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(71) Applicant *(for all designated States except BB, US)*: **TEVA PHARMACEUTICAL INDUSTRIES LTD.** [IL/IL]; 5 Basel Street, P.O.Box 3190, Petah Tiqva 49131 (IL).

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

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **INI, Santiago** [IL/IL]; 51 Ruth St., Haifa 34404 (IL). **ABRAMOV, Mili** [IL/IL]; 83/4 Shenkin Street, Givataim (IL). **LIBERMAN, Anita** [IL/IL]; 14 Michael Neeman, Tel-aviv (IL).

(74) Agents: **BRAINARD, Charles, R.** et al.; KENYON & KENYON LLP, One Broadway, New York, NY 10004-1050 (US).

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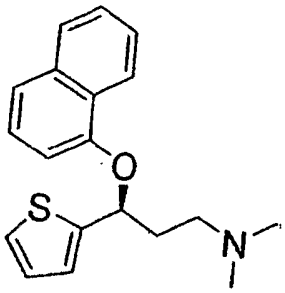
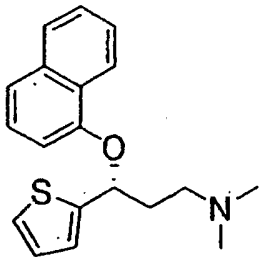
(54) **Title:** PROCESS FOR THE PREPARATION OF OPTICALLY ACTIVE (S)-(+)-N,N-DIMETHYL-3-(1-NAPHTHALENYLOXY)-3-(2-THIENYL)PROPANAMINE





(57) **Abstract:** Diasteromerically enriched salts Of (S)-DNTH$^+$ EPA$^-$ and (R)-DNTH$^+$ EPA$^-$, methods of preparing such diasteromerically enriched salts Of (S)-DNTH$^+$ EPA$^-$ and (R)-DNTH$^+$ EPA$^-$, and methods of preparing enantiomerically enriched (S)-DNT and enantiomerically enriched (R)-DNT are provided.

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PROCESS FOR THE PREPARATION OF OPTICALLY ACTIVE (*S*)-(+)-*N,N*-DIMETHYL-3-(1-NAPHTHALENYLOXY)-3-(2-THIENYL)PROPANAMINE

RELATED APPLICATIONS

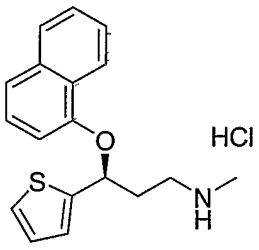
[0001] This application claims benefit of U.S. Provisional Application Nos. 60/726,502, filed October 12, 2005, 60/736,746, filed November 14, 2005, 60/661,711, filed March 14, 2005, and 60/773,593, filed February 14, 2006.

Field of the Invention

[0002] The present invention provides processes for synthesis of duloxetine intermediate. The present invention also provides processes for converting these duloxetine intermediate into pharmaceutically acceptable salts of duloxetine.

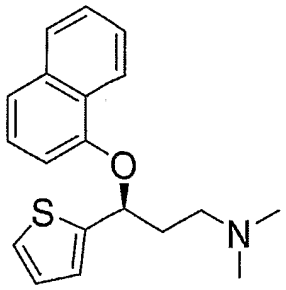
Background

[0003] Duloxetine is a dual reuptake inhibitor of the neurotransmitters serotonin and norepinephrine. It is used for the treatment of stress urinary incontinence (SUI), depression, and pain management. Duloxetine hydrochloride, CAS Registry No. 136434-34-9, has the chemical structure Formula I.



