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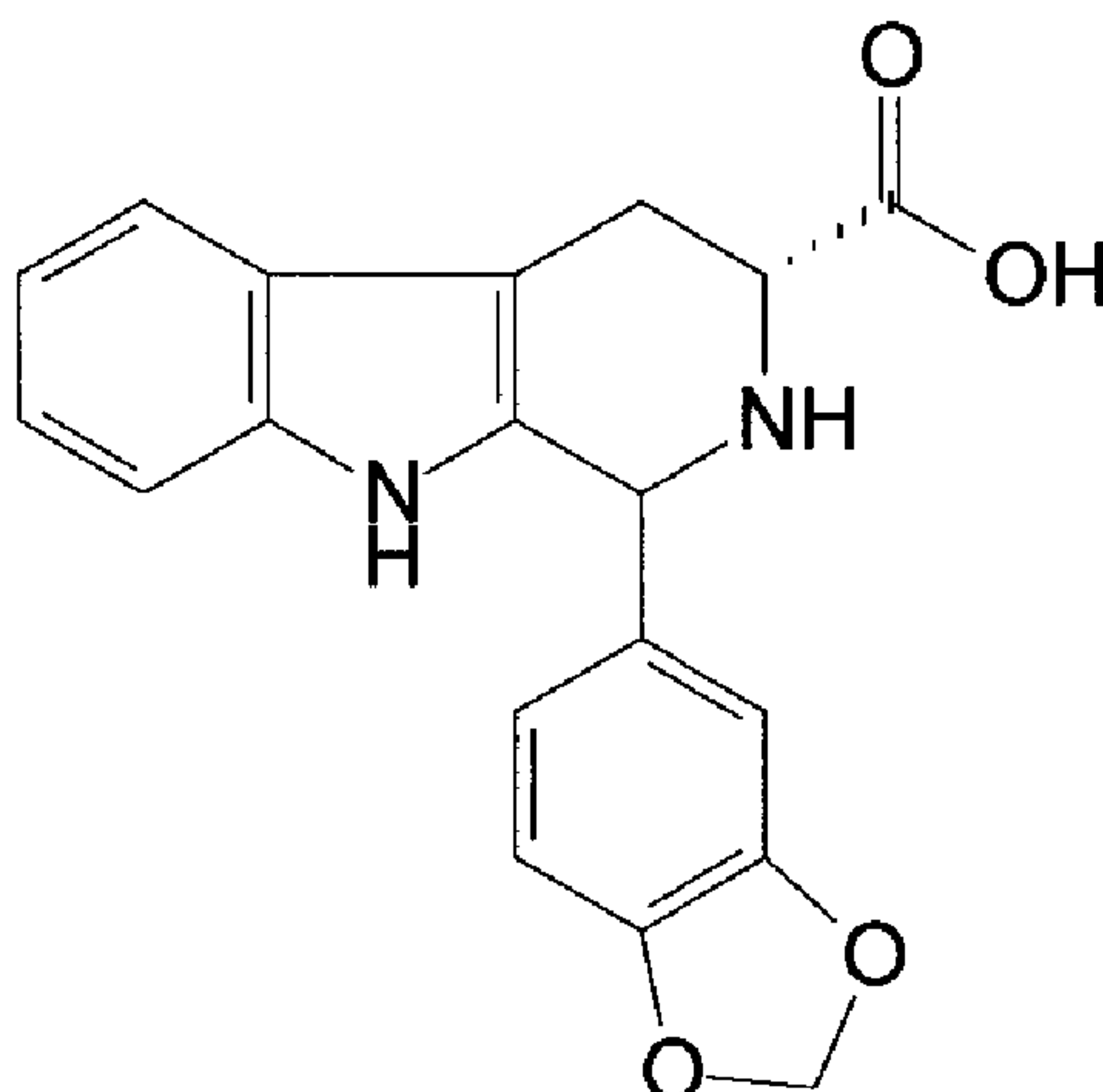
(71) Demandeur/Applicant:
APOTEX INC., CA

(72) Inventeurs/Inventors:
BODHURI, PRABHUDAS, CA;
CECCARELLI, ALFREDO PAUL, CA;
WEERATUNGA, GAMIMI, CA;
GORIN, BORIS, CA

(74) Agent: GOODMAN'S LLP

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(54) Title: PROCESSES FOR THE PREPARATION OF TADALAFIL AND INTERMEDIATES THEREOF



(4)

(57) **Abrégé/Abstract:**

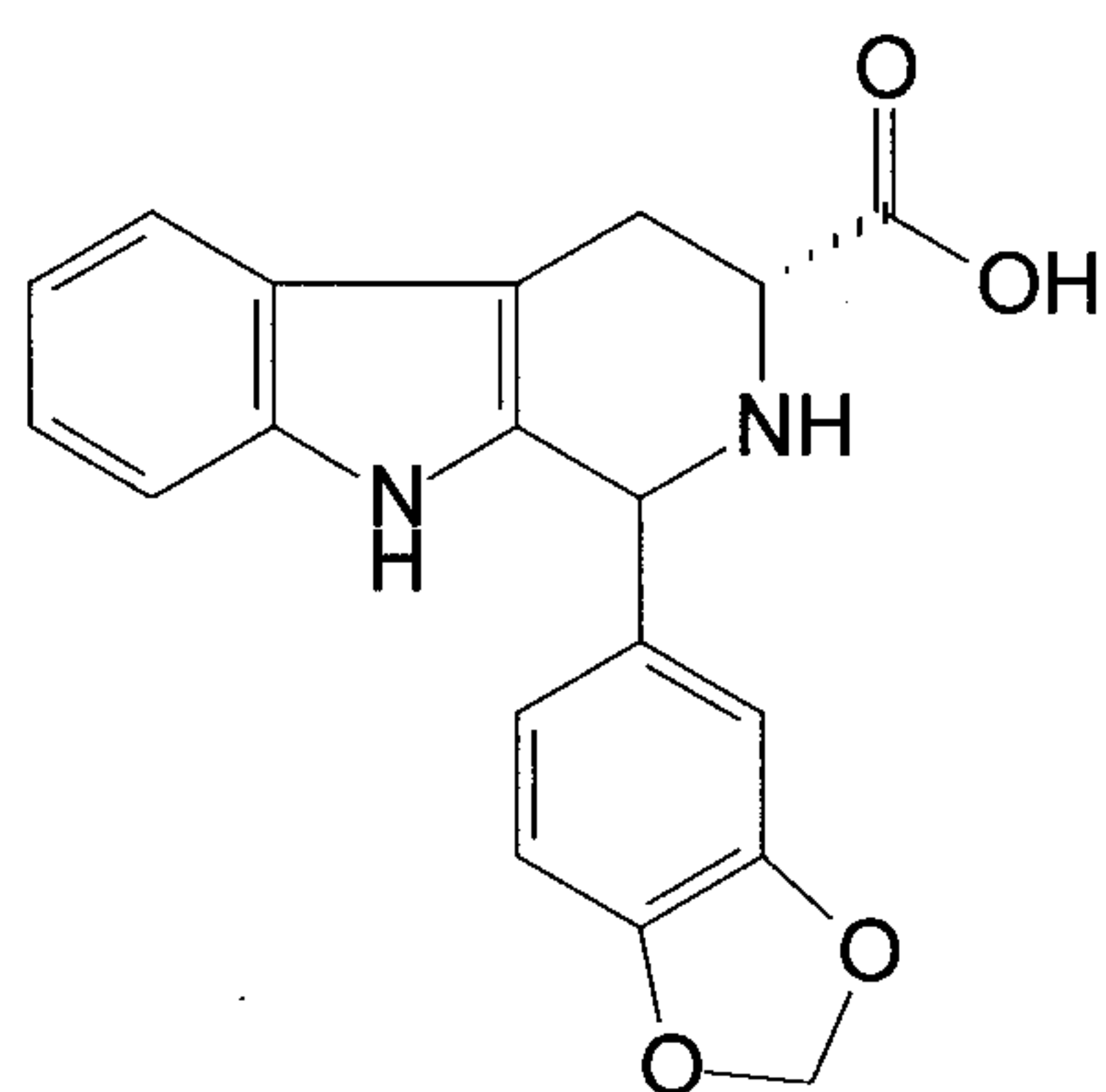
The present invention provides processes for the preparation of Tadalafil (1), and in particular, improvements in the preparation of the compound of Formula (4), through the use of substantially anhydrous inorganic acids.

(see formula 4).

ABSTRACT

The present invention provides processes for the preparation of Tadalafil (1), and in particular, improvements in the preparation of the compound of Formula (4), through the use of substantially anhydrous inorganic acids.

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(4).

