Abstract:

A process for preparing terbinafine or a salt thereof having high purity.

Title: PROCESS FOR PREPARING TERBINAFINE
PROCESS FOR PREPARING TERBINAFINE

INTRODUCTION TO THE INVENTION

The present invention relates to a process for the preparation of terbinafine and its pharmaceutically acceptable salts. More specifically, the invention relates to a process for the preparation of pure terbinafine and its pharmaceutically acceptable salts.

Terbinafine is chemically known as (E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-V-methyl-1-naphthalenemethanamine and is represented by the structural Formula I.

![Formula I](image)

Terbinafine belongs to the class of allylamine antifungals and is effective upon both oral and topical administration, in a wide range of fungal infections. It is particularly useful against dermatophytes, contagious fungi that invade dead tissues of the skin or its appendages such as the stratum corneum, nails and hair.

Pharmaceutical products containing a salt of terbinafine, terbinafine hydrochloride, as the active ingredient are commercially available in the market as LAMISIL™ in the form of a topical solution, a gel, and a cream containing 1% of the drug compound, and a tablet formulation containing the equivalent of 250 mg of terbinafine base.

European Patent No. 24587 and U.S. Patent No. 4,755,534 disclose terbinafine, its pharmaceutically acceptable salts, pharmaceutical compositions comprising terbinafine and their use in the treatment of fungal infections. Also disclosed is a process for the preparation of terbinafine, which can be depicted by Scheme 1.
In brief, the process includes the reaction of 3,3-dimethyl-1-butyne of Formula III with acrolein in the presence of n-butyl lithium in a tetrahydrofuran medium to yield 6,6-dimethyl-1-hepten-4-yn-3-ol of Formula IV as a residue, which is purified by vacuum distillation. This purified product on reaction with 40% HBr and PBr₃ in an alcohol yields a 3:1 mixture of trans- and cis-1-bromo-6,6-dimethyl-2-hepten-4-yne of Formula V. The compound of Formula V on coupling with N-methyl-1-naphthaienemethylamine of Formula VI in the presence of potassium carbonate in dimethylformamide gives terbinafine of Formula I as a residue, which is chromatographed over Kieselgel using toluene/ethyl acetate 4:1 as the eluent to first give the trans-isomer of terbinafine as an oil, followed by the cis-isomer.

The aforementioned process involves the chromatographic separation of trans-isomer from the residue containing cis- and trans-isomers, leading to poor yields. The process also uses n-butyl lithium as a reagent in the reaction for preparing the compound of Formula IV, resulting in a process that is expensive and difficult to operate on an industrial scale.

It has also been found that terbinafine prepared according to the procedure described in the aforementioned European Patent No. 24587, and U.S. Patent No. 4,755,534 contains impurities; in particular it contains a compound having the names (E)-4-[4,4-dimethylpentyn-(E)-ylidene]-N₁,N₅-dimethyl-N₁,N₅-bisnaphthalen-1-ylmethyl-pent-2-en-1,5-diamine, or 2(E),4(Z)-N-[4-[(N'-methyl-N'-1-naphthylmethyl)aminomethyl]-8,8-dimethyl-2,4-nonadien-6-inyl]-N-methyl-1-naphthylmethanamine, of Formula II (hereinafter referred as the "genotoxic
impurity") that is suspected to be genotoxic and hence control is required in the
drug compound manufacturing process to be sure that the impurity is present at
the lowest possible levels.

purification process to eliminate the genotoxic impurity from terbinafine. The
process comprises short path distillation of terbinafine free base mixed with
peanut oil at a temperature of about 110-170 °C under a reduced pressure such
as about 0.2 mbar. Terbinafine free base boils at about 140° C at 0.3 mbar
pressure, and at that temperature its thermal stability is limited, so product
decomposition can occur.

Processes for the preparation of terbinafine have also been described in
U.S. Patent Nos. 5,440,049, 5,819,875, 6,515,181, 6,570,044, and 6,689,913,
International Application Publication Nos. WO 01/28976 and WO 06/089746, and

Although the processes described in the above documents overcome some
of the difficulties of the process described in European Patent No. 24587, and
U.S. Patent No. 4,755,534, none of the processes completely overcomes the
difficulties.