Formula I

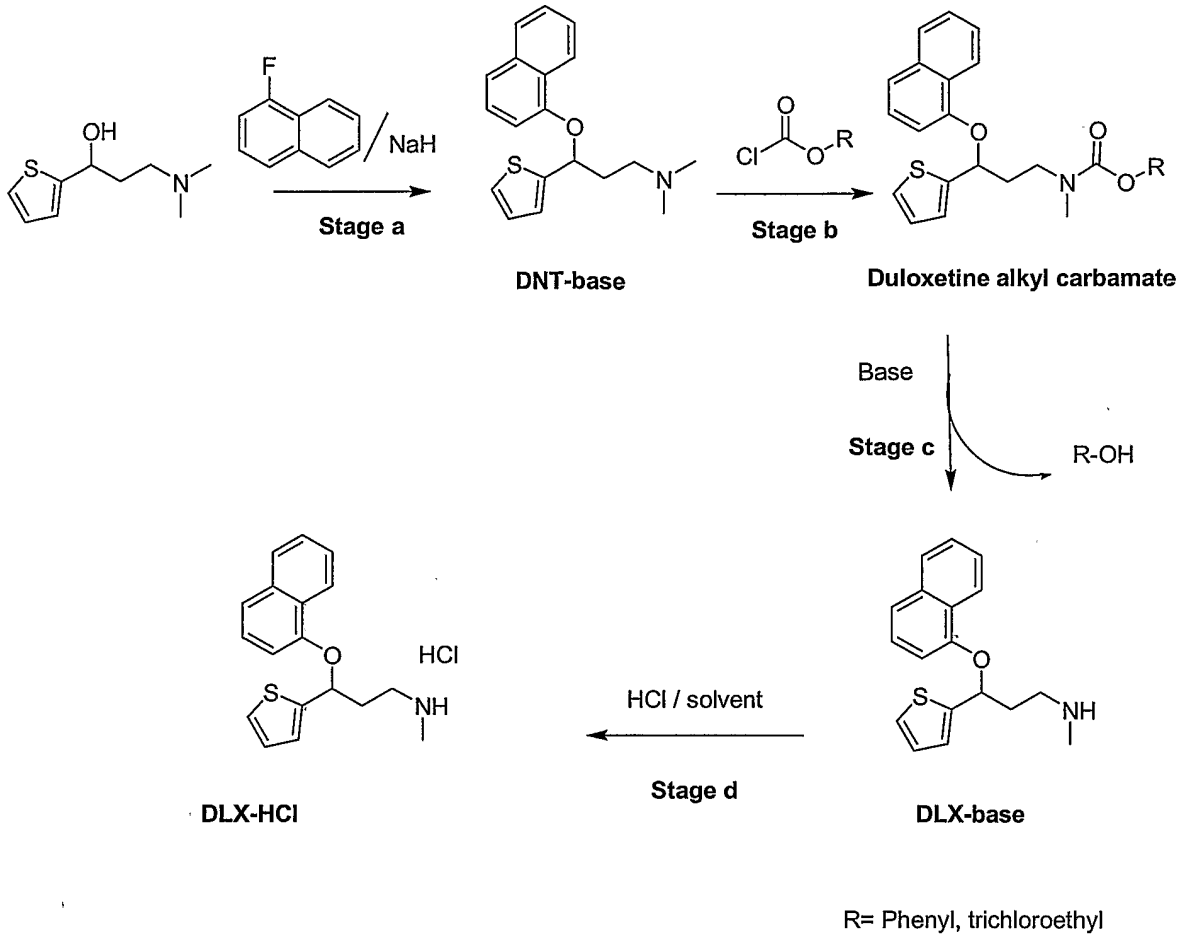
[0004] An intermediate in the synthesis of duloxetine is (S)-(+)-N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine. The intermediate is also known as (S)-(+)-DNT, has been assigned the CAS Registry No. 132335-46-7, and has the chemical structure Formula II.



Formula II

[0005] U.S. Patents Nos. 4,956,388 ("the '388 patent") and 5,023,269 ("the '269 patent"), incorporated herein by reference in their entirety, disclose 3-aryloxy-3-substituted propanamines capable of inhibiting the uptake of serotonin and norepinephrine. The '269 patent describes the preparation of duloxetine by reacting (S)-(-)-N,N-Dimethyl-3-(2-thienyl)-3-hydroxypropanamine with fluoronaphtalene (Stage a) to produce *N,N*-Dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine (DNT), followed by demethylation with phenyl chloroformate or trichloroethyl chloroformate (Stage b) and basic hydrolysis (Stage c) in accordance with the following Scheme 1.

Scheme 1: Synthesis of Duloxetine Hydrochloride



[0006] U.S. Patent No. 5,491,243, incorporated herein by reference in its entirety, discloses a stereospecific process for the synthesis of (S)-(+)-DNT.

[0007] U.S. Patent No. 6,541,668, incorporated herein by reference in its entirety, discloses the preparation of 3-aryloxy-3-arylpropylamines and intermediates thereof using a nucleophilic aromatic displacement in 1,3-dimethyl-2-imidazolidinone or N-methylpyrrolidinone.