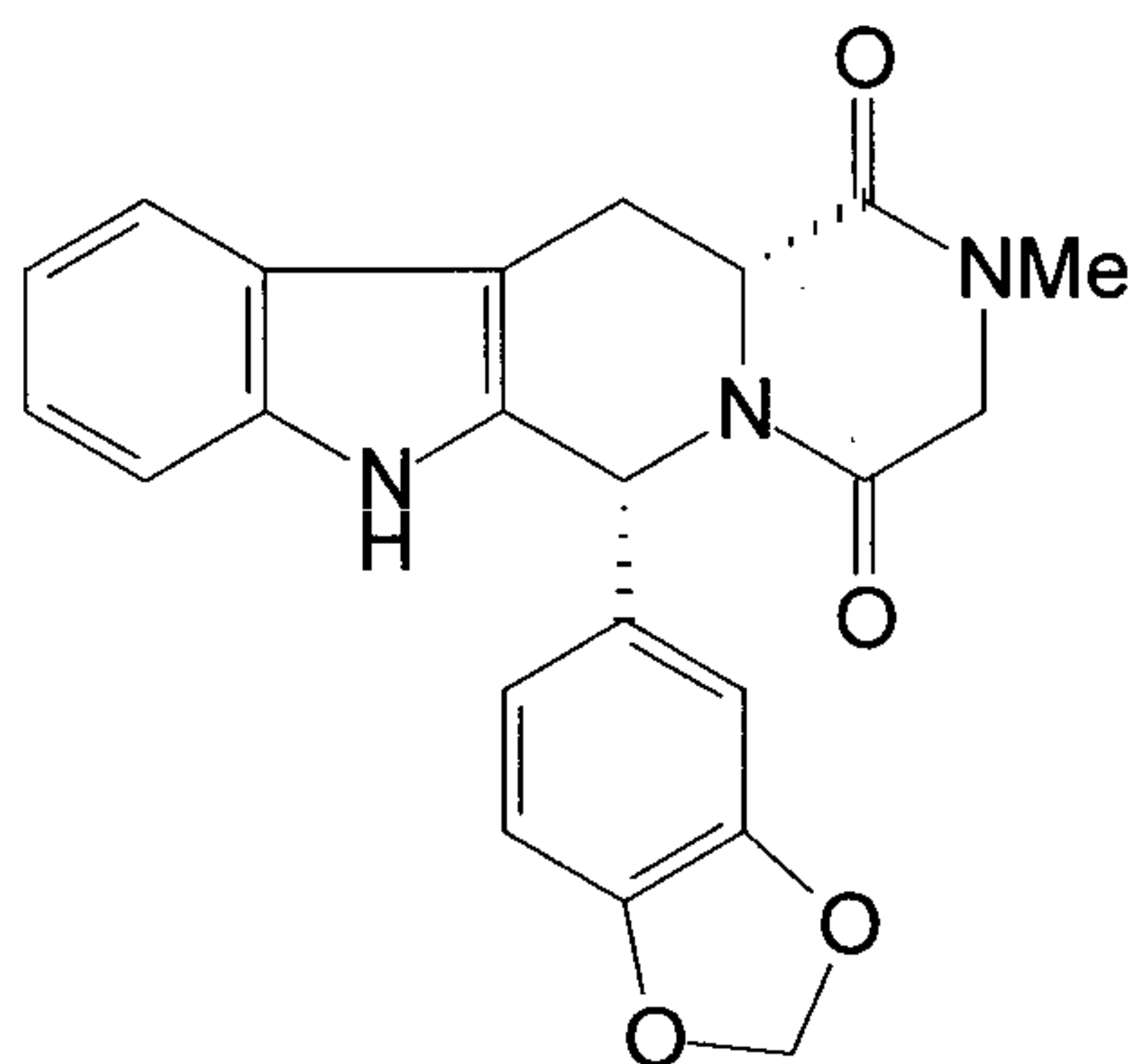
PROCESSES FOR THE PREPARATION OF TADALAFIL AND INTERMEDIATES THEREOF

TECHNICAL FIELD

[0001] The present invention relates to processes for the preparation of Tadalafil and intermediates used in the preparation thereof.

BACKGROUND

[0002] Tadalafil (1), or (6R, 12aR)-6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexa hydro-2-methylpyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, which is the active pharmaceutical ingredient in CIALIS®, is indicated for the treatment of erectile dysfunction, has the following structural formula:

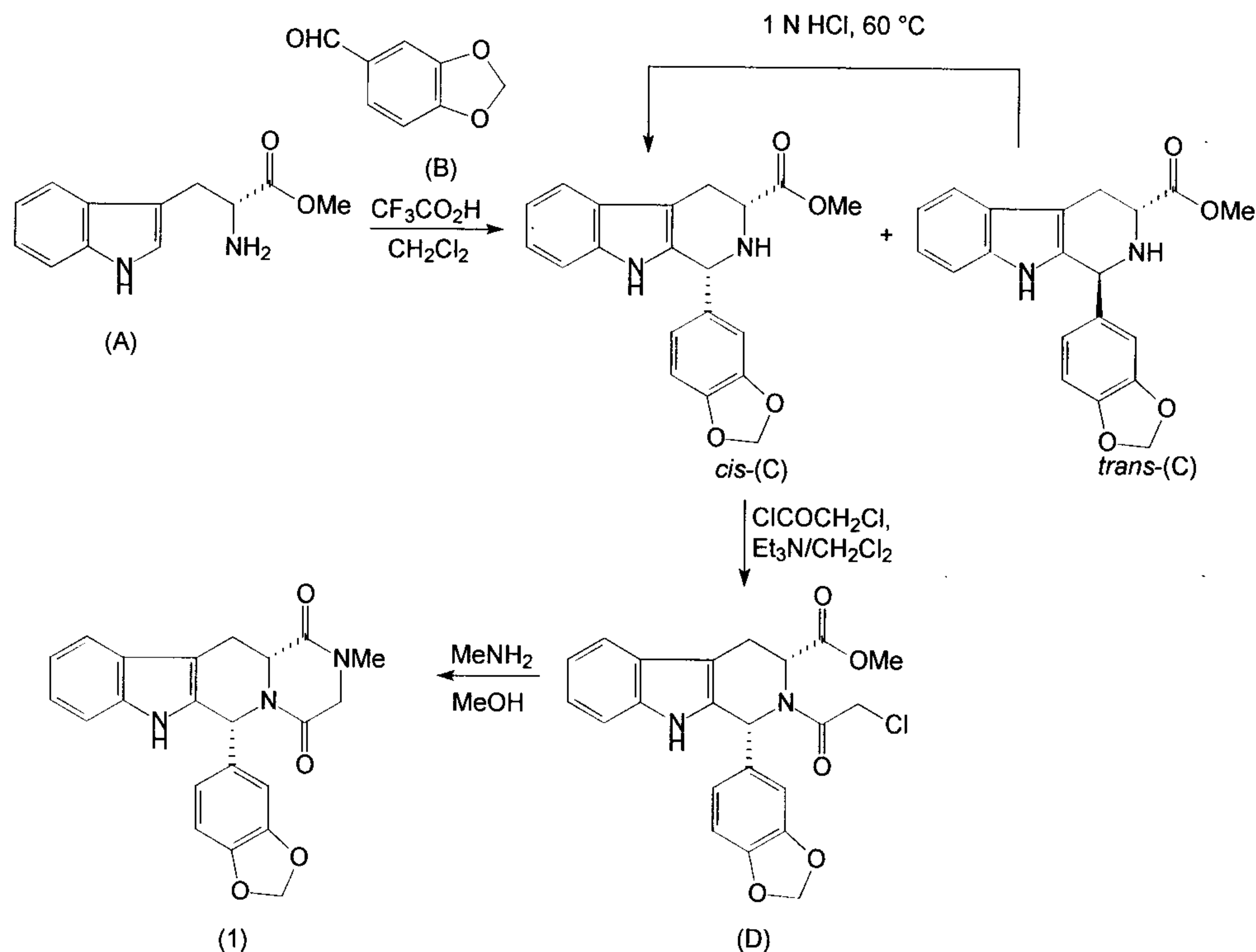


(1).

[0003] Tadalafil was disclosed in WO 95/19978 A1 as one compound in a group of tetracyclic compounds exhibiting inhibition of cyclic guanosine 3',5'-monophosphate specific phosphodiesterase (cGMP specific PDE), and was prepared by the process described in Scheme 1. The key step of this approach involves a Pictet-Spengler reaction between (D)-tryptophan methyl ester (A) and piperonal (B), which yields a mixture of *cis*- and *trans*-1,3-tetrahydro- β -carboline (C) in a ratio of about 60/40. Following separation of the *cis*- and *trans*- isomers of the compound of Formula (C) by fractional crystallization or column chromatography, the undesired *trans*-isomer is subjected to epimerization in aqueous HCl to produce further *cis*-isomer in the form of a hydrochloride salt. The pure *cis*-isomer of the compound of Formula (C), obtained in a total yield of about 62%, is treated with chloroacetyl chloride to provide the compound of Formula (D), which undergoes reaction with

methylamine to afford Tadalafil (1) with an overall yield of about 25% from the compound of Formula (A).

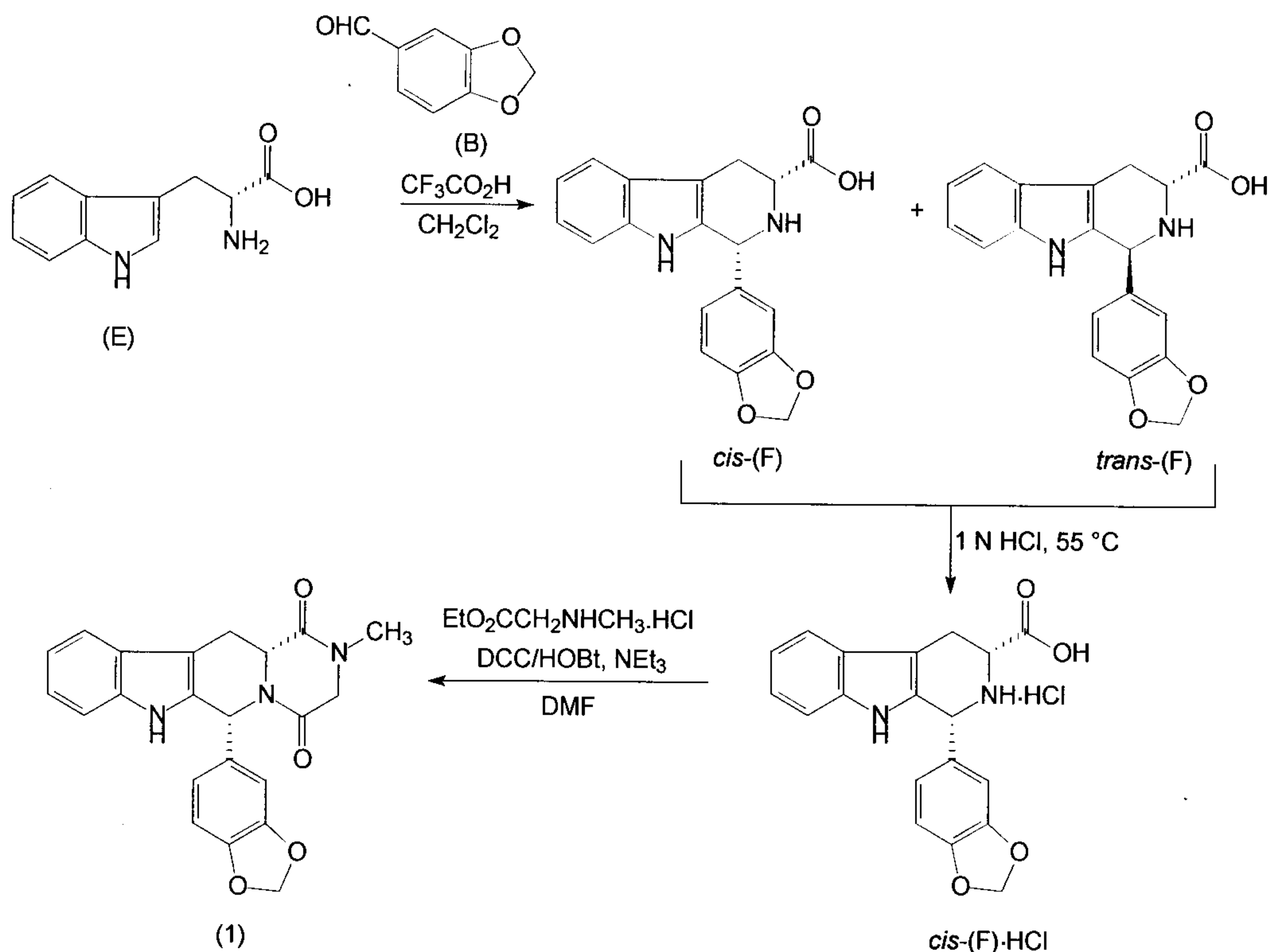
Scheme 1 (Prior Art)