There is always a need for newer routes of synthesis of commercially
important pharmaceutically active compounds, especially routes that are
commercially feasible, using reactants and conditions, which are non-toxic, which
would be cost effective, and environmentally friendly.
Consequently, it would be a significant contribution to the art to provide newer and improved processes for the synthesis of a commercially important compound such as terbinafine.

SUMMARY OF THE INVENTION

The present invention relates to a process for the preparation of pure terbinafine.

In one aspect, the present invention provides a process for the preparation of pure terbinafine comprising the steps of:

a) purification of 6,6-dimethyl-1-heptene-4-yne-3-ol of Formula IV by distillation;

b) reacting the purified compound of Formula IV with a mixture of an acid initiator and a chlorinating agent in a suitable solvent, followed by purification by distillation to give 1-chloro-6,6-dimethyl-2-heptene-4-yne of Formula VII;

c) condensation of a purified compound of Formula VII with N-methyl-1-naphthalene methylamine of Formula VI or a salt thereof in the presence of a suitable base in a suitable solvent to give terbinafine of Formula I.

In another aspect, the present invention provides a pharmaceutical composition comprising pure terbinafine or its pharmaceutically acceptable salts along with one or more pharmaceutically acceptable carriers, excipients or diluents.

An embodiment of the invention comprises a process for preparing terbinafine or a salt thereof, comprising purifying an intermediate compound 6,6-dimethyl-1-heptene-4-yne-3-ol by distillation under vacuum, then reacting to form 1-chloro-6,6-dimethyl-2-heptene-4-yne.

Another embodiment of the invention comprises a process for preparing terbinafine or a salt thereof, comprising purifying an intermediate compound 1-chloro-6,6-dimethyl-2-heptene-4-yne by distillation under vacuum, then reacting to form terbinafine.

A further embodiment of the invention comprises a process for preparing terbinafine or a salt thereof, comprising:

- purifying 6,6-dimethyl-1-heptene-4-yne-3-ol by distillation under vacuum;
- reacting purified 6,6-dimethyl-1-heptene-4-yne-3-ol with a chlorinating agent to form 1-chloro-6,6-dimethyl-2-heptene-4-yne;
purifying 1-chloro-6,6-dimethyl-2-heptene-4-yne by distillation under vacuum; and
reacting purified 1-chloro-6,6-dimethyl-2-heptene-4-yne with N-methyl-1-naphthalene methylamine or a salt thereof to form terbinafine.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of pure terbinafine.

By "pure terbinafine" it is meant that terbinafine free base or any of the pharmaceutically acceptable salts of terbinafine prepared in accordance with the present invention contains less than about 20 ppm, or less than about 5 ppm, of the genotoxic impurity.

Terbinafine hydrochloride prepared by the process of the present invention is substantially free from the genotoxic impurity of Formula II. It contains less than about 20 ppm, or less than about 5 ppm, of the genotoxic impurity as analyzed by a high performance liquid chromatography (HPLC) chromatogram obtained from a mixture comprising the desired compound and the impurity.

In one aspect, the present invention provides a process for the preparation of pure terbinafine, comprising the steps of:

a) purification of 6,6-dimethyl-1-heptene-4-yno-3-ol of Formula IV by distillation;
b) reacting pure 6,6-dimethyl-1-heptene-4-yne-3-ol of Formula IV with a mixture of an acid initiator and a chlorinating agent in a suitable solvent, followed by purification to give 1-chloro-6,6-dimethyl-2-heptene-4-yne of Formula VII; and

c) condensation of pure 1-chloro-6,6-dimethyl-2-heptene-4-yne of Formula VII with N-methyl-1-naphthalenemethylamine of Formula VI or a salt thereof in the presence of a suitable base in a suitable solvent to give terbinafine of Formula I.

It is preferable to eliminate impurities at earlier stages of a process to have a better control over the process. The process of the present invention involves purification of the intermediates using vacuum distillation, which is carried out at relatively lower temperatures thus preventing decomposition. Also, as pure intermediates are being used, reagents used in the next stages will be consumed efficiently leading to high yields and low cost.

All the intermediates used for the preparation of terbinafine are in the liquid form, hence their purification can be done using vacuum distillation. Adverse consequences resulting from exposing the terbinafine product to high temperatures can be avoided, since the use of purified intermediates results in directly forming terbinafine having a low impurity content.

