therewith.

25 The inventors have surprisingly found that the present invention process, which mixes a reaction mixture containing a compound of Formula Ia (after workup) with a purifying solvent, and after subsequent concentration and volatiles stripping, precipitates therefrom either a monoacetone solvate form or a mono-2-methyl-tetrahydrofuran solvate form of a compound of Formula Ia, for example, the
30 monoacetone solvate form of the compound of Formula I, providing the compound of

Formula Ia in a form containing substantially lower percentages of impurities present in the precipitated material in comparison with the precipitated material comprising the compound of Formula Ia obtained from mixing the reaction mixture workup with ethanol/water solvent in accordance with the process described in the '450 publication.

5

When the process of the present invention is part of a reaction scheme for preparing a compound of Formula Ia, preferably, the process of providing a compound of Formula Ia is carried out in accordance with the methodology described in the above-referenced '450 publication (see Example 7 therein) up through the step of
10 extracting the product in the reaction mixture into methyl-tertiarybutyl ether (MTBE). In accordance with the present invention, the extract thus obtained which contains the compound of Formula Ia is then mixed with a purifying solvent, for example, 2-methyl-tetrahydrofuran or acetone, and concentrated by distilling off the mixture, azeotropically, until the solvent remaining in the concentrate substantially comprises
15 the purifying solvent. The temperature of the concentrate thus provided is then reduced to a temperature (first crystallization temperature) at which formation of a crystalline solvate form of the compound of Formula Ia commences, for example, the crystalline monoacetone solvate of the compound of Formula I, forming a crystalline suspension or precipitation product comprising the desired crystalline mono-solvate
20 product of the compound of Formula Ia. In some embodiments of the process providing the monoacetone solvate form of the compound of Formula I, it is preferred to hold the concentrate at a first crystallization temperature of from about 45 °C to about 60 °C.

25 In some embodiments wherein the compound of Formula Ia is purified using either acetone or 2-methyl-tetrahydrofuran as the purifying solvent, after holding the concentrate at a first crystallization temperature for a period of time sufficient to commence precipitation of the compound of Formula Ia in a monoacetone solvate crystalline form or the 2-methyl-tetrahydrofuran crystalline form, respectively, the
30 temperature of the solution is lowered to a subambient temperature in a controlled

manner, wherein the cooling rate and the final temperature are selected to maximize the amount of the crystalline solvate form of the compound precipitated from the concentrate while preserving in the precipitated crystalline material the low level of impurities provided by the precipitation process. Preferably, when the compound of

5 Formula Ia is the compound of Formula I, the first crystallization temperature is a temperature of from about 45 °C to about 60 °C, and the second crystallization temperature is a temperature of from about (-5 °C) to about (+10 °C), although it will be appreciated that temperature values lying outside of these ranges can be employed without departing from the process of the present invention. In some embodiments it is

10 preferred to maintain the first crystallization temperature for a period of up to 1 hour, more preferably about 1 hour, although longer periods may also be employed without departing from the process of the present invention. In some embodiments it is preferred to lower the temperature from the first crystallization temperature to the second crystallization temperature over a period of about 3 hours, although faster and

15 slower cooling rates may also be employed without departing from the process of the present invention. In some embodiments it is preferred to hold the second crystallization temperature for a period of from about 1 to about 2 hours, although it will be appreciated that longer and shorter holding periods may be employed without departing from the process of the present invention. In some embodiments it will be

20 appreciated that the slurry may be agitated for some or all of the second crystallization temperature holding period.

Although it will be appreciated that the advantages of the present invention can be realized utilizing aliquots of a compound of Formula Ia prepared by any means, and

25 dissolving the aliquot of the compound in a purifying solvent, for example, acetone and 2-methyl-tetrahydrofuran, from which it is reprecipitated as the mono-solvate crystalline form of the compound of Formula Ia (for example, the monoacetone solvate of the compound of Formula I), it is believed that the invention will find its best utility when integrated into a process for preparing a compound of Formula Ia as part of the workup

procedure leading to isolation of the compound from the reaction mixture in the form of an acetone solvate.