[0008] EP 273,658, which corresponds to the '388 and '269 patents, and is incorporated herein by reference in its entirety, discloses 3-aryloxy-3-substituted propanamines capable of inhibiting the uptake of serotonin and norepinephrine.

[0009] Wheeler W.J., et al, J. Label. Cpds. Radiopharm, 1995, 36, 312, incorporated herein by reference in its entirety, discloses the conversion of duloxetine to its hydrochloride salt.

[00010] The prior art discloses that enantiomerically pure duloxetine may be prepared by different routes than those shown in Scheme 1. These prior art routes for preparing enantiomerically pure duloxetine may be summarized as follows:

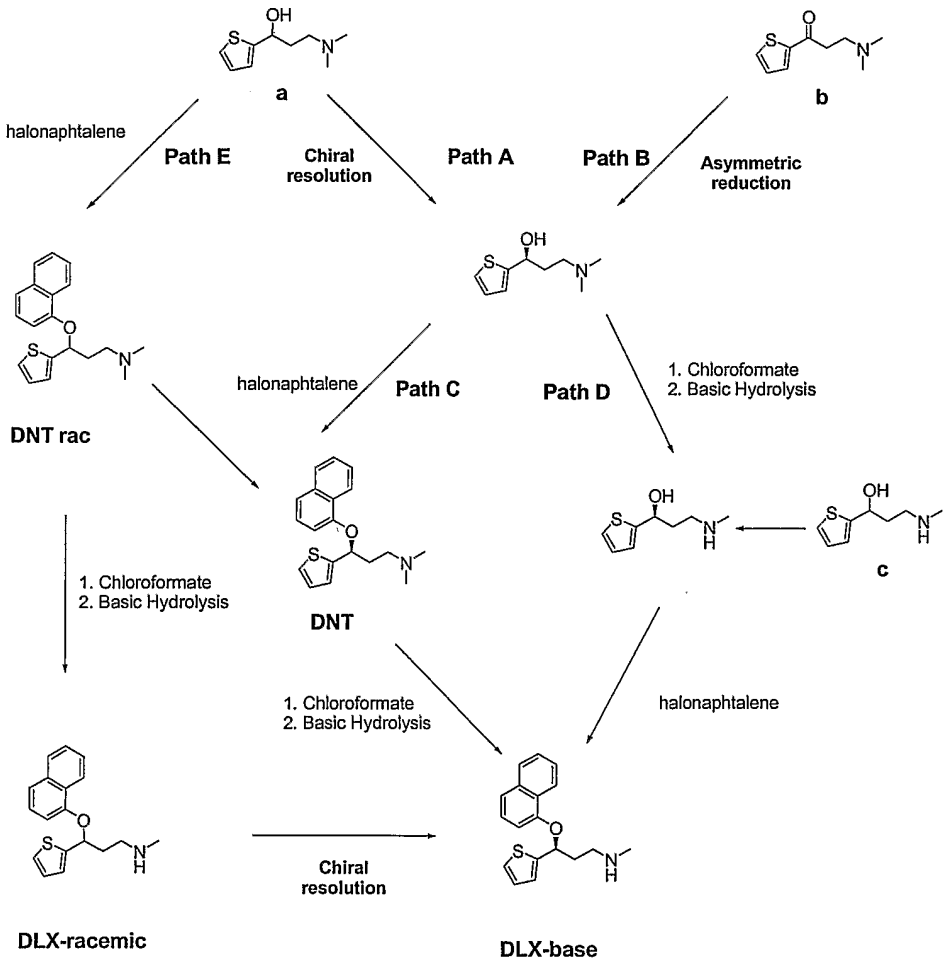
a. Chiral resolution of 3-(Dimethylamino)-1-(2-thienyl)-1-propanol (alcohol **a** in Scheme 2), Path A, followed by Path C or D;

b. Asymmetric reduction of 3-(Dimethylamino)-1-(2-thienyl)-1-propanone (amino ketone **b** in Scheme 2), Path B, followed by Path C or D;

c. Chiral resolution of 3-methylamino-1-(2-thienyl)-1-propanol (alcohol **c** in Scheme 2); and,

d. Chiral resolution of the racemic duloxetine.