- 5 [0004] A number of other procedures for the preparation of Tadalafil (1) employing a Pictet-Spengler reaction between (D)-tryptophan methyl ester (A) and piperonal (B) are reported in, for example, WO 2004/011463 A1; WO 2005/068464 A2; WO 2006/110893 A2; WO 2007/052283 A1; WO 2009/004557 A2; Ganesan, A. *et al. Synlett* **2004**, 8, 1428-1430; Wu, X. *et al. Org. Prep. Proc. Int.* **2005**, 37(1), 99-102; Shi, X.-X *et al. Tetrahedron: Asymmetry* **2008**, 19, 435-442; Shi, X.-X *et al. Tetrahedron: Asymmetry* **2009**, 20, 2090-2096; and Shi, X.-X *et al. Tetrahedron: Asymmetry* **2013**, 24, 883-893. In these procedures, the diastereoselectivity of the Pictet-Spengler reaction is reported to be influenced by a number of factors, particularly the reaction temperature and solvent. For example, a procedure described in WO 2004/011463 A1 states that the desired diastereomer of the compound of Formula (C) is provided in greater than 90% yield by conducting the condensation reaction in isopropyl alcohol. However, like the process
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described in WO 95/19978, each of these procedures requires conversion of (D)-tryptophan (the compound of Formula (E) in Scheme 2) to the corresponding methyl ester (the compound of Formula (A)) prior to the key condensation reaction.

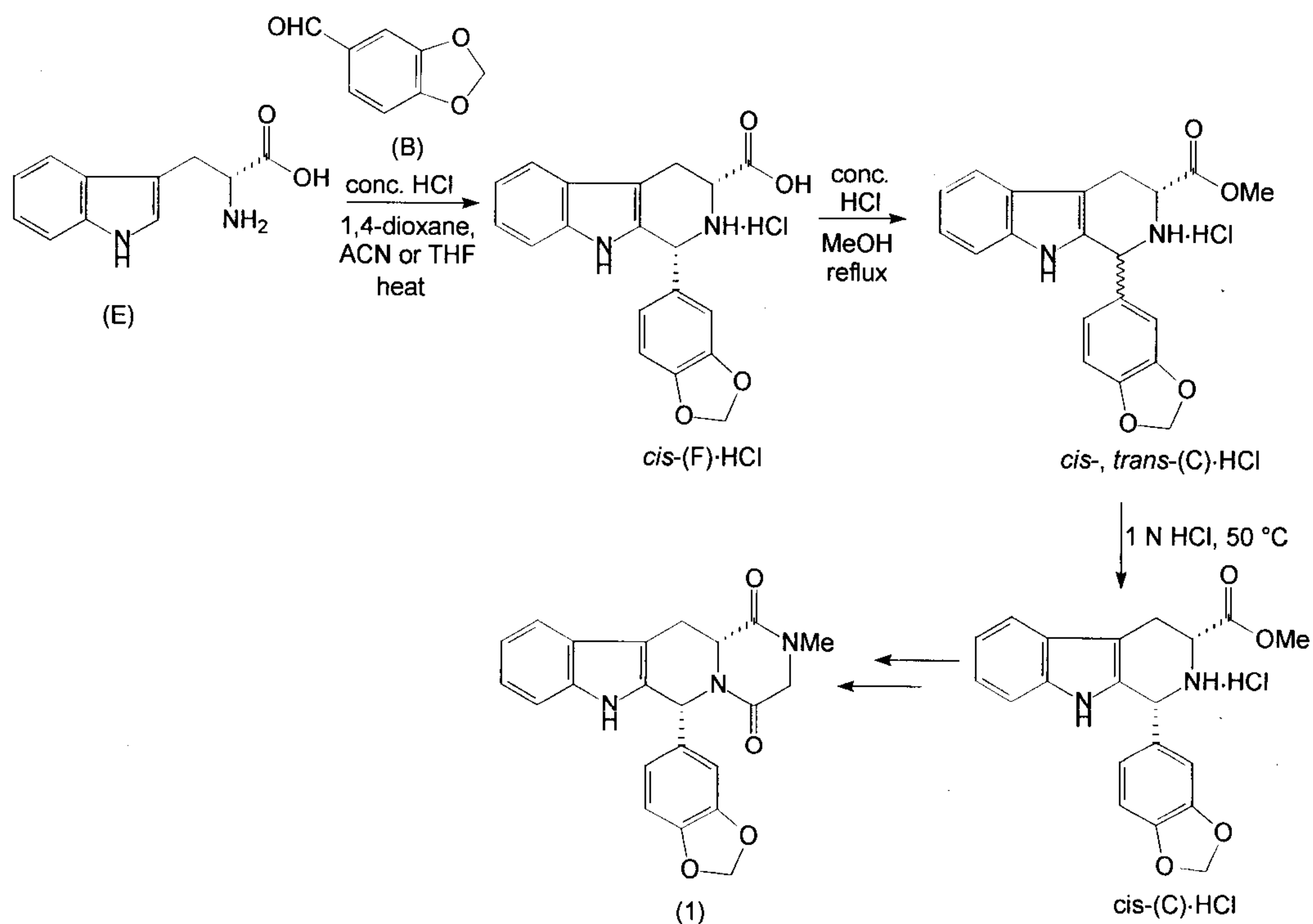
5 [0005] WO 2007/100387 A2 and Anumula *et al.* *Synth. Commun.* **2008**,
38, 4265-4271 disclose a process, shown in Scheme 2, for the preparation of
Tadalafil involving a Pictet-Spengler reaction between (D)-tryptophan (E) and
10 piperonal (B). The condensed product, comprised of the *cis*- and *trans*-
isomers of the compound of Formula (F), is treated with aqueous acid to
generate pure *cis*-isomer of the compound of Formula (F) as the HCl salt,
which is reacted with sarcosine ethyl ester hydrochloride in the presence of
amide coupling agents (DCC (*N,N'*-dicyclohexyldiimide)/HOBt
(hydroxybenzotriazole)) to provide Tadalafil (1). In this procedure, the key
15 reaction between tryptophan and piperonal is conducted in dichloromethane
using trifluoroacetic acid. However, the aqueous work-up conditions following
this condensation are complex and impractical to operate on an industrial
scale. Furthermore, the process requires the use of amide coupling agents
DCC and HOBt in the final step, which are associated with increased cost,
20 generation of by-products such as DCU (dicyclohexylurea), and safety
considerations.

Scheme 2 (Prior Art)

- [0006] Further processes for the preparation of Tadalafil involving the condensation of (D)-tryptophan (E) and piperonal (B) are reported in Anderson, M. *et al. Eur. J. Org. Chem.* **2014**, 1653-1665 and WO 2009/121791 A1. However, the processes reported in the Anderson *et al.* involve microwave irradiation, which is impracticable for use in the large-scale batch synthesis of Tadalafil.
- [0007] WO 2009/121791 A1 discloses two approaches for the preparation of Tadalafil, both involving the condensation of (D)-tryptophan (E) and piperonal (B) in the presence of an aqueous inorganic acid. In one approach, depicted in Scheme 3, the condensation of (D)-tryptophan (E) and piperonal (B) is conducted in the presence of a non-chlorinated solvent and an aqueous inorganic acid to selectively yield the *cis*-isomer of the compound of Formula (F) as a hydrochloride salt. The compound of Formula (F) can be further converted to Tadalafil (1) by coupling with sarcosine ethyl ester using DCC/HOBt conditions, which suffer from the problems noted. Alternatively, as shown in Scheme 3, the acidic compound of Formula (F) is first converted to

the corresponding methyl ester, which can be transformed to Tadalafil as above. Methylation of the compound of Formula (F) is performed in refluxing concentrated aqueous hydrochloric acid and methanol. However, due to a reversal of the *cis*-isomer selectivity under these conditions, the methyl ester of Formula (C) that is produced in this step must be subsequently subjected to isomerization in aqueous hydrochloric acid to afford the required *cis*-isomer of the compound of Formula (C) as the hydrochloride salt. Using this approach, the reaction of (D)-tryptophan (E) to provide the *cis*-isomer of the compound of Formula (C) as the HCl salt takes approximately 76 hours (the shortest overall reaction time reported) and affords the product in only overall 30% yield.