Without wanting to be bound by theory, it is believed that the present invention
5 can be carried out as part of a workup process using reaction mixtures in which the
imine of Formula Ic' is present to various levels as an unreacted impurity without
adversely effecting the purity of the crystalline solvate provided by the present process,
however, in some embodiments it is preferred to react the imine as closely as possible
to completion, maximizing the utilization of the compound of Formula Ic', an expensive
10 reagent with several chiral centers.

It will be appreciated that, if desired, recrystallization of the isolated purified
mono-acetone solvate compound of Formula Ia from acetone can be further purified by
recrystallization from acetone. Accordingly, the present process can be coupled with
15 additional purification processes to further improve the purity of the material provided,
but in most applications, the present invention process for precipitating the crystalline
acetone solvate of the compound of Formula I from acetone workup of the reaction
mixture provides suitably pure material to employ in the preparation of the compound
of Formula II. In some embodiments the process of the invention is employed to
20 provide impurity levels in the compound of Formula Ia of less than about 3.0 mole%.
In some embodiments the process of the invention is employed to provide impurity
levels in the compound of Formula Ia of less than about 2.0 mole%, the impurity levels
attained depending upon the level of impurities in the reaction mixture being worked
up, the temperatures regimes selected in which the process is run and the contact time
25 between the purifying solvent and the solids obtained from the process. It will be
appreciated that when other purification solvents are employed in the workup of the
reaction mixture providing a compound of Formula I the precipitation product may also
be further purified by other known means if desired.

There follows examples which illustrate the inventive precipitation process and compare it to the product obtained when the product of Formula Ia is precipitated directly from an ethanol/water reaction medium.

5

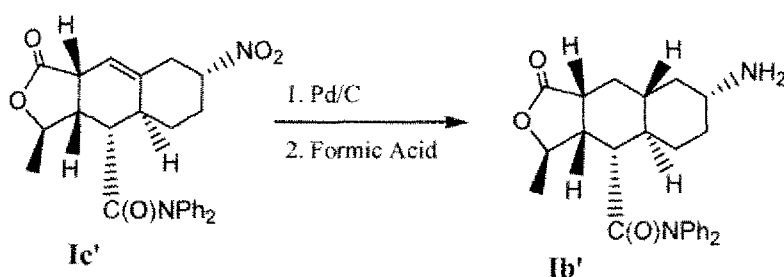
EXAMPLES

The reagents and solvents used in the examples are articles of commerce which, unless otherwise noted, were used as received. Completion of a reaction step is generally taken to be when 99% of the substrate used has been consumed, generally as determined by published chromatography methods.

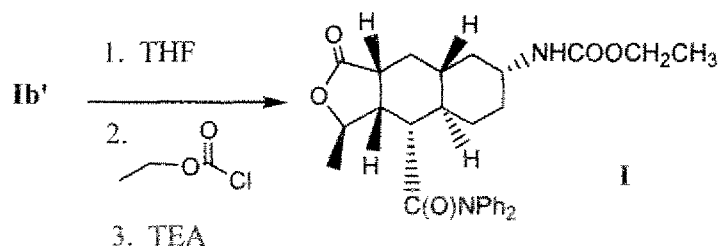
10

Example 1: Preparation of the Compound of Formula I

Using An Acetone Precipitation Process



15



Into a three-neck flask equipped with an agitator, thermometer and nitrogen inlet were sequentially added the compound of Formula **Ic'** (100 g), THF (600 ml), 10% palladium on carbon (50% wet, 35g) and water (400 ml). The mixture was agitated for 10 minutes at room temperature and then heated to 50 °C. Formic acid