Step a) involves purification of 6,6-dimethyl-1-heptene-4-yne-3-ol of Formula IV by distillation.
Distillation and/or fractionation are presently the most important thermal purification methods available for purifying liquid compounds. Many different distillation and/or fractionation processes are available, each process describing specific reaction conditions with respect to, for example, temperature and pressure, and each process specifically fine-tuned to provide compounds with specific properties.

Processes according to the present invention may be batch, semi-batch, or continuous processes. From an economic point of view, it is preferred to have only continuous processes.

The vacuum distillation step of the present invention is based on a vacuum distillation method that can involve techniques such as, for example, thin film evaporation, (centrifugal) molecular distillation, wiped film distillation, or falling film distillation. However, no special equipment, such as a short path distillation apparatus, is necessary; distillation can be conducted in any available apparatus that permits application of a suitable vacuum.

Each of these distillation technologies allows the use of very low pressure (high vacuum) during the distillation process, such as below about 10 torr. For the present distillation process, a pressure of about 10 to about 50 torr, or from about 20 to about 40 torr, and a temperature of about 30°C to about 110°C, or about 90°C to about 110°C, are used for the distillation.

Step b) involves reaction of purified 6,6-dimethyl-1-heptene-4-yn-3-ol of Formula IV with a mixture of an acid initiator and a chlorinating agent, optionally in a suitable solvent, followed by purification to give 1-chloro-6,6-dimethyl-2-heptene-4-yn-3-ol of Formula VII.

Suitable solvents which can be used for this step include, but are not limited to, any solvent or mixture of solvents, in which the required compounds are soluble. Examples include: chlorohydrocarbon solvents such as Ci-C₆ straight chain or branched chain chlorohydrocarbons, including dichloromethane, ethylene dichloride, chloroform, carbon tetrachloride, chlorobenzene, dichlorobenzene and the like, or mixtures thereof; hydrocarbon solvents such as C₆-C₁₂ straight chain, branched or cyclic hydrocarbons; nitrile solvents such as acetonitrile, propionitrile and the like; ethers such as tetrahydrofuran; and mixtures thereof.
Suitable acid initiators which can be used include, but are not limited to, hydrochloric acid, hydrobromic acid, acetic acid, formic acid and the like.

Suitable chlorinating agents include, but are not limited to, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride, and the like.

Suitable temperatures for conducting the reaction range from about -15 to 50° C, or about 10 to 40° C, or about 25 to 35° C.

After completion of the reaction, the reaction mass can be quenched by diluting with water and then extracted with a suitable water immiscible solvent. Organic layer can be washed with water and concentrated under vacuum to give a residue.

Suitable solvents which can be used for extraction include, but are not limited to: ether solvents such as diethyl ether, dimethyl ether, di-isopropyl ether, methyl tertiary-butyl ether, tetrahydrofuran, 1,4-dioxane and the like; halogenated solvents such as dichloromethane, 1,2-dichloroethane, chloroform, carbon tetrachloride and the like; hydrocarbon solvents such as toluene, xylene, n-heptane, cyclohexane, n-hexane and the like; nitrile solvents such as acetonitrile, propionitrile and the like; and mixtures thereof.

The product is purified by distillation at about 20 to 110° C, or about 40 to 100° C, or about 55 to 95° C, and under reduced pressure, such as about 10-50 torr, or about 20-40 torr, or about 25-35 torr.

Step c) involves condensation of purified 1-chloro-6,6-dimethyl-2-heptene-4-yne of Formula VII with N-methyl-1-naphthalenemethylamine hydrochloride of Formula VI in the presence of a suitable base in a suitable solvent to give crude terbinafine of Formula I.

Suitable bases which can be used in the reaction include, without limitation: alkyl amines such as tributylamine, triethylamine, diisopropylamine ethylamine and the like; hydroxides of alkali metals such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; and bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate and the like.

Suitable solvents which can be used for the reaction include, but are not limited to any solvent or mixture of solvents, in which the required compounds are soluble. Examples include: chlorohydrocarbon solvents such as Ci-C₆ straight
chain or branched chlorohydrocarbons, including dichloromethane, ethylene dichloride, chloroform, carbon tetrachloride, chlorobenzene, dichlorobenzene and the like; ketone solvents such as acetone, methyl ethyl ketone, ethyl isopropyl ketone, methyl propyl ketone, and the like; polar solvents like water, dimethyl sulfoxide dimethyl formamide and the like; and mixtures thereof.