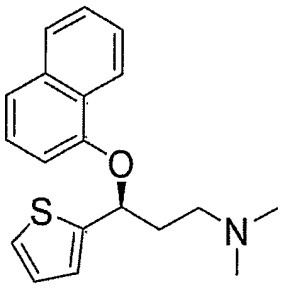
Scheme 2: Prior art synthetic options for the preparation of enantiomerically pure Duloxetine



[00011] The drawback of the processes described in Scheme 2 is the lack of processes for synthesizing an enantiomerically pure DNT and a racemization process for the reprocessing of the undesirable enantiomer.

Summary of the Invention

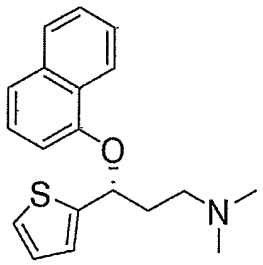
[00012] The present invention is directed to a method of synthesizing (S)-(+)-DNT of Formula II.



Formula II

The method of the invention comprises: (a) treating a solution of (R,S)-DNT with an enantiomerically pure acid (H-EPA); (b) crystallizing a diastereomerically enriched salt of (S)-(+)-DNTH$^+$ EPA$^-$; and, (c) separating the enriched salt.

[00013] The present invention also provides a method of synthesizing (R)-(-)-N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine ((R)-(-)-DNT) of formula III.



Formula III

The method of the invention comprises: (a) treating a solution of (R,S)-DNT with an H-EPA; (b) crystallizing a diastereomerically enriched salt of (R)-(-)-DNTH$^+$ EPA$^-$; and, (c) separating the enriched crystalline diastereomeric salt.

[00014] In alternative embodiments the invention provides a diasteromerically enriched salt of (S)-DNTH$^+$ EPA$^-$ and a diasteromerically enriched salt of (R)-DNTH$^+$ EPA$^-$.

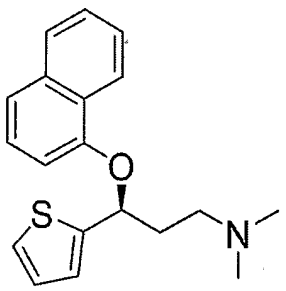
[00015] In a further embodiment, the invention provides a process for the racemization of DNT. The process comprises providing a mixture of DNT, a polar aprotic solvent, and an alkaline metal base, heating the mixture to a temperature of from about room temperature to the reflux temperature of the solvent, and recovering substantially racemic (R,S)-DNT.

[00016] The present invention further provides pharmaceutically acceptable salts of duloxetine, prepared by obtaining (S)-(+)-DNT as described above, and converting the (S)-(+)-DNT to pharmaceutically acceptable salts of duloxetine. Preferably the (S)-(+)-DNT is converted to duloxetine hydrochloride.

Detailed Description of the Invention

[00017] Unless stated otherwise, as used herein, the term "percent" refers to percent by weight.

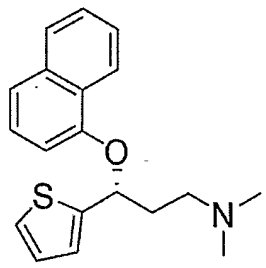
[00018] The present invention provides a method of synthesizing (S)-(+)-DNT of formula II.



Formula II

The method comprises: (a) treating a solution of (R,S)-DNT with an H-EPA;
(b) crystallizing a diastereomerically enriched salt of (S)-(+)-DNTH$^+$ EPA$^-$; and,
(c) separating the enriched salt.

[00019] The present invention provides a method of synthesizing (R)-(-)-DNT of formula III.



III

The method comprises: (a) treating a solution of racemic DNT with an H-EPA; (b) crystallizing a diastereomerically enriched salt of (R)-(-)-DNTH$^+$ EPA$^-$; and, (c) separating the enriched crystalline diastereomeric salt.

[00020] As used herein, "H-EPA" refers to an enantiomerically pure acid. Preferably, the H-EPA is greater than about 75 percent pure enantiomeric acid; i.e., the H-EPA comprises greater than about 75 percent of one enantiomer of the enantiomerically pure acid. More preferably, the H-EPA is greater than about 85 percent pure enantiomeric acid; i.e., the H-EPA comprises greater than about 85 percent of one enantiomer of the enantiomerically pure acid. Most preferably, the H-EPA is greater than about 95 percent pure enantiomeric acid; i.e., the H-EPA comprises greater than about 95 percent of one enantiomer of the enantiomerically pure acid.