20

(70 mL) was added slowly while the temperature was maintained between 45 °C and 55°C. The reaction mixture was agitated for 7 hours while maintaining the temperature between 45 °C and 55 °C. After the reaction was judged complete by HPLC, the reaction mixture was cooled to 20°C and the pH was adjusted until the pH of the
5 reaction mixture was between pH 1 and pH 2 by adding 60 mL of 25% sulfuric acid. After adjusting the pH of the reaction mixture, THF (200 mL) was added to the reaction mixture, and the mixture was filtered through a pad of Celite to remove the catalyst. The flask was rinsed with an aliquot of a mixture of THF (300 mL), water (300 mL) and 25% H₂SO₄ (1.5 mL). This rinse was passed through the Celite and
10 catalyst cake. The combined reaction mixture solution was charged back into a clean flask and the solution was cooled to below 10°C. The temperature of the solution was maintained at a temperature below 10 °C, and the pH of the solution was adjusted to pH 9 by adding 30 mL of 25% NaOH while maintaining the temperature. Following the pH adjustment, 150 g of NaCl was then added to the solution and it was warmed
15 to 20°C and two phases were separated. The aqueous phase was extracted with 400 mL of THF and combined with the organic phase. The combined organics were washed with a brine solution (40 g of NaCl in 200 ml of water). The organic phase was cooled and maintained between 0°C and 10 °C, then ethyl chloroformate (30 ml) was added to the combined organics. After addition of ethylchloroformate was complete,
20 56 mL of triethyl amine was slowly added to the reaction mixture while maintaining the temperature between 0-10°C. The mixture was stirred for 30 minutes while maintaining the temperature of the reaction mixture between 0 °C and 10°C. When the reaction was judged complete by HPLC, 200 ml of MTBE and 200 ml of water were added to the reaction mixture and the two phases were separated. To the
25 organic phase was added another 200 ml water and 30 ml 5% sodium bicarbonate solution. The mixture was agitated for 1 hour maintaining the temperature of the mixture between 15 °C and 25°C. At the end of one hour of agitation, 25% aqueous sulfuric acid was added to the mixture until the pH of the mixture was between pH 6 and pH 7.5 and the two phases were separated. The separated organic layer was
30 atmospherically concentrated to 300 mL and acetone (1000 mL) was added to the

concentrated organic layer. The resulting solution was azeotropically distilled, to a volume of 300 mL. Additional acetone (800 mL) was added to the concentrated solution and the resulting solution was concentrated atmospherically to a volume of 450 mL. The compound of Formula I was precipitated from the concentrated acetone solution by cooling the solution and maintaining the temperature between 45 °C and 60°C until a precipitate was observed (about 1 hour) followed by cooling the solution over three hours to a temperature of from (-5 °C) to (+10 °C). The temperature of the resulting slurry was maintained between (-5 °C) and (+10 °C) and agitated for an additional 1-2 hours. After a cold agitation period was complete, the precipitated solids were isolated by vacuum filtration. The filter cake was washed with 250 ml of acetone maintained at a temperature between (-5°C) and (+10°C). The solid product was dried for 6 hours under vacuum at a temperature maintained between at 15 °C and 25 °C to provide a monoacetone solvate form of the compound of Formula I as a white to off-white powder (90g, 84 mole% yield, 99.3 area% purity). MP 134-139°C; ¹H NMR (CDCl₃) δ 7.25 - 7.55 (m, 10 H), 4.89(m, 1H), 4.51 (bs, 1H), 4.09 (d, J = 6.98 Hz, 2H), 3.49 (brs, 1H), 2.41 (m, 2H), 2.25 (m, 1H), 2.19(s, H Acetone), 2.06 (d, J = 10.8 Hz, 2H), 1.96 (d, J = 10.9 Hz, 1H), 1.83 (ddd, J = 13.5, 6.09, 2.51 Hz, 1H), 1.63(m, 1H), 1.52 (d, J = 5.8 Hz, 3H), 1.23 (m, 5H), 1.17 (q, J = 11.5 Hz, 2H), 0.92 (q, J = 11.5 Hz, 1H)