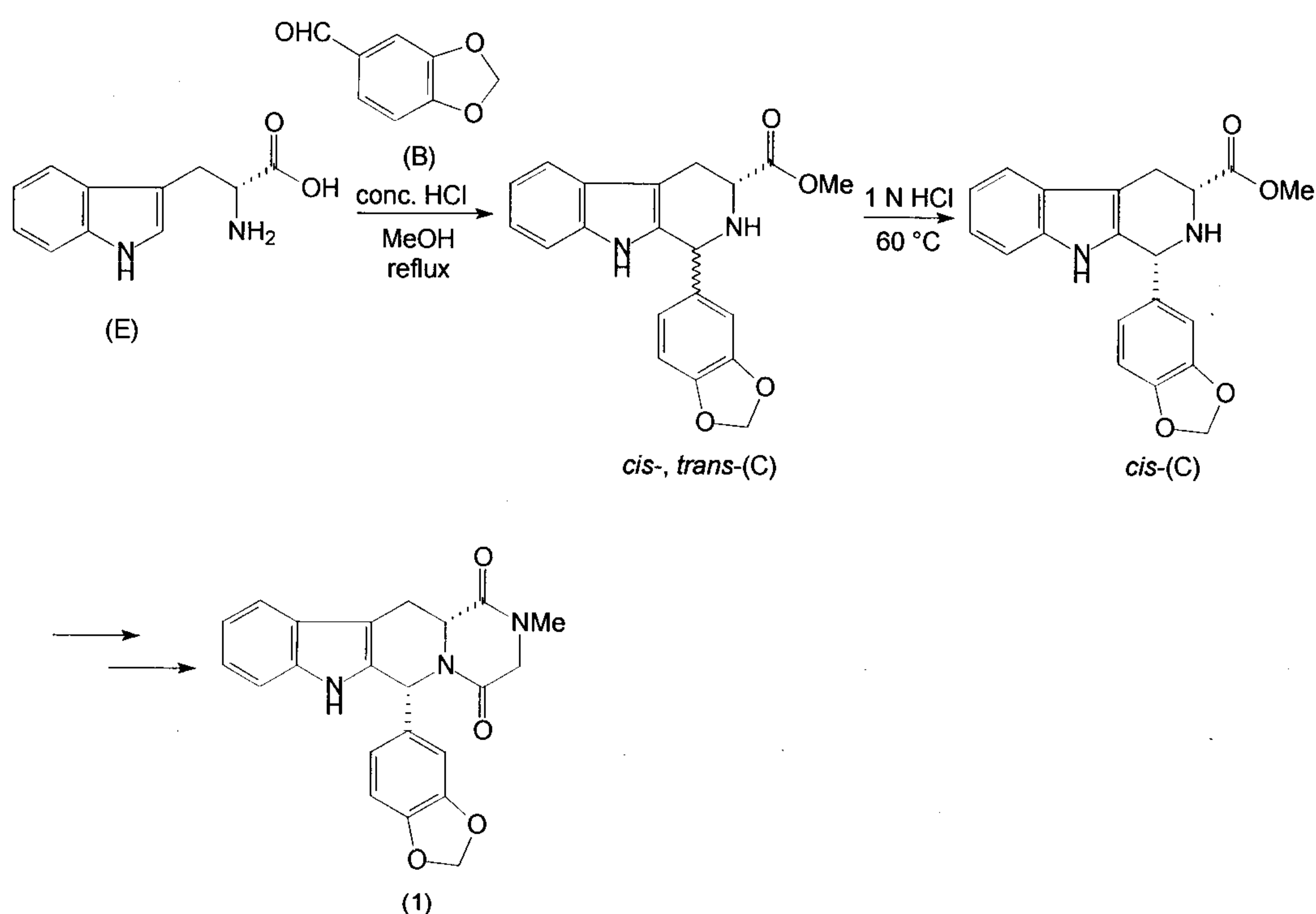
Scheme 3 (Prior Art)



[0008] In the second approach for the preparation of Tadalafil reported in WO 2009/121791 A1, depicted in Scheme 4, the condensation of (D)-tryptophan (E) and piperonal (B) is conducted in the presence of alcoholic media and inorganic acid to directly yield the condensed product as a mixture of the *cis*- and *trans*-isomers of the compound of Formula (C). In the reported examples, the shortest reaction time to generate the mixture of the *cis*- and

trans-isomers of the compound of Formula (C) is 3 days. Furthermore, as for the process described in Scheme 3, owing to the poor *cis*-isomer selectivity when the reaction is conducted in acidic alcoholic media, the compound of Formula (C) must be further subjected to isomerization conditions in aqueous hydrochloric acid to generate the desired *cis*-isomer. Using this approach, the shortest reaction time reported for the generation of the *cis*-isomer of the compound of Formula (C) from (D)-tryptophan (E) is 108 hours with a yield of 61%.

Scheme 4 (Prior Art)



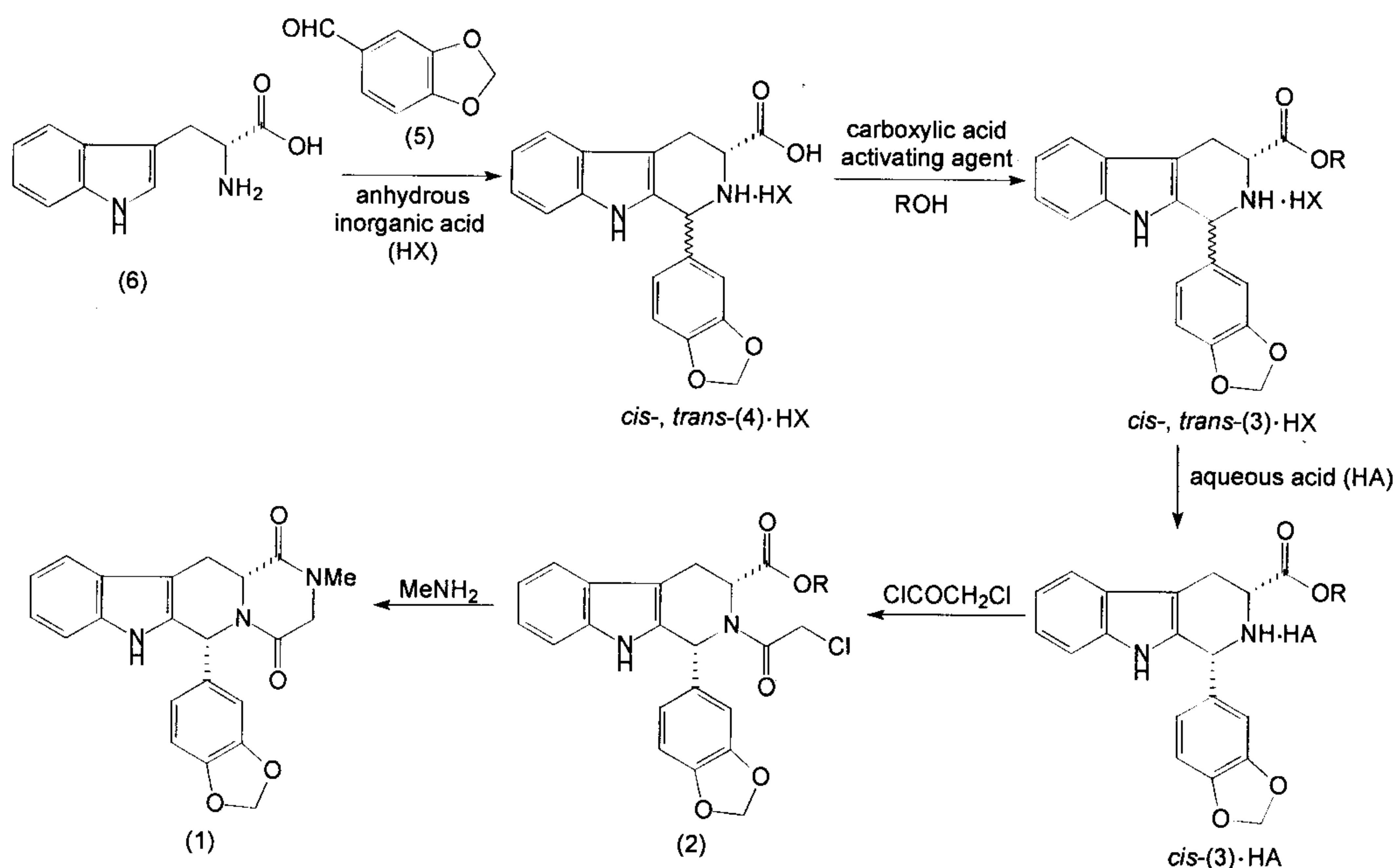
[0009] Accordingly, there remains a need in the art for improved processes for the preparation of Tadalafil and the intermediates used in such processes.