Suitable temperatures for conducting the reaction can range from about 0 to 100° C, or about 20 to 80° C, or about 40 to 60° C.

Suitably, terbinafine base obtained above can be converted into its pharmaceutically acceptable salts in a suitable solvent.

Suitable pharmaceutically acceptable salts include, but are not limited to, the hydrochloride, hydrobromide, hydrogen sulfate, tosylate, fumarate, maleate, tartrate and methane sulfonate salts, and the like.

In one embodiment, terbinafine free base is converted into a hydrochloride salt using suitable reagents like methanolic hydrochloride, isopropanolic hydrochloride, ethyl acetate hydrochloride, aqueous hydrochloric acid and the like.

Optionally, the pharmaceutically acceptable salt of terbinafine obtained can be purified further in a suitable solvent(s) to provide the purified pharmaceutically acceptable salt of terbinafine.

In an embodiment, a purification process comprises:

a) providing a solution of terbinafine hydrochloride in a suitable solvent;
b) removing solvent from the solution;
c) adding an anti-solvent to precipitate the solid;
d) isolating the precipitated solid; and
e) optionally, drying the solid of step (d) to get pure terbinafine hydrochloride.
The step of providing a solution of terbinafine hydrochloride may include dissolving any form of terbinafine hydrochloride in a suitable organic solvent or obtaining an existing solution from a previous processing step.

Suitable solvents that can be used in step a) include but are not limited to any solvent or mixture of solvents in which the compound is soluble. Examples include, without limitation: ester solvents such as ethyl acetate, propyl acetate and the like; and chlorohydrocarbons such as dichloromethane, ethylene dichloride, chloroform and the like.

The solution is optionally washed with water to remove water-soluble components, and filtered through a filtration medium such as a flux calcined diatomaceous earth ("Hyflow") bed to remove extraneous matter.

Solvent removal of step b) can be done by conventional methods such as evaporation, distillation with vacuum or without vacuum, and expelling with an inert gas such as nitrogen.

A suitable solvent that can be used in step c) includes any solvent or mixture of solvents, in which terbinafine hydrochloride has a low solubility. Examples include ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like, and nitrile solvents such as acetonitrile, propionitrile and the like.

The reaction mass of step c) can be stirred at the reflux temperature of the solvent used, to make sure that all the impurities are completely soluble. The reaction mass then can be cooled to a temperature that may range from about -50 to 50° C or about 0 to 5° C.

The isolation of solid of step d) can be carried out by using conventional techniques, such as centrifugation, gravity filtration, or vacuum filtration or other techniques known in the art for the separation of solids.

The drying operation of step e) is carried out by using any technique, such as for example fluid bed drying, aerial drying, oven drying or other techniques known in the art. The drying can be conducted at temperatures of about 20-100° C or about 60-70° C with or without application of vacuum. It is also conceived that the drying can be carried out under inert conditions.

Terbinafine hydrochloride prepared by the process of the present invention contains less than about 0.5%, or less than about 0.1%, of the corresponding impurities like terbinafine 4-methyl impurity, N-methyl-bis-1-naphthalene
methanamine dimer impurity, terbinafine dimer impurity, and terbinafine beta and Z-isomers, as characterized by a high performance liquid chromatography ("HPLC") chromatogram obtained from a mixture comprising the desired compound and one or more of the said impurities. The percentages are determined using area-% of the peaks representing the said impurities, and area-% of peaks from samples containing suitable standard amounts of the impurities.

As used herein "terbinafine 4-methyl impurity" refers to (E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-4-methyl-1-naphthalene methanamine represented by Formula VIII;

![Formula VIII](image)

As used herein "terbinafine Z-isomer" refers to (Z)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalene methanamine represented by Formula IX.

![Formula IX](image)

As used herein "terbinafine dimer impurity" refers to (E)-N,N-Bis-(6,6-Dimethyl-2-hepten-4-ynyl-N-methyl)-1,4-naphthalene methanamine, represented by Formula X.