Example 1a: Preparation of the Compound of Formula I

Using A 2-Methyl-Tetrahydrofuran Precipitation Process

The reaction outlined in Example 1 was carried out a second time using a 2-methyl-tetrahydrofuran purification solvent to precipitate the compound of Formula I after workup of the reaction products. Thus, into a three-neck flask equipped with an agitator, thermometer and nitrogen inlet were sequentially added the compound of Formula Ic' (100g), THF (600 ml), 10% palladium on carbon (50% wet, 35g) and water (400 ml). The mixture was agitated for about 10 minutes at room temperature and then heated to 50°C. Formic acid (70 ml) was added slowly while the temperature

was maintained between 45°C and 55°C, then, while maintaining this temperature range, the reaction mixture was agitated for 4 hours. After the reaction was judged complete by HPLC, the reaction mixture was cooled to 20°C and the pH was adjusted to a pH between pH1 and pH 2 with the addition of 60 mL of 25% H₂SO₄. THF
5 (200mL) was added to the reaction mixture, which was then filtered through a pad of Celite to remove the catalyst. A mixed solution of THF (300 mL), water (300 ml) and 25% H₂SO₄(1.5 mL) was used to rinse the flask and catalyst, and filtered through the Celite. The combined solution containing compound of Formula Ib' was charged back into a clean flask and the mixture was cooled to below 10°C. The pH was adjusted to
10 pH 9 with the addition of 30 mL of 25% aqueous NaOH (30 mL) while maintaining the temperature of the reaction mixture below 10°C.

Following the addition of NaOH, and while continuing to maintain the temperature of the reaction mixture, 150 g of NaCl was added. The reaction mixture
15 was warmed to 20°C and two phases were separated. The aqueous phase was extracted with THF (400 mL). The extract and organic phase were combined and washed with a brine solution (40 g of NaCl in 200 mL of water).

The organic phase was separated and cooled, and maintained at a
20 temperature of from 0 °C to 10°C. Into the cooled organic phase was added ethyl chloroformate (30 ml). The mixture was maintained at a temperature of from 0 °C to 10°C while 56 mL of triethyl amine was slowly added to it. When addition of the ethyl chloroformate was complete, the mixture was stirred while maintaining the temperature. After the reaction was judged complete by HPLC, 200 ml of MTBE and
25 100 mL of water were added to the reaction mixture, followed by the slow addition of 100 mL of 25% H₂SO₄. The resulting organic phase was separated and concentrated to a volume of 300 mL by distilling off volatiles from the organic phase at a temperature between 70 °C and 80°C. To the concentrate was added 1000 ml of 2-methyl-tetrahydrofuran and the mixture was concentrated by atmospheric distillation to
30 a volume of 300 mL. To this concentrate was added 800 mL of 2-methyl-

tetrahydrofuran and the resulting mixture was concentrated atmospherically to a volume of 500 ml. The compound of Formula I was precipitated from the concentrated 2-methyl-tetrahydrofuran solution by cooling the solution and maintaining the temperature between 45 °C and 60°C until a precipitate was observed (about 1 hour) followed by cooling the solution over three hours to a temperature of from (-5 °C) to (+10 °C). The temperature of the resulting slurry was maintained between (-5 °C) and (+10 °C) and agitated for an additional 1-2 hours. After a cold agitation period was complete, the precipitated solids were isolated by vacuum filtration. The filter cake was washed with 200 ml 2-methyl-tetrahydrofuran of maintained at a temperature between (-5°C) and (+10°C). The isolated solid product was dried for 12 hours in an air draft oven at a temperature maintained at 70 °C to provide the compound of Formula I as a mono-2-methyl-tetrahydrofuran solvate white to off-white powder (90g, 80 mole % yield, 98.4% pure by HPLC area% purity); ¹HNMR (CDCl₃) δ 7.25 - 7.55 (m, 10 H), 4.89(m, 1H), 4.51 (bs, 1H), 4.09 (d, J = 6.98 Hz, 2H), 3.98-3.86 (m, 2H, 2-Me-THF), 3.73-3.68 (m, 1H, 2-Me-THF), 3.49 (brs, 1H), 2.41 (m, 2H), 2.25 (m, 1H), 2.06 (d, J = 10.8 Hz, 2H), 1.96 (d, J = 10.9 Hz, 1H), 1.92-1.79(m, 3H, 2-Me-THF), 1.83 (ddd, J = 13.5, 6.09, 2.51 Hz, 1H), 1.63(m, 1H), 1.52 (d, J = 5.8 Hz, 3H), 1.45-1.36(m, 1H, 2-methyl-THF) 1.23 (m, 5H), 1.22 (d, 3H, 2-Me-THF) 1.17 (q, J = 11.5 Hz, 2H), 0.92 (q, J = 11.5 Hz, 1H).