[00021] As used herein, "EPA$^-$" refers to the anion of the corresponding H-EPA. A salt of (S)-(+)-DNT and H-EPA is referred to as (S)-(+)-DNTH$^+$ EPA$^-$. A salt of (R)-(-)-DNT and H-EPA is referred to as (R)-(-)-DNTH$^+$ EPA$^-$.

[00022] Preferred enantiomerically pure acids may be selected from the group consisting of di-R-L-sub-tartaric acid, (R)-(-)-mandelic acid and (-)-2,3:4,6-Di-O-isopropylidene-2-keto-L-gulonic acid, and the opposite enantiomerically pure acids. Preferred subgroups include, but are not limited to, toluoyl, benzoyl, and pyvaloyl. Most preferably, the subgroup is toluoyl.

[00023] As used herein, a diasteromerically enriched salt of (S)-DNTH$^+$ EPA$^-$ is preferably a salt which is greater than about 60 percent enriched (S)-DNTH$^+$ EPA$^-$. More preferably, the diasteromerically enriched salt is greater than about 75 percent enriched (S)-DNTH$^+$ EPA$^-$. Even more preferably, the diasteromerically enriched salt is greater than

about 90 percent enriched (S)-$DNTH^+$ EPA^-. Most preferably, the diasteromerically enriched salt is greater than about 95 percent enriched (S)-$DNTH^+$ EPA^-.

[00024] As used herein, a diasteromerically enriched salt of (R)-$DNTH^+$ EPA^- is preferably a salt which is greater than about 60 percent enriched (R)-$DNTH^+$ EPA^-. More preferably, the diasteromerically enriched salt is greater than about 75 percent enriched (R)-$DNTH^+$ EPA^-. Even more preferably, the diasteromerically enriched salt is greater than about 90 percent enriched (R)-$DNTH^+$ EPA^-. Most preferably, the diasteromerically enriched salt is greater than about 98 percent enriched (R)-$DNTH^+$ EPA^-.

[00025] In further embodiments the invention provides a diasteromerically enriched salt of (S)-$DNTH^+$ EPA^- and a diasteromerically enriched salt of (R)-$DNTH^+$ EPA^-.

[00026] The step of treating a solution of (R,S)-DNT with an H-EPA may be performed in an organic solvent or water. Preferred organic solvents may be selected from the group consisting of toluene, ethyl acetate, and dichloromethane.

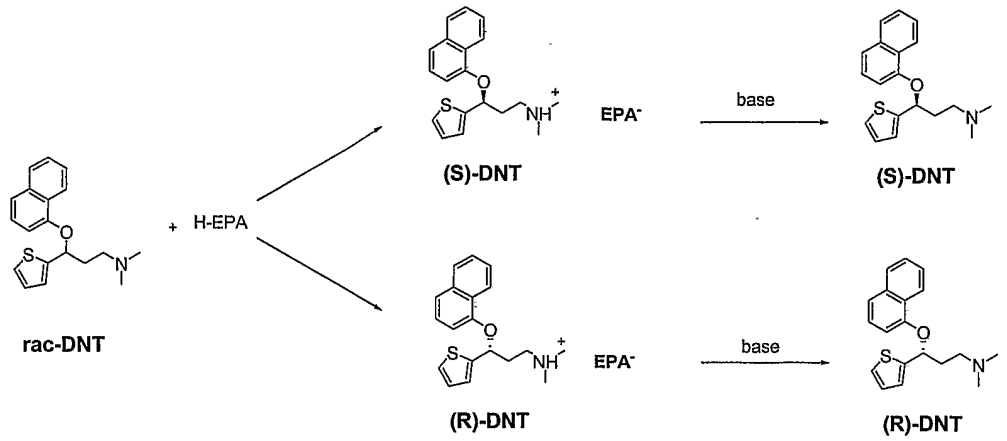
[00027] The step of treating a solution of (R,S)-DNT with an H-EPA may also comprise a step of treating a solution of (R,S)-DNT with H-EPA at a temperature of from about room temperature to about the reflux temperature of the solvent, preferably at a temperature of from about 50° to about 95°C. Preferably, the heating is for about 5 minutes to about 48 hours.

[00028] Preferably, the step of separating the enriched crystalline diastereomeric salt comprises a step of filtration.

[00029] A preferred embodiment embraces a process whereby (R,S)-DNT is reacted with an H-EPA to form a diasteromerically enriched salt. Separation of the salt followed by basic hydrolysis results in enantiomerically enriched (S)-DNT and enantiomerically enriched (R)-DNT accordingly. This process is illustrated in Scheme 3.