![Formula X](image)
As used herein "terbinafine beta isomer" refers to (E)-N-(6,6-Dimethyl-2-hepten-4-ynyl)-N-methyl-2-naphthalene methanamine, represented by Formula XI.

As used herein "N-methyl-Bis-1-naphthalene methanamine dimer impurity" refers to (N-methyl)-Bis-i-naphthalene methanamine, represented by Formula XII.

In general, the terbinafine or terbinafine salt product purity, as determined by HPLC, will be at least about 95 %, or about 99 %, or about 99.5 %, by weight.

A goal that was not achieved by the prior processes is providing an economically feasible process to produce terbinafine with good color quality and color stability in good yield. It is noted that the term "color quality" refers to the color just after preparation of the terbinafine, whereas the term "color stability" relates to the color of terbinafine when measured after storage in a closed container for at least 21 days at 45 °C at ambient humidity. The product of the present invention has shown acceptable color and stability for more than 200 days.
Terbinafine hydrochloride prepared in this process is also substantially free from color forming impurities. A 5% w/v solution of terbinafine hydrochloride in methanol (such as by dissolving 0.5 g of sample in methanol to produce a 10 ml volume) has an absorbance less than about 0.2, or less than about 0.1, or less than about 0.05, as measured by spectrophotometry at 430 nm using a cell providing a 10 mm path length.

Terbinafine hydrochloride prepared by this process contains residual solvents at concentrations equal to or less than the requirement of ICH guidelines. For example terbinafine hydrochloride prepared according to this process contains the residual solvents: acetone at less than about 5000 ppm, or less than about 1000 ppm, or less than about 300 ppm; methanol at less than about 3000 ppm, or less than about 1000 ppm, or less than about 100 ppm; acetonitrile at less than about 410 ppm, or less than about 200 ppm, or less than about 50 ppm; dimethylformamide at less than about 880 ppm, or less than about 200 ppm, or less than about 50 ppm; dichloromethane at less than about 600 ppm, or less than about 300 ppm, or less than about 100 ppm; and petroleum ether at less than about 200 ppm, or less than about 100 ppm, or less than about 50 ppm,

Terbinafine hydrochloride prepared according to this embodiment has a mean particle size less than about 200 microns, or less than about 100 microns, or less than about 25 microns. This means that about 50 volume percent of the particles have sizes less than, or equal to, the specified size, such as is measured using a laser light scattering instrument.

Another aspect of the present invention provides a pharmaceutical composition comprising pure terbinafine or its pharmaceutically acceptable salts obtained using the process of the present invention along with one or more pharmaceutically acceptable carriers, excipients or diluents.

The pharmaceutical composition comprising pure terbinafine or its pharmaceutically acceptable salts along with one or more pharmaceutically acceptable carriers of this invention may further formulated as: solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as but not limited to syrups, suspensions, dispersions, and emulsions; and injectable preparations such as but not limited to solutions, dispersions, and freeze dried compositions. Formulations may be in the form of immediate release, delayed release or modified release. Further,
immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared by direct blending, dry granulation or wet granulation or by extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated or modified release coated. Compositions of the present invention may further comprise one or more pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients that find use in the present invention include, but are not limited to: diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinyl pyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, pregelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, crospovidone, croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins, resins; release rate controlling agents such as hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose, methyl cellulose, various grades of methyl methacrylates, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but are not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

Terbinafine and its salts may alternatively be administered topically, e.g. in the form of formulations such as lotions, solutions, ointments, creams or nail lacquers, or parenterally, or intravenously. The concentration of active substance will, of course, vary depending on the treatment desired and the nature of the form or formulation used. In general, satisfactory results are obtained in topical
formulations at concentrations of from about 0.1% to about 10%, or about 0.5% to about 2% by weight.

In the compositions of present invention terbinafine or its pharmaceutically acceptable salts is a useful active ingredient in the range of 0.5 mg to 50 mg, or 1 mg to 25 mg.

Certain specific aspects and embodiments of the processes and forms described herein are further described in the following examples. These examples are provided solely for the purpose of illustrating the particular aspects and embodiments of the invention, and therefore should not be construed as limiting the scope of the invention.