20

Example 2: Preparation of the Compound of Formula I**Using an Ethanol/Water Precipitation Process**

The reaction outlined in Example 1 was carried out a third time using an ethanol/water purification solvent to precipitate the compound of Formula I after workup of the reaction products. Thus, into a three-neck flask equipped with an agitator, thermometer and nitrogen inlet were sequentially added the compound of Formula Ic' (100g), THF (600 ml), 10% palladium on carbon (50% wet, 35g) and water (400 ml). The mixture was agitated for about 10 minutes at room temperature and then heated to 50°C. Formic acid (70 ml) was added slowly while the temperature

30

was maintained between 45°C and 55°C, then, while maintaining this temperature range, the reaction mixture was agitated for 4 hours. After the reaction was judged complete by HPLC, the reaction mixture was cooled to 20°C and the pH was adjusted to a pH between pH1 and pH 2 with the addition of 60 mL of 25% H₂SO₄. THF

5 (200mL) was added to the reaction mixture, which was then filtered through a pad of Celite to remove the catalyst. A mixed solution of THF (300 mL), water (300 ml) and 25% H₂SO₄(1.5 mL) was used to rinse the flask and catalyst, and filtered through the Celite. The combined solution containing compound of Formula Ib' was charged back into a clean flask and the mixture was cooled to below 10°C. The pH was adjusted to

10 pH 9 with the addition of 30 mL of 25% aqueous NaOH (30 mL) while maintaining the temperature of the reaction mixture below 10°C. While maintaining the temperature of the reaction mixture, 150 g of NaCl was added. The reaction mixture was warmed to 20°C and two phases were separated. The aqueous phase was extracted with THF (400 mL). The extract and organic phase were combined and washed with a brine

15 solution (40 g of NaCl in 200 mL of water). The resulting organic phase was separated and cooled to 5°C. While maintaining the temperature of the organic phase, 56 mL of triethyl amine was added to the cold organic phase followed by slow addition of 23.6 mL of ethyl chloroformate. When addition of the ethyl chloroformate was complete, the mixture was warmed to 20°C and stirred for 30 minutes. After the

20 reaction was judged complete by HPLC, 200 ml of MTBE and 100 mL of water were added to the reaction mixture, followed by the slow addition of 100 mL of 25% H₂SO₄. The resulting organic phase was separated and concentrated to a volume of 300 mL by distilling off volatiles from the organic phase at a temperature between 70 °C and 80°C. To the concentrate was added 1000 ml of ethanol, and the mixture was

25 concentrated by atmospheric distillation to a volume of 300 mL. To the concentrate was added another 800 mL of ethanol and atmospheric distillation was repeated to provide a concentrate of 300 mL volume. In general, addition of ethanol with subsequent concentration by distillation is repeated until THF content is observed to be below 5% normalized area by GC.