Scheme 3

H-EPA: Enantiomerically pure acid



[00030] In a further embodiment, the invention provides a process for the racemization of DNT. The process comprises providing a mixture of DNT, a polar aprotic solvent, and an alkaline metal base, heating the mixture to a temperature of from about room temperature to about the reflux temperature of the solvent, and recovering substantially racemic (R,S)-DNT. The DNT used in the process of the invention can be either enantiomerically pure or enantiomerically rich.

[00031] Preferably, the polar aprotic solvent is selected from the group consisting of dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), dimethylacetamide (DMA), 1-methyl-2-pyrolidinone (NMP) and hexamethylphosphoramide (HMPA). More preferably, the polar aprotic solvent is DMSO.

[00032] Preferably, the alkaline metal base is selected from the group consisting of lithium hydride, lithium N,N-diisopropylamide, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium amide, potassium amide, sodium tert-butoxide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium methoxide, potassium ethoxide. More preferably, the alkaline metal base is potassium hydroxide or potassium tert-butoxide.

[00033] Preferably, the mixture is heated to a temperature of from about 50° to about 140°C, and, more preferably, to about 80°. Preferably, after heating, the mixture is maintained for about fifteen minutes to about 48 hours, and, more preferably, the mixture is

maintained for about 18 hours. The racemic (R,S)-DNT may be recovered by any methods known in the art.

[00034] The present invention further provides pharmaceutically acceptable salts of duloxetine prepared by obtaining (S)-(+)-DNT as described above, and converting the (S)-(+)-DNT to pharmaceutically acceptable salts of duloxetine. Preferably, the (S)-(+)-DNT is converted to duloxetine hydrochloride.

[00035] The function and advantage of these and other embodiments of the present invention will be more fully understood from the examples below. These examples are intended to illustrate the benefits of the present invention, but are not intended to limit the scope of the invention.

Examples

Example 1: Preparation of (S)-DNT di-p-toluoyl-L-tartarate in toluene

[00036] A 1.24 g portion of di-p-toluoyl-L-tartaric acid was added to a solution of 2 g (R,S)-DNT in 10 ml of toluene. The resulting mixture was heated to 75°C for 10 minutes, and then cooled to room temperature. The resulting solid was filtered, and dried in a vacuum oven to give 1.15 g of (S)-DNT di-p-toluoyl-L-tartarate.

Example 2: Preparation of (S)-DNT di-p-toluoyl-L-tartarate in EtOAc/Ether

[00037] A 1.24 g portion of di-p-toluoyl-L-tartaric acid was added to a solution of 2 g (R,S)-DNT in 10 ml of ethyl acetate, and the resulting mixture was stirred at room temperature for an hour. The addition of 6 ml of ether resulted in a precipitate. The mixture was then heated to reflux, and an additional 20 ml of ethyl acetate were added. The mixture was cooled to room temperature, filtered, washed with 10 ml of ether, and dried in a vacuum oven to give 1.41 g of (S)-DNT di-p-toluoyl-L-tartarate.

Example 3: Preparation of (S)-DNT

[00038] A solution of 10 percent by weight NaOH was added to a mixture of 1 g of (S)-DNT di-p-toluoyl-L-tartarate in 30 ml of water and 30 ml of dichloromethane to provide a pH of 14, and stirred for an hour. After phase separation, the organic phase was washed with water (30 ml), dried over Na_2SO_4, filtered, and concentrated to dryness to give 0.4 g of brownish oil (62.17 percent ee).

Example 4: Preparation of (S)-DNT-(R)-mandelate in water

[00039] A 0.49 g portion of (R)-mandelic acid was added to a mixture of 2 g of (R,S)-DNT in 15 ml of water, and the mixture was heated to 95°C, followed by cooling to room temperature over a period of 2 hours. The solid was filtered out, and the mother liquor was allowed to stand overnight. The resulting solid was filtered out, and the resulting solution analyzed by HPLC giving 45 percent ee of (S)-DNT-(R)-mandelate.