**EXAMPLE 1**

**PREPARATION OF 6,6-DIMETHYL-1-HEPTENE-4-YNE-3-OL (FORMULA IV)**

49.5 kg of magnesium turnings were taken into a clean and dry reactor containing 360 liters of tetrahydrofuran under stirring. 45 g of iodine was charged to the reaction mass and 12 kg of ethyl bromide was added slowly to the reaction mixture. Initiation of a reaction was observed and temperature sharply rose to 63 °C. Then a mixture of 237 kg of ethyl bromide and 60 liters of tetrahydrofuran was added to the reaction mass at 52 °C. The reaction mass was maintained at 52 °C for 2 hours and then cooled to 5 °C and 120 liters of tetrahydrofuran was added to it. 150 kg of 3,3-dimethylbutyne was added to the reaction mass slowly at -2 °C to 4 °C and maintained for 90 minutes at the same temperature. 60 liters of tetrahydrofuran was charged to the reaction mass and 120 liters of acrolein was added slowly at -3 to -2 °C. The reaction mass was maintained at the same temperature for 90 minutes and then the temperature was raised to about 50 °C. The maintenance was continued at 55 °C for 2.5 hours and then the mass was cooled to 15 °C. 750 liters of cold water was added to the reaction mass and 180 liters of 36% aqueous hydrochloric acid was added slowly at 15 °C. The reaction mass was extracted twice with 600 liters and 300 liters of dichloromethane respectively. The organic layers were combined and washed three times with water (3x900 liters). Final organic layer was distilled completely under vacuum below 78 °C to obtain 210 kg of the title compound as a residue.
50 kg of the residue thus obtained was charged into a clean reactor containing 125 liters of dichloromethane and stirred for 15 minutes to get a clear solution. The solutions was washed three times with water (3*50 liters) and the solvent was distilled completely under vacuum at below 60 °C to get a residue.

The residue was charged into a clean and dry reactor and purified by fractional distillation. The main fraction was collected at 90-95 °C under reduced pressure of 18 to 40 torr to get 44.3 kg of purified 6,6-dimethyl-1-heptene-4-yne-3-ol.

EXAMPLE 2

PREPARATION OF 1-CHLORO-6,6-DIMETHYL-2-HEPTENE-4-YNE (FORMULA VII)

30 kg of pure 6,6-dimethyl-1-heptene-4-yne-3-ol obtained in Example 1 was taken into a reactor containing 103 liters of acetonitrile under stirring. The mass was cooled to 10 °C and a homogeneous mixture of 7.1 liters of phosphorous oxychloride in 52 liters of aqueous hydrochloric acid was added to the mass slowly at 12 °C. The mass was maintained at this same temperature for 60 minutes and then the temperature was raised to 25 °C. Temperature was maintained at 28 °C for 5 hours and then 130 liters of water was charged. The mass was stirred for 20 minutes and was extracted three times with petroleum ether (3*90 liters). The combined organic layers were washed with water (4*100 liters) and the solvent was distilled completely below 80 °C to get 42.8 kg of the title compound as a residue.

The residue thus obtained was charged into a clean and dry reactor and was purified by fractional distillation. The main fraction was collected at 57-98 °C under reduced pressure of 30-60 torr to get 22.2 kg of the purified 1-chloro-6,6-dimethyl-2-heptene-4-yne.