The temperature of the concentrate was maintained between 60 °C and 85 °C, and water (250 mL) was added to the concentrate. The mixture was cooled to a temperature of between 55 °C and 65 °C and the compound of Formula I was precipitated from the mixture with seeding. After agitating for 1 hour and maintaining
5 the temperature of the concentrate at a temperature between 55 °C and 65 °C, 150 ml water was added at this temperature and the mixture was held at a temperature between 55 °C and 65 °C for 1 hour. The mixture was then cooled and maintained at a temperature between 15 °C and 25°C, with agitation for an additional 3 hours and then the product was separated from the concentrate by vacuum filtration and washed
10 with ethanol-water. The product was dried at 50-60°C to provide an off-white solid (86g, Yield: 85%), Mp 188.2°C ¹HNMR (CDCl₃) δ 7.25 - 7.55 (m, 10 H), 4.89(m, 1H), 4.51 (bs, 1H), 4.09 (d, J = 6.98 Hz, 2H), 3.49 (brs, 1H), 2.41 (m, 2H), 2.25 (m, 1H), 2.06 (d, J = 10.8 Hz, 2H), 1.96 (d, J = 10.9 Hz, 1H), 1.83 (ddd, J = 13.5, 6.09, 2.51 Hz, 1H), 1.63(m, 1H), 1.52 (d, J = 5.8 Hz, 3H), 1.23 (m, 5H), 1.17 (q, J = 11.5 Hz, 2H),
15 0.92 (q, J = 11.5 Hz, 1H). MS (ESI) for M+H calcd. 491 Found: 491.

**Example 3: Comparison of Impurity Levels in Compound Prepared
In Accordance With the Process of Examples 1 and 2**

20 The procedures described in Examples 1 and 1a for the preparation of the monoacetone solvate and mono-2-methyl-tetrahydrofuran solvate respectively of the compound of Formula I and in Example 2 for the preparation of crystalline material precipitated from ethanol/water were repeated. For each of the repeated procedures, the level of impurities present in a sample of each procedure were evaluated by HPLC
25 methods. The results are presented below in Table I.

Table I

Sample No.	Impurity Level Observed in Sample (Product / total of detected impurities)*		
	Process of Example 1	Process of Example 1a	Process of Example 2
1	99.29 / 0.71	98.4 / 1.60	87.11 / 10.67
2	99.39 / 0.61	98.2 / 1.80	82.64 / 14.74
3	99.18 / 0.82	98.3 / 1.70	87.22 / 10.41

*Determined by HPLC of sample of isolated precipitate, expressed as area of HPLC peak associated with precipitated product/total of HPLC peak areas associated with detectable impurities present in sample normalized to 100%.

5

These data show that the process of the present invention provides about a reduction of about a factor of 10 in the impurity level present in the 2-methyl-tetrahydrofuran solvate and well in excess of a factor of 10 reduction in the total amount of impurities present in the acetone solvate precipitation product. These data show also that the process of the present invention, while providing improvements in the level of impurities present in the precipitate, maintains or exceeds the yields of the compound of Formula I obtained from the prior process.

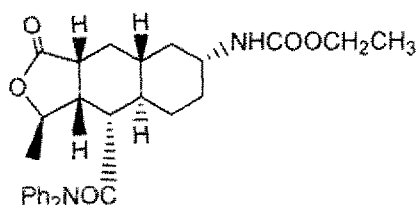
10

The above description of the invention is intended to be illustrative and not limiting. Various changes or modifications in the embodiments described herein may occur to those skilled in the art. These changes can be made without departing from the scope or spirit of the invention

15

What is claimed is:

1. A process for providing a purified, precipitated form of the compound of Formula I,

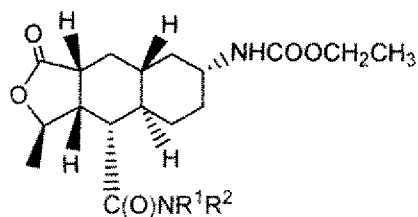


Formula I,

the process comprising:

- a. providing a saturated solution comprising the compound of Formula I in a solvent comprising substantially acetone or 2-methyl-tetrahydrofuran (2-Me-THF), at a first temperature, wherein the first temperature is above ambient and is selected to be in a range suitable to form a suspension comprising crystals of the compound of Formula I and maintaining the solution at said first temperature for a period of time sufficient to form a suspension of the compound of Formula I, optionally while agitating the mixture;
 - b. optionally reducing the temperature of the suspension formed in Step "a" to a second temperature, wherein said second temperature is subambient;
 - c. optionally agitating the suspension from step "b" while holding it at said second temperature for a period sufficient to precipitate a crystalline product having less than about 3.0 mole% impurity and comprising at least about 80% of the compound of Formula I initially present in the solution provided in Step "a"; and
 - d. optionally isolating the crystalline product precipitated in Step "c".
2. The process of claim 1 wherein, when step "c" is carried out it is carried out at a second temperature and for a period sufficient to precipitate a crystalline product having less than about 2.0 mole% impurity.

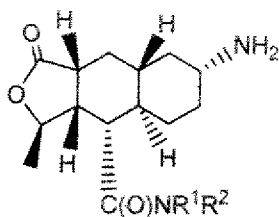
3. The process of claim 2 wherein, said first temperature is a temperature of from about 45 °C to about 60 °C.
4. The process of claim 3 wherein said second temperature is a temperature of from about (-5) °C to about (+10) °C.
5. The process of claim 4 wherein the solution in Step "a" is maintained at said first temperature for about 1 hour.
6. The process of claim 5 wherein the period of time over which the temperature is reduced from said first temperature to said second temperature in Step "b" is a period of about 3 hours.
7. The process of claim 6 wherein, the solution in Step "a" is provided by adding a purification solvent which is acetone or 2-methyl-tetrahydrofuran to a solution comprising: the compound of Formula I; methyl tertiarybutylether; and tetrahydrofuran, and distilling off volatiles until the solvent remaining is substantially the purification solvent.
8. A process for synthesis of the compound of Formula Ia



Formula Ia,

the process comprising:

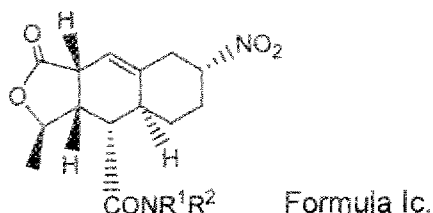
- (a) providing a THF solution of the compound of Formula Ib



Formula Ib;

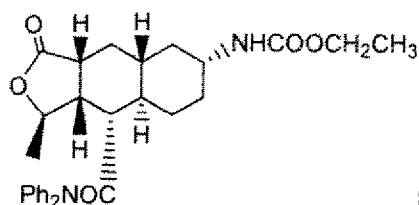
- (b) forming the amide of Formula Ia in a reaction mixture provided by treating the THF solution from Step "a" first with ethylchloroformate and adding thereafter triethyl amine;
- (c) working up the reaction mixture from Step "b" by adding equal volumes of water and methyl tert-butyl ether (MTBE) and then separating the resulting organic and aqueous phases;
- (d) mixing the separated organic phase from Step "c" with an equal volume of water and an aliquot of a carbonate base solution;
- (e) adjusting the pH of the mixture provided in Step "d" with an aqueous acid to a pH of from about pH 6 to about pH 7.5 and separating the aqueous and organic portions of the mixture;
- (f) modifying the solvent in the separated organic phase obtained in Step "e" by a process comprising:
 - (i) mixing a purifying solvent with the separated organic phase obtained in Step "e", wherein the purifying solvent is acetone or 2-Me-THF;
 - (ii) azotropically distilling the mixture from step "f(i)" until it is concentrated; and
 - (iii) repeating steps "f(i)" and "f(ii)" until the solvent in the mixture of step "f(ii)" comprises substantially the purifying solvent; and
- (g) cooling the phase provided in Step "f(iii)", thereby precipitating a substantially pure solvate form of the compound of Formula Ia.

9. The process of claim 8 wherein the compound of Formula Ib is provided by hydrogenating the compound of Formula Ic,



using a palladium catalyst and a mixed water/THF reaction medium.