Example 5: Preparation of (S)-DNT di-p-toluoyl-L-tartarate in toluene

[00040] A 6.2 g portion of Di-p-toluoyl-L-tartaric acid was added to a solution of 10 g (R,S)-DNT in 100 ml of toluene. The resulting mixture was heated to 75°C for 30 minutes, and then cooled to room temperature. The resulting solid was filtered, and dried in a vacuum oven to give 5.13 g of (S)-DNT di-p-toluoyl-L-tartarate (ee: 77%).

Example 6: Preparation of (S)-DNT di-p-toluoyl-L-tartarate in toluene

[00041] A 0.72 g portion of di-p-toluoyl-L-tartaric acid was added to a solution of 1.16 g (R,S)-DNT (ee: 77%) in 11.6 ml of toluene. The resulting mixture was heated to 75°C for 20 minutes, and then cooled to room temperature. The resulting solid was filtered, and dried in a vacuum oven to give 1.1 g of (S)-DNT di-p-toluoyl-L-tartarate (ee: 98%).

Example 7: Racemization of (S)-DNT with KOH

[00042] A 5.3 g sample of KOH was added to a solution of 55 g of enantiomerically pure DNT (ee: 99.80%) dissolved in 50 ml of DMSO, and the resulting mixture was heated to 80°C. After six hours, the mixture was cooled to room temperature. Water was added to the reaction mixture, followed by the addition of ethyl acetate and AcOH in an amount sufficient to provide a pH of from 8 to 9. After phase separation, the water phase was extracted with ethyl acetate, and the organic extracts were combined and concentrated to dryness to give brownish oil with an ee less than 1%.

Example 8: Racemization of (S)-DNT with potassium tert-butoxide

[00043] A 2.7 g sample of KtBuO was added to a solution of 3.74 g of enantiomerically pure DNT (ee: 99.80%) dissolved in 37 ml of DMSO, and the resulting mixture was heated to 60°C. After eighteen hours, the mixture was cooled to room temperature. Water was added to the reaction mixture, followed by the addition of ethyl acetate and AcOH in an amount sufficient to provide a pH of from 8 to 9. After phase

separation, the water phase was extracted with ethyl acetate, and the organic extracts were combined and concentrated to dryness to give brownish oil with an ee less than 1%.

Example 9: Racemization of (R)-DNT with KOH

[00044] An 8.4 g sample of KOH was added to a solution of 7.5 g of enantiomerically rich DNT dissolved in 75 ml of DMSO, and the resulting mixture was heated to 80°C. After six hours, the mixture was cooled to room temperature. Water was added to the reaction mixture, followed by the addition of ethyl acetate and AcOH in an amount sufficient to provide a pH of from 8 to 9. After phase separation, the water phase was extracted with ethyl acetate, and the organic extracts were combined and concentrated to dryness to give brownish oil with an ee less than 1%.

[00045] While it is apparent that the invention disclosed herein is well calculated to fulfill the objects stated above, it will be appreciated that numerous modifications and embodiments may be devised by those skilled in the art. Therefore, it is intended that the appended claims cover all such modifications and embodiments as falling within the true spirit and scope of the present invention.

What is claimed:

1. A method of synthesizing (S)-(+)-DNT, comprising:
   a) treating a solution of (R,S)-DNT with an H-EPA;
   b) crystallizing a diastereomerically enriched salt of (S)-(+)-DNTH+ EPA-; and
   c) separating the enriched salt.

2. A method of synthesizing (R)-(-)-DNT, comprising:
   a) treating a solution of (R,S)-DNT with an H-EPA;
   b) crystallizing a diastereomerically enriched salt of (R)-(-)-$DNTH^+$ EPA^-; and
   c) separating the enriched salt.

3. The method of any of claims 1 or 2, wherein the H-EPA is greater than about 75 percent pure enantiomeric acid.

4. The method of claim 3, wherein the H-EPA is greater than about 85 percent pure enantiomeric acid.

5. The method of claim 4, wherein the H-EPA is greater than about 98 percent pure enantiomeric acid.

6. The method of any of claims 1 or 2, wherein the H-EPA is selected from the group consisting of di-R-L-sub-tartaric acid, (R)-(-)-mandelic acid, (-)-2,3:4,6-Di-O-isopropylidene-2-keto-L-gulonic acid, and the opposite enantiomerically pure acids.

7. The method of claim 6, wherein the subgroup is selected from the group consisting of toluoyl, benzoyl, and pyvaloyl.

8. The method of claim 7, wherein the subgroup is toluoyl.

9. The method of any of claims 1 or 2, wherein step a) is performed in an organic solvent or water.

10. The method of claim 9, wherein the organic solvents is selected from the group consisting of toluene, ethyl acetate, and dichloromethane.