EXAMPLE 3

PREPARATION OF TERBINAFINE HYDROCHLORIDE

29 kg of N-methyl-1-naphthalene methylamine hydrochloride was charged into a reactor containing 70.4 liters of dimethylformamide and 11 liters of water, under stirring. The contents were stirred for 15 minutes for clear dissolution and 11 kg of sodium carbonate was added to it. The reaction mass was cooled to 13
°C and 22 kg of 1-chloro-6,6-dimethyl-2-heptene-4-yne was added slowly at 11 to 14 °C. The reaction mixture was stirred at 12 to 14 °C for 60 minutes and then heated to 55 °C. The reaction mass was maintained at 60 °C for 5 hours and reaction completion was confirmed by thin layer chromatography. The reaction mass was cooled to room temperature and 99 liters of water was added. Reaction mass was extracted three times with a total of 75 liters of dichloromethane (3x25 liters). Total organic layer was washed twice with 88 liters of water (2x44 liters); 18 liters of water was charged to the final organic layer and was cooled to 13 °C. Reaction mass pH was adjusted to 0.2 by adding 15 liters of 36% aqueous hydrochloric acid and stirring for 30 minutes. The organic layer was separated and washed three times with a total of 267 liters of water (3x89 liters). Final organic layer was transferred into a reactor and the solvent was distilled completely below 45° C. 11.8 liters of petroleum ether was charged and the solvent distilled completely at below 50° C. Again 68 liters of petroleum ether was charged and heated to reflux. The mass was stirred at reflux for 30 minutes and cooled to 50 °C. The solid thus formed was allowed to settle for 60 minutes and the top petroleum ether layer was decanted. The decantation process was repeated two more times. Finally 44 liters of petroleum ether was charged, heated to reflux, maintained for 30 minutes at reflux and then cooled to 25 °C. The contents were stirred for 60 minutes at 20 to 25 °C and centrifuged to recover the solid. The centrifuged solid was washed twice with petroleum ether (2x16 liters) and spin-dried for about 60 minutes to get 29.3 kg of crude terbinafine hydrochloride as a semi-dry solid.

EXAMPLE 4
PURIFICATION OF TERBINAFINE HYDROCHLORIDE

27.4 kg of crude terbinafine hydrochloride was taken into a clean reactor containing 100 liters of dichloromethane under stirring. The contents were stirred for 25 minutes and then 40 liters of water was added. The mass was stirred for 10 minutes and the organic layer was separated. The organic layer was again washed with 40 liters of water. Final organic layer was heated and solvent distilled completely under vacuum below 45 °C. 15 liters of acetone was the added to the residue and distilled completely under vacuum below 65 °C. The residue was
cooled to 30 °C and then 25 liters of acetone was charged. The mixture was then heated to reflux and maintained for 30 minutes, then cooled to 5 °C and stirred for 60 minutes. The material was centrifuged and the solid washed with 25 liters of chilled acetone. The solid was dried at 74 °C for 3 hours, 30 minutes and subjected to multi-milling using a 40 mesh screen at 30 °C. The milled material was then sieved through a 40-mesh sieve yielding 16.8 kg of the pure terbinafine hydrochloride as a white crystalline solid.

Purity by HPLC: 99.93 %.
Genotoxic impurity: less than 2.5 ppm by HPLC.

EXAMPLE 5
DETERMINATION OF GENOTOXIC IMPURITY CONTENT IN TERBINAFINE

A method for determining the level of genotoxic impurity in terbinafine and its salts using HPLC uses the analysis conditions described in Table 1.

Table 1: HPLC method for detecting the level of genotoxic impurity.

<table>
<thead>
<tr>
<th>Column:</th>
<th>Xterra RP18, 150×3.0 mm, 3.5 μ.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile Phase A:</td>
<td>1 ml triethylamine in 1000 ml degassed water.</td>
</tr>
<tr>
<td>Mobile Phase B:</td>
<td>1 ml triethylamine in 1000 ml degassed acetonitrile.</td>
</tr>
<tr>
<td>Gradient program:</td>
<td>Time (in minutes)</td>
</tr>
<tr>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>18.0</td>
</tr>
<tr>
<td></td>
<td>24.0</td>
</tr>
<tr>
<td></td>
<td>26.0</td>
</tr>
<tr>
<td></td>
<td>30.0</td>
</tr>
<tr>
<td></td>
<td>35.0</td>
</tr>
<tr>
<td></td>
<td>40.0</td>
</tr>
<tr>
<td>Temperature:</td>
<td>27° C</td>
</tr>
<tr>
<td>Injection volume:</td>
<td>20 μL</td>
</tr>
<tr>
<td>Flow rate:</td>
<td>1.0 mL per minute</td>
</tr>
<tr>
<td>Detector:</td>
<td>225 nm</td>
</tr>
</tbody>
</table>
CLAIMS:

1. A process for preparing terbinafine or a salt thereof, comprising purifying an intermediate compound 6,6-dimethyl-1-heptene-4-yne-3-ol by distillation under vacuum, then reacting to form 1-chloro-6,6-dimethyl-2-heptene-4-yne.