10. The process of claim 9, wherein R^1 and R^2 in each occurrence is phenyl, and therefore the compound of Formula Ia formed is the compound of Formula I,



Formula I.

11. The process of claim 10 wherein, in Step "d", the carbonate base solution is an aqueous 5% sodium bicarbonate solution.
12. The process of claim 11 wherein, in Step "e", the aqueous acid used to adjust the solution pH is an aqueous sulfuric acid solution.
13. The process of claim 12 wherein, said separated organic portion formed in step "e" is concentrated by distilling off solvent prior to adding the purifying solvent in Step "f".
14. The process of claim 13 wherein Step "g", the cooling step, comprises: (i) adjusting the temperature of said modified organic phase prepared in step "f" to a first temperature, wherein the first temperature is a temperature above ambient and is selected to permit formation of a suspension comprising the compound of Formula Ia, and maintaining said modified organic phase at said first temperature for a period sufficiently long to form a suspension comprising the compound of Formula Ia; and (ii) adjusting the temperature of the suspension formed in step "i" to a second temperature, wherein said second temperature is subambient, and holding the suspension at that temperature for a period sufficient to produce a crystalline product having less than about 2.0 mole% impurity and comprising at least about 80% of the compound of Formula Ia initially present in said modified organic phase prepared in step "f".

15. The process of claim 14 wherein, said first temperature is a temperature of from about 45 °C to about 60 °C.
16. The process of claim 15 wherein, during step "g(i)", the suspension is stirred.
17. The process of claim 16 which further comprises isolating the precipitated solids from step "g(ii)".
18. The process of claim 16, wherein said second temperature is from about (-5 °C) to about (+10) °C.
19. The process of claim 18 wherein, the temperature of the suspension is adjusted in step "g(ii)" from said first temperature to said second temperature over a period of about three hours.
20. A compound prepared by the process of claim 19, wherein the purifying solvent is acetone, and the product provides an NMR spectrum in deuteriochloroform having the following features: ¹HNMR (CDCl₃) δ 7.25 - 7.55 (m, 10 H), 4.89(m, 1H), 4.51 (bs, 1H), 4.09 (d, J = 6.98 Hz, 2H), 3.49 (brs, 1H), 2.41 (m, 2H), 2.25 (m, 1H), 2.19(s, 6 H Acetone), 2.06 (d, J = 10.8 Hz, 2H), 1.96 (d, J = 10.9 Hz, 1H), 1.83 (ddd, J = 13.5, 6.09, 2.51 Hz, 1H), 1.63(m, 1H), 1.52 (d, J = 5.8 Hz, 3H), 1.23 (m, 5H), 1.17 (q, J = 11.5 Hz, 2H), 0.92 (q, J = 11.5 Hz, 1H).
21. A compound prepared by the process of claim 19, wherein the purifying solvent is 2-methyl-tetrahydrofuran, and the product provides an NMR spectrum in deuteriochloroform having the following features: ¹HNMR (CDCl₃) δ 7.25 - 7.55 (m, 10 H), 4.89(m, 1H), 4.51 (bs, 1H), 4.09 (d, J = 6.98 Hz, 2H), 3.98-3.86 (m, 2H, 2-Me-THF), 3.73-3.68 (m, 1H, 2-Me-THF), 3.49 (brs, 1H), 2.41 (m, 2H), 2.25 (m, 1H), 2.06 (d, J = 10.8 Hz, 2H), 1.96 (d, J = 10.9 Hz, 1H), 1.92-1.79(m, 3H, 2-Me-THF), 1.83 (ddd, J = 13.5, 6.09, 2.51 Hz, 1H), 1.63(m, 1H), 1.52 (d, J = 5.8 Hz, 3H), 1.45-1.36 (m, 1H, 2-methyl-THF) 1.23 (m, 5H), 1.22 (d, 3H, 2-Me-THF) 1.17 (q, J = 11.5 Hz, 2H), 0.92 (q, J = 11.5 Hz, 1H).