11. The method of any of claims 1 or 2, wherein step a) is performed at a temperature of from about room temperature to about the reflux temperature of the solvent.

12. The method of claim 11, wherein step a) is performed at a temperature of from about 50° to about 95°C.

13. The method of claim 11, wherein the heating is for about 5 minutes to about 48 hours.

14. The method of claim 1, wherein step c) is followed by basic hydrolysis, obtaining enantiomerically enriched (S)-DNT.

15. The method of claim 2, wherein step c) is followed by basic hydrolysis, obtaining enantiomerically enriched (R)-DNT.

16. A diasteromerically enriched salt of (S)-$DNTH^+$ EPA^-.

17. The diasteromerically enriched salt of claim 16, wherein the salt is enriched with greater than about 60 percent of (S)-$DNTH^+$ EPA^-.

18. The diasteromerically enriched salt of claim 17, wherein the salt is enriched with greater than about 75 percent of (S)-$DNTH^+$ EPA^-.

19. The diasteromerically enriched salt of claim 18, wherein the salt is enriched with greater than about 90 percent of (S)-$DNTH^+$ EPA^-.

20. The diasteromerically enriched salt of claim 19, wherein the salt is enriched with greater than about 95 percent of (S)-$DNTH^+$ EPA^-.

21. A diasteromerically enriched salt of (R)-$DNTH^+$ EPA^-.

22. The diasteromerically enriched salt of claim 21, wherein the salt is enriched with greater than about 60 percent of (R)-$DNTH^+$ EPA^-.

23. The diasteromerically enriched salt of claim 22, wherein the salt is enriched with greater than about 75 percent of (R)-$DNTH^+$ EPA^-.

24. The diasteromerically enriched salt of claim 23, wherein the salt is enriched with greater than about 90 percent of (R)-$DNTH^+$ EPA^-.

25. The diasteromerically enriched salt of claim 24, wherein the salt is enriched with greater than about 98 percent of (R)-$DNTH^+$ EPA^-.

26. A process for the racemization of DNT, comprising:
    a) providing a mixture of DNT, a polar aprotic solvent, and an alkaline metal base;
    b) heating the mixture to a temperature of from about room temperature to about the reflux temperature of the solvent; and
    c) recovering substantially racemic (R,S)-DNT.

27. The process of claim 26, wherein the DNT is enantiomerically pure or enantiomerically rich.

28. The process of either of claims 26 and 27, wherein the polar aprotic solvent is selected from the group consisting of dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), dimethylacetamide (DMA), 1-methyl-2-pyrolidinone (NMP) and hexamethylphosphoramide (HMPA).

29. The process of claim 28, wherein the polar aprotic solvent is DMSO.

30. The process of any of claims 26 to 29, wherein the alkaline metal base is selected from the group consisting of lithium hydride, lithium N,N-diisopropylamide, sodium hydride, potassium hydride, sodium hydroxide, potassium hydroxide, sodium amide, potassium amide, sodium tert-butoxide, sodium methoxide, sodium ethoxide, potassium tert-butoxide, potassium methoxide, potassium ethoxide. More preferably, the alkaline metal base is potassium hydroxide or potassium tert-butoxide.

31. The process of claim 30, wherein the alkaline metal base is potassium hydroxide or potassium tert-butoxide.

32. The process of any of claims 26 to 31, wherein the mixture is heated to a temperature of from about 50° to about 140°C.

33. The process of claim 32, wherein the mixture is heated to a temperature of about 80°.

34. The process of any of claims 26 to 33, wherein, after step b), the mixture is maintained for about fifteen minutes to about 48 hours.

35. The process of claim 34, wherein the mixture is maintained for about 18 hours.

36. A pharmaceutically acceptable salt of duloxetine prepared by obtaining the (S)-(+)-DNT in accordance with the method of any of claims 1 and 3 to 14, and converting the (S)-(+)-DNT to a pharmaceutically acceptable salt of duloxetine.

37. The process of claim 36, wherein the (S)-(+)-DNT is converted to duloxetine hydrochloride.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2006/009247

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D233/22 A61K31/38 A61P25/24 A61P13/00 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 July 2006	24/07/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Bourghida, E.M.

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INTERNATIONAL SEARCH REPORT

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