SUMMARY

[0010] The present invention provides processes for the preparation of Tadalafil, as well as intermediates useful in the preparation thereof, as exemplified in Scheme 5. These processes provide an improved method for preparation of Tadalafil (1) starting from (D)-tryptophan (6), which provides intermediates (4) and (3) using simple isolation steps, that are conveniently used

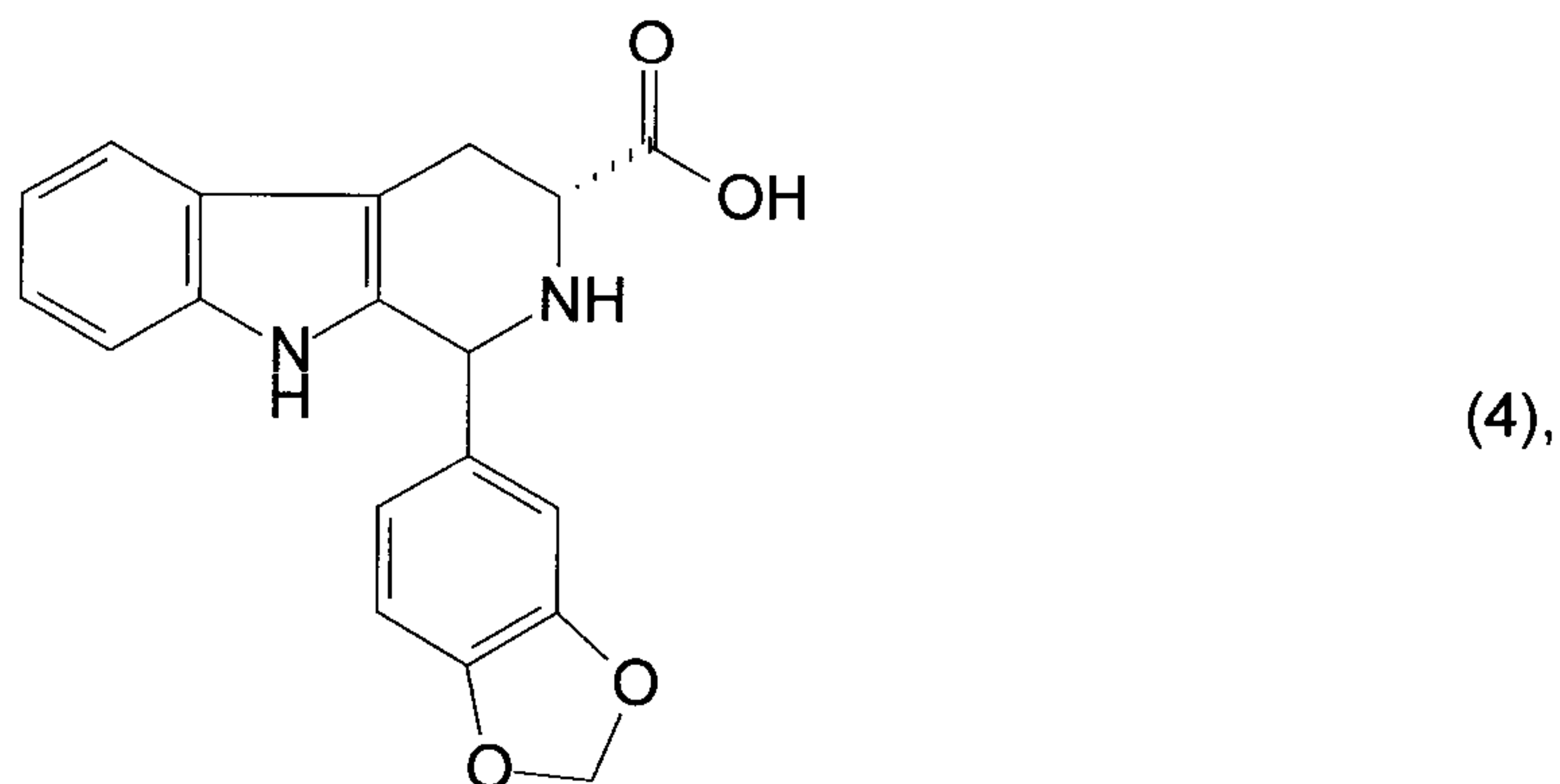
on a commercial scale, in good yield and in reasonable reaction times. Furthermore, in preferred embodiments, the process of the present invention avoids the necessity of using amide coupling agents DCC and HOBt and the associated issues related to cost, safety and by-product removal.

5 Scheme 5

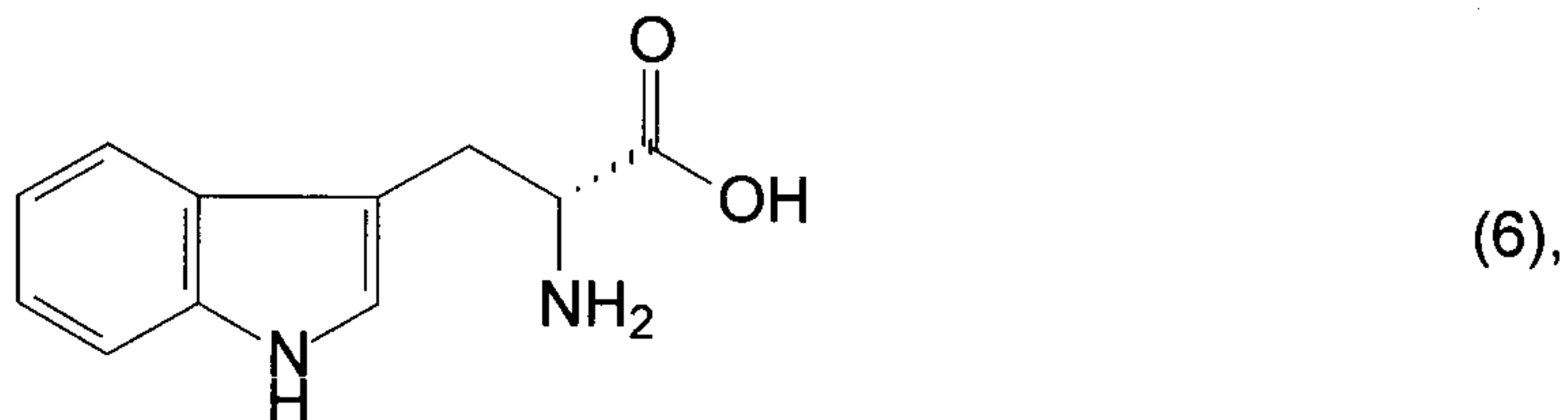


wherein R is a C1-C4 alkyl group.

[0011] Accordingly, in a first aspect of the present invention, there is provided a process for the preparation of a compound of Formula (4):



or a salt thereof, the process comprising condensing, under substantially anhydrous conditions in the presence of an inorganic acid (HX) and an organic solvent (S1), a compound of Formula (6):



or a salt thereof, and a compound of Formula (5):

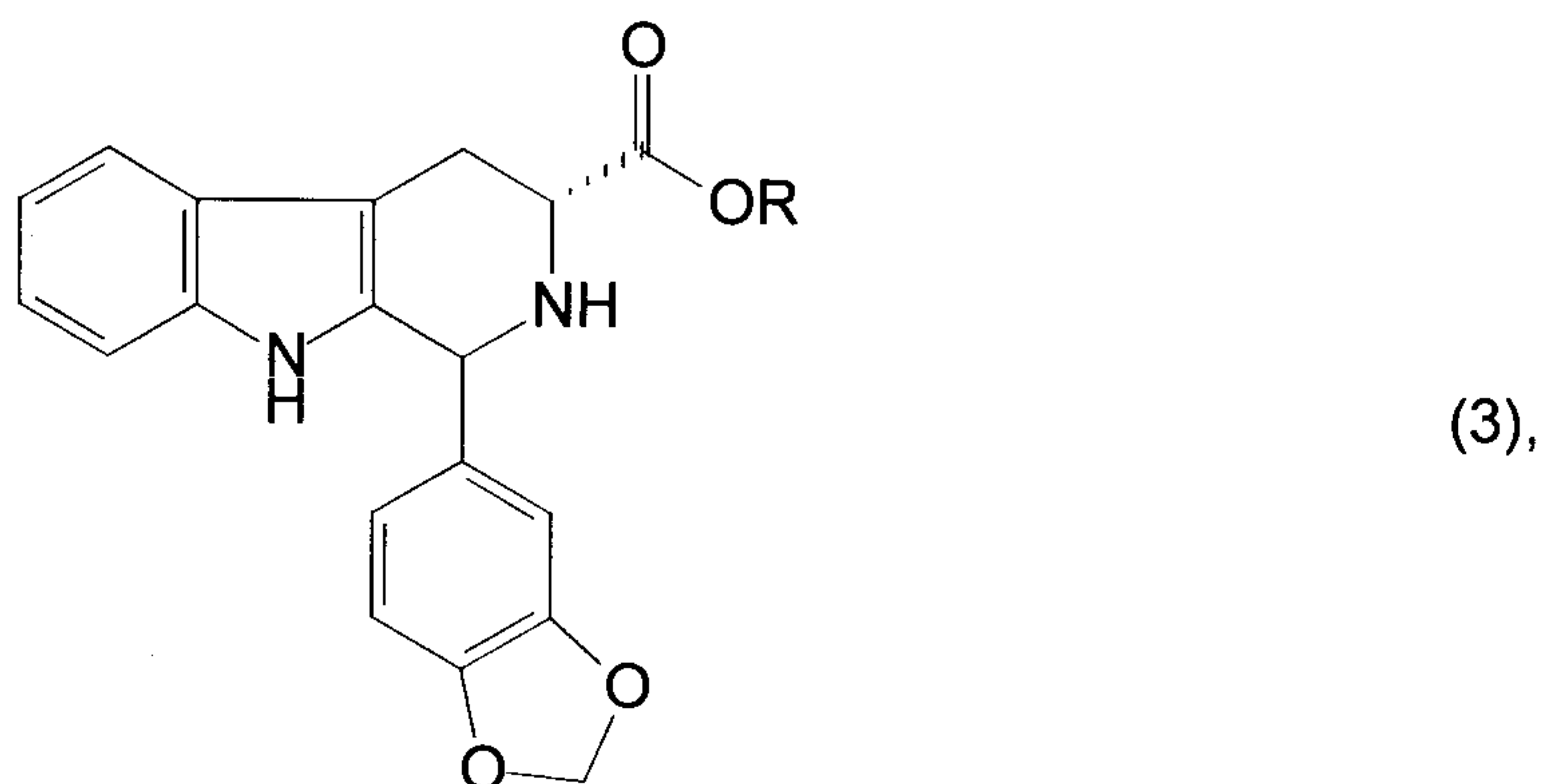


5 [0012] In a preferred embodiment of the first aspect, the process is conducted under substantially anhydrous conditions where the initial water content is less than about 3 wt%, more preferably, less than about 1 wt%. In another preferred embodiment of the first aspect, the inorganic acid (HX) used is selected from the group consisting of hydrogen halides, sulfuric acid, nitric acid, and phosphoric acid. Most preferably, the inorganic acid (HX) is hydrogen chloride. Within this first aspect of the invention, the solvent (S1) is an ether selected from the group consisting of 1,4-dioxane, tetrahydrofuran, methyl *t*-butyl ether and 2-methyl tetrahydrofuran, and is most preferably 1,4-dioxane. Within the first embodiment, the process is preferably conducted at 10 a temperature of about 55 °C to about 75 °C.

15 [0013] Within the first aspect of the invention, the compound of Formula (4) is preferably provided as a salt with acid (HX). Preferably, the compound of Formula (4) is enriched in the *cis*-isomer relative to the *trans*-isomer. Most preferably, the dr is at least 90% enriched with respect to the *cis*-isomer.

20 [0014] In a second aspect of the invention, there is provided a process wherein the compound of Formula (4), or a salt thereof, prepared according to the process of the first aspect of the invention is further converted to Tadalafil (1).

[0015] In a third aspect of the invention, there is provided a process wherein the compound of Formula (4), or a salt thereof, prepared according to the process of the first aspect of the invention is further subjected to esterification in the presence of an alcohol (ROH) and a carboxylic acid activating agent, to provide a compound of Formula (3):



or a salt thereof, wherein R is a C1-C4 alkyl group.

[0016] In a preferred embodiment of the third aspect, the carboxylic acid activating agent is selected from the group consisting of hydrogen chloride, oxalyl chloride, thionyl chloride, alkyl chloroformate and 1,1'-carbonyldiimidazole. Most preferably, the carboxylic acid activating agent is thionyl chloride or hydrogen chloride. Preferably, the esterification of the third aspect of the invention is carried out at a temperature of about 55 °C to about 75 °C.

[0017] Within the third aspect of the invention, the compound of Formula (3) is preferably provided as a salt. Preferably, the compounds of Formulas (3) and (4) are enriched in the *cis*-isomer relative to the *trans*-isomer.

[0018] Preferably, the process of the third aspect of the invention is conducted under substantially anhydrous conditions.

[0019] In a fourth aspect of the invention, there is provided a process wherein the compound of Formula (3), or a salt thereof, prepared according to the process of the third aspect of the invention is converted to the compound of Formula (1) (Tadalafil) by a process comprising:

- (i) heating the compound of Formula (3), or a salt thereof, in the presence of aqueous acid (HA) to isomerize the *trans*-isomer to the *cis*-isomer of the compound of Formula (3), or a salt thereof; and

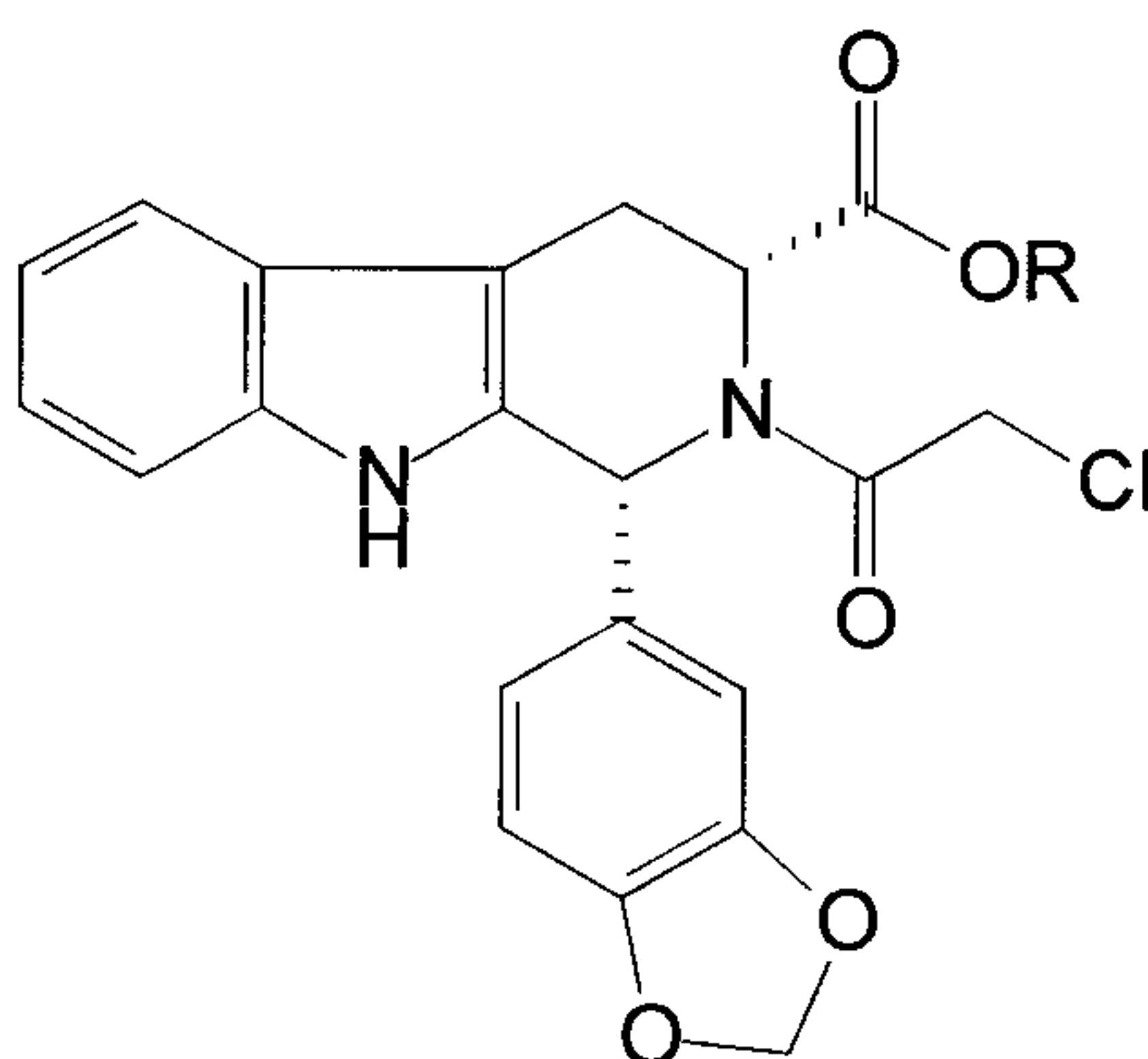
- 5 (ii) converting the *cis*-isomer of the compound of Formula (3), or a salt thereof, to Tadalafil (1).

10 [0020] In a preferred embodiment of the fourth aspect of the invention, the acid (HA) is hydrochloric acid. In another preferred embodiment of the fourth aspect, the compound of Formula (3) obtained following step (i), or a salt thereof, has a diastereomeric composition of greater than 90% of the *cis*-isomer.

[0021] In a further preferred embodiment of the fourth aspect, the heating during step (i) is conducted over less than about 25 hours.

15 [0022] In a further preferred embodiment of the fourth aspect of the invention, converting the *cis*-isomer of the compound of Formula (3) to the compound of Formula (1) comprises:

- (a) reacting the *cis*-isomer of the compound of Formula (3), or a salt thereof, with chloroacetyl chloride to provide a compound of Formula (2):



(2); and

- 20 (b) reacting the compound of Formula (2) with methylamine to provide the compound of Formula (1),
wherein R is a C1-C4 alkyl group.

[0023] In the processes of the above aspects and embodiments of the invention, R is preferably methyl.

DETAILED DESCRIPTION

5 [0024] The present invention provides processes for the preparation of Tadalafil and intermediates useful in the preparation thereof. Through the use of these processes, Tadalafil and the intermediates useful in the preparation thereof can be prepared in a straightforward manner directly from (D)-tryptophan (6) in good yield and using reasonable reaction times. By conducting the Pictet-Spengler reaction between tryptophan (6) and piperonal (5) in the processes of
10 the invention using inorganic acid (HX) under substantially anhydrous conditions, it has surprisingly been found that the formation of certain impurities is reduced, and the yield of the product (4) is improved relative to the analogous reaction conducted using an aqueous acid. Additionally, when performed according to a preferred embodiment described herein, the product of the condensation reaction can be isolated as a salt of acid HX by a simple filtration operation, thus avoiding the complicated work-up conditions described in the art. Further, in preferred embodiments of the present invention, the processes provided herein also avoid the need for costly and potentially hazardous amide coupling agents such as DCC and HOBt, which are used in the processes
15 known in the art.
20

[0025] As used herein, the designation C1-Cx refers to the total number of carbon atoms in the indicated group, including substituent groups, with C1-Cx including C1, C2, C3 and C4. For example, a group designated as "C1-C4" indicates that there are one to four carbon atoms in the moiety, *i.e.*, groups
25 containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C1-C4 alkyl" indicates that there are one to four carbon atoms in the alkyl group, *i.e.*, the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

30 [0026] As used herein, the term "alkyl", alone or as part of another substituent, means, unless otherwise stated, a straight or branched chain, saturated hydrocarbon radical having the number of carbon atoms designated

(e.g., C1-C4 means one to four carbon atoms). Examples of saturated hydrocarbon groups include methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *t*-butyl, *iso*-butyl and *sec*-butyl.

5 [0027] As used herein, the term "diastereomeric ratio" refers to the molar ratio of the percentage of one diastereomer in a mixture to that of the other. The diastereomeric composition refers to the absolute molar percentage of the *cis*- and *trans*-isomers.

[0028] As used herein, wt% or % w/w refers to weight percent and is used to express weight solute/weight solution as a percentage.

10 [0029] As used herein, the term "volumes" refers to the parts of solvent or liquids by volume (mL) with respect to the weight of solute (g). For example, when a reaction is conducted using 1 g of starting material and 100 mL of solvent, it is said that 100 volumes of solvent are used.

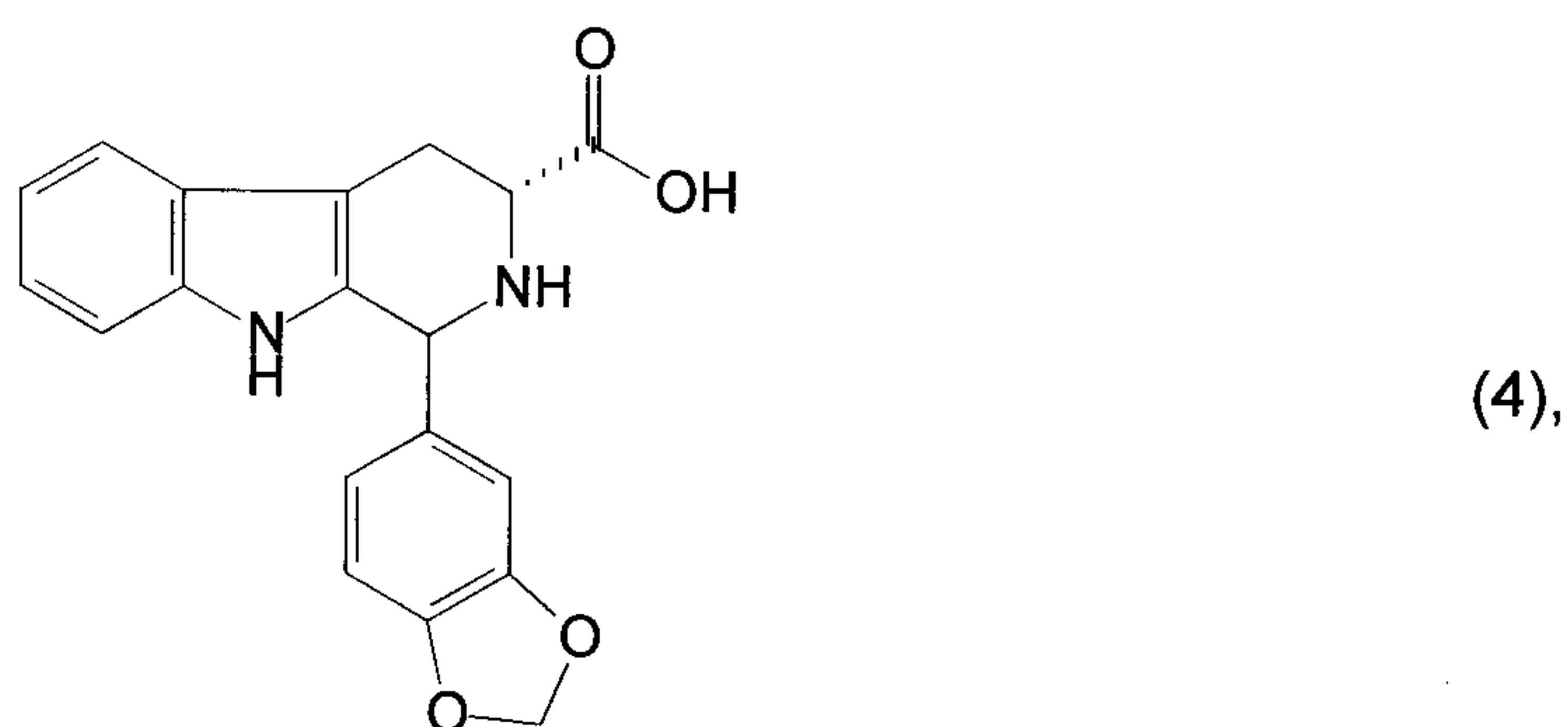
15 [0030] As used herein, "room temperature" generally refers to a temperature of 20-25 °C.

20 [0031] As used herein, the term "about" means "close to" and that variation from the exact value that follows the term is within amounts that a person of skill in the art would understand to be reasonable. For example, when the term "about" is used with respect to temperature, a variation of ± 5 °C is generally acceptable when carrying out the processes of the present invention; when used with respect to mole equivalents, a variation of ± 0.1 moles is generally acceptable; and when used with respect to volumes, a variation of $\pm 10\%$ is generally acceptable.

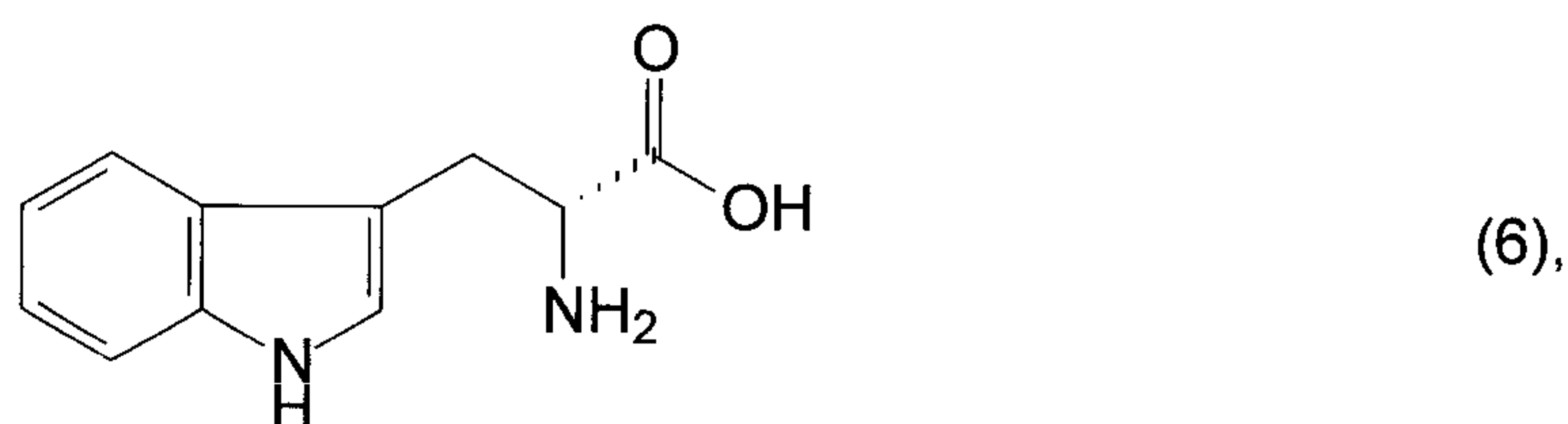
25 [0032] As used herein, "substantially anhydrous conditions" refers to conditions created by the use of organic solvents, reagents and raw materials lacking adventitious water, typically corresponding with less than about 3 wt%, more preferably less than about 1 wt%, and most preferably less than about 0.5 wt% water in the initial reaction system. Any water generated as a by-product during the reaction is not part of this definition. Preferably, organic
30 solvents, reagents and raw materials classified as being anhydrous are used, optionally with further treatment to minimize the water content, if desired.

[0033] Tadalafil and intermediates useful in the preparation thereof may be prepared by the exemplary processes set out in Scheme 5, using the exemplary reagents and conditions disclosed herein. In the processes provided herein, R is a C1-C4 alkyl group selected from the group consisting of methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl. Preferably, R is methyl.

[0034] In one embodiment of the present invention, a process is provided for the preparation of a mixture of the *cis*- and *trans*-isomers of the compound of Formula (4):



or a salt thereof, the process comprising condensing, under substantially anhydrous conditions and in the presence of an inorganic acid (HX) and an organic solvent (S1), a compound of Formula (6):



or a salt thereof, and a compound of Formula (5)



[0035] In the condensation of the compound of Formula (5) and the compound of Formula (6), or a salt thereof, substantially anhydrous conditions may be obtained, for example, by conducting the reaction in standard grade

organic solvents using an anhydrous inorganic acid (HX). Preferably, the amount of water in the initial reaction mixture is less than about 3 wt%, more preferably, less than about 1 wt%, and most preferably, less than about 0.5 wt%. Alternatively, if desired, the process can be conducted using organic solvents designated as being anhydrous.

[0036] In the condensation of the compound of Formula (5) and the compound of Formula (6), inorganic acid (HX) is selected from the group consisting of hydrogen halides, sulfuric acid, nitric acid, and phosphoric acid. Anhydrous forms of the hydrogen halide may be provided as solutions of the acid in an organic solvent such as an ether or acetic acid, or a mixture thereof, or the acid may be provided in the form of a gas. Anhydrous forms of sulfuric acid, nitric acid and phosphoric acid, containing a minimal amount of water, typically less than about 3 wt% may be used. Preferably, the inorganic acid (HX) is hydrogen chloride, and is provided as a solution in 1,4-dioxane.

[0037] The condensation of the compound of Formula (5) and the compound of Formula (6) is conducted in the presence of a solvent (S1). Solvent (S1) may be selected from the group consisting of 1,4-dioxane, tetrahydrofuran, methyl *t*-butyl ether and 2-methyl tetrahydrofuran. Preferably, solvent (S1) is 1,4-dioxane.

[0038] The condensation of the compound of Formula (5) and the compound of Formula (6) is ideally conducted at an elevated temperature to minimize reaction time. Preferably, the reaction temperature is in the range of about 55 °C to about 75 °C. More preferably, the reaction temperature is in the range of about 60 °C to about 70 °C.

[0039] The condensation of the compound of Formula (5) and the compound of Formula (6) provides the product as a salt of the compound of Formula (4) with inorganic acid (HX). Preferably, the salt is a hydrogen chloride salt. Preferably, when conducting the condensation reaction, the hydrogen chloride salt of the compound of Formula (4) is directly isolated from the reaction mixture by filtration, thus facilitating the use of the process on a commercial scale.

[0040] Condensation of the compound of Formula (6) and the compound of Formula (5) produces a mixture of *cis*- (1*R*, 3*R*) and *trans*- (1*S*, 3*R*) isomers of the compound of Formula (4), or a salt thereof. The diastereomeric ratio of the compound of Formula (4), or a salt thereof, may be in the range of about 50/50 *cis/trans* to about 90/10 *cis/trans*. Preferably, the diastereomeric ratio is enriched in the *cis*-isomer. The diastereomeric ratio may be enriched to as much as 90% *cis*-isomer. Often, the diastereomeric ratio may be in the range of about 55/45 *cis/trans* to about 75/25 *cis/trans*.

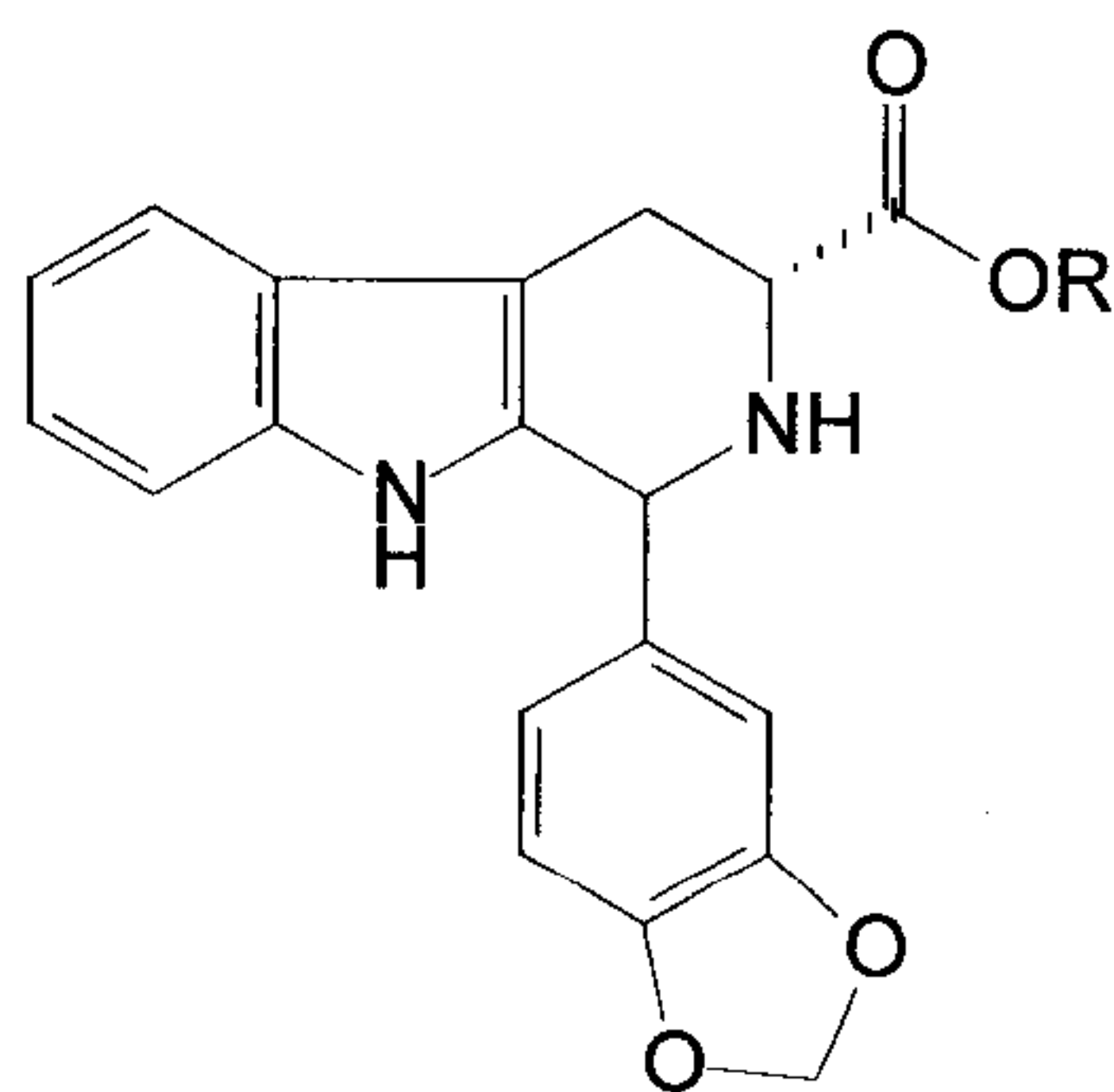
[0041] Comparative monitoring of this reaction shows that, by performing the condensation of the compounds of Formula (6) and Formula (5) using inorganic acid (HX) under anhydrous conditions (see Example 1) rather than the aqueous conditions reported in, for example, WO 2009/121791 A1 (see Comparative Example 1), the levels of two unknown impurities were reduced (from about 40 mole % to about 20 mole % in the Examples) with respect to product. This reduction in impurities contributed to an overall improvement in yield for the compound of Formula (4) (from 39% to 85% in the Examples).

[0042] Additionally, as described in Comparative Example 2, when the condensation described in WO 2007/100387 A2, using an organic acid (trifluoroacetic acid) and dichloromethane, was undertaken, the aqueous work-up was complicated by the formation of a glutinous solid that prevented separation of the aqueous and organic layers. Recovery of the glutinous solid containing the product was slow, so the need to execute the process on industrial scale limits the practicality of this approach. In comparison, as described in Example 1, embodiments of the present invention provide a hydrogen chloride salt of the compound of Formula (4) as a solid that is directly isolatable from the reaction mixture by a straightforward filtration operation that is readily amenable to implementation of an industrial scale.

[0043] In another embodiment of the present invention, a process is provided wherein the compound of Formula (4), or a salt thereof, as prepared according to the first embodiment is further converted to Tadalafil (1) using the methods reported in the art for the conversion of a compound of Formula (4), comprised of a *cis/trans* mixture, to Tadalafil. For example, WO

2007/100387 A2 and Anumula *et al. Synth. Commun.* **2008**, 38, 4265-4271 report procedures for coupling of *cis*-isomer of the compound of Formula (4), obtained following an isomerization of the *trans*-isomer in the *cis/trans* mixture, with sarcosine ethyl ester hydrochloride in the presence of amide coupling agents (DCC/HOBt) to provide Tadalafil (1). Although amide coupling agents are used in these known processes, when the compound of Formula (4) is prepared according to the processes of the present invention the benefits accrued through the reduction of impurities/improved yield and the more facile work-up and isolation of the product balance the disadvantages associated with use of these agents. However, in preferred embodiments, the compound of Formula (4) is further converted to Tadalafil (1) using the further embodiments of the present invention described below, which do not employ DCC and HOBt amide coupling agents.

[0044] In another embodiment of the present invention, a process is provided wherein the compound of Formula (4) or a salt thereof, preferably as prepared according to the embodiments described herein, is subjected to esterification in the presence of an alcohol (ROH) and a carboxylic acid activating agent, to provide a compound of Formula (3):



(3),

or a salt thereof, wherein R is a C1-C4 alkyl group.

[0045] In the esterification of the compound of Formula (4), the carboxylic acid activating agent refers to an agent that enhances the reactivity of a free carboxylic acid group towards esterification reactions in the presence of an alcohol. Preferably, the carboxylic acid activating agent is a catalyst, such as hydrogen chloride. The carboxylic acid activating agent may also be an activating agent that reacts with the carboxylic acid for Formula (4) to form an

activated acid derivative. Preferably, the active acid derivative is selected from the group consisting of an acyl chloride, an acyl imidazole, a mixed anhydride or reactive ester. The carboxylic acid activating agent is selected from the group consisting of hydrogen chloride, oxalyl chloride, thionyl chloride, alkyl chloroformate, 1,1'-carbonyldiimidazole and pivaloyl chloride and similar reagents. Most preferably, the carboxylic activating agent is thionyl chloride or hydrogen chloride. When used, hydrogen chloride is preferably prepared *in situ*, for example, by the reaction between trimethylsilyl chloride and the alcohol (ROH) used for esterification.

[0046] Esterification of the compound of Formula (4) is conducted in the presence of alcohol (ROH). Preferably, alcohol (ROH) also acts as a solvent for the reaction. Preferably, the esterification of the compound of Formula (4) is conducted in substantially anhydrous conditions.

[0047] To minimize the reaction time, the esterification of the compound of Formula (4) is preferably conducted at an elevated temperature. Preferably, the reaction temperature is in the range of about 55 °C to about 75 °C. More preferably, the reaction temperature is in the range of about 60 °C to about 70 °C.

[0048] The compound of Formula (4) used in the esterification reaction may be a salt of Formula (4) or the free base. Similarly, the compound of Formula (3) may be provided as a salt, for example, with a by-product released from reaction with the carboxylic acid activating agent, or in its free base form. Preferably, both the compound of Formula (4) and the compound of Formula (3) are provided as hydrogen chloride salts.

[0049] In another embodiment of the present invention, a process is provided wherein a mixture of the *cis*- and *trans*-isomers of the compound of Formula (3), or salts thereof, is converted to Tadalafil by a process comprising:

(i) heating the mixture of the *cis*- and *trans*-isomers of the compound of Formula (3), or salts thereof, in the presence of

aqueous acid (HA) to isomerize the *trans*-isomer to the *cis*-isomer of the compound of Formula (3), or a salt thereof; and

- (ii) converting the *cis*-isomer of the compound of Formula (3) to Tadalafil (1),

5 wherein R is a C1-C4 alkyl group.

[0050] For the isomerization step, the aqueous acid (HA) may be any
suitable inorganic or organic acid provided as an aqueous solution. Suitable
acids are preferably selected from the group consisting of hydrochloric acid,
sulphuric acid, trifluoroacetic acid, formic acid, acetic acid, methanesulfonic
10 acid, camphorsulfonic acid and *para*-toluenesulfonic acid. Most preferably,
the aqueous acid (HA) is hydrochloric acid.

[0051] The isomerization may be conducted by heating at a suitable
elevated temperature to reduce the reaction time when compared to the
reaction time require for isomerization at room temperature. Preferably, the
15 reaction temperature is in the range of about 40 °C to about 60 °C. More
preferably, the reaction temperature is in the range of about 45 °C to about 55
°C. For the isomerization step, the isomerization may be conducted for a
suitable time to achieve the desired diastereomeric ratio. Preferably, the
reaction time for the isomerization is in the range of about 16 hours to about
20 25 hours. It has been found that prolonging the time for the isomerization
step past this point, leads to gradual reductions in yield owing to the
hydrolysis of the compound of Formula (3) back to the compound of Formula
(4).

[0052] The *cis*-isomer of the compound of Formula (3) may be provided as
25 a salt with acid (HA). Preferably, the salt of the compound of Formula (3) is a
hydrogen chloride salt. Preferably, the hydrogen chloride salt of the *cis*-
isomer of the compound of Formula (3) is directly isolated from the reaction
mixture by filtration.