2. The process of claim 1, wherein distillation is conducted at temperatures about 30°C to about 110°C.

3. The process of claim 1, wherein distillation is conducted at temperatures about 90°C to about 110°C.

4. A process for preparing terbinafine or a salt thereof, comprising purifying an intermediate compound 1-chloro-6,6-dimethyl-2-heptene-4-yne by distillation under vacuum, then reacting to form terbinafine.

5. The process of claim 4, wherein distillation is conducted at temperatures about 20°C to about 110°C.

6. The process of claim 1, wherein distillation is conducted at temperatures about 40°C to about 100°C.

7. The process of claim 1, wherein distillation is conducted at temperatures about 50°C to about 95°C.

8. A process for preparing terbinafine or a salt thereof, comprising:
   - purifying 6,6-dimethyl-1-heptene-4-yne-3-ol by distillation under vacuum;
   - reacting purified 6,6-dimethyl-1-heptene-4-yne-3-ol with a chlorinating agent to form 1-chloro-6,6-dimethyl-2-heptene-4-yne;
   - purifying 1-chloro-6,6-dimethyl-2-heptene-4-yne by distillation under vacuum; and
   - reacting purified 1-chloro-6,6-dimethyl-2-heptene-4-yne with N-methyl-1-naphthalene methylamine or a salt thereof to form terbinafine.

9. The process of claim 8, wherein distillation of 6,6-dimethyl-1-heptene-4-yne-3-ol is conducted at temperatures about 90°C to about 110°C.

10. The process of claim 8, wherein a chlorinating agent comprises phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, or thionyl chloride.
11. The process of claim 8, wherein distillation of 1-chloro-6,6-dimethyl-2-heptene-4-yne is conducted at temperatures about 40°C to about 100°C.

12. The process of claim 8, wherein purified 1-chloro-6,6-dimethyl-2-heptene-4-yne is reacted with a salt of N-methyl-1-naphthalene methylamine.

13. The process of claim 8, further comprising reacting terbinafine with an acid to form a salt.

14. The process of claim 8, further comprising reacting terbinafine with hydrochloric acid to form terbinafine hydrochloride.

15. The process of claim 14, further comprising purifying terbinafine hydrochloride by crystallization from an acetone solution.

16. Terbinafine or a salt thereof prepared by the process of any one of claims 1-15, wherein a 5 percent w/v solution has an absorbance less than about 0.2, as measured by spectrophotometry at 430 nm using a cell having a 10 mm path length.

17. Terbinafine or a salt thereof prepared by the process of any one of claims 1-15, wherein a 5 percent w/v solution has an absorbance less than about 0.1, as measured by spectrophotometry at 430 nm using a cell having a 10 mm path length.

18. Terbinafine or a salt thereof prepared by the process of any one of claims 1-15, wherein a 5 percent w/v solution has an absorbance less than about 0.05, as measured by spectrophotometry at 430 nm using a cell having a 10 mm path length.

19. Terbinafine or a salt thereof prepared by the process of any one of claims 1-18, having less than about 2.5 ppm of the impurity (E)-4-[4,4-dimethylpentyn-(E)-ylidene]-N\(^1\),N\(^5\)-dimethyl-N\(^1\),N\(^5\)"bisnaphthalen-1-ylmethyl-pent-2-en-1,5-diamine.
# INTERNATIONAL SEARCH REPORT

**International application No.**

PCT/US06/38292

## A. CLASSIFICATION OF SUBJECT MATTER

**IPC(8):**

- C07C 1700( 2006.01),1700( 2006.01),C07C 2090( 2006.01),21100( 2006.01)

**USPC:**

- 570/216.217.242.564/386.337

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)**

U.S.: 570/216, 217, 242, 564/386, 337

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 practicable, search terms used)

CAS ONLINE, EAST AND WEST

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 6,770,786 B1 (BOD ET AL) 03 August 2004, see Examples 1-6, col. 5-11.</td>
<td>1-19</td>
</tr>
</tbody>
</table>

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

| * Special categories of cited documents: |  | T | Later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |
|  |  | X | Document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |
|  |  | Y | Document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |

Date of the actual completion of the international search: 04 March 2007 (04.03.2007)

Date of mailing of the international search report: 19 Mar 2007

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Facsimile No. (571) 273-3201

Autonz

Fajar Parsi

Telephone No. (571) 272-2717

Form PCT/ISA/210 (second sheet) (April 2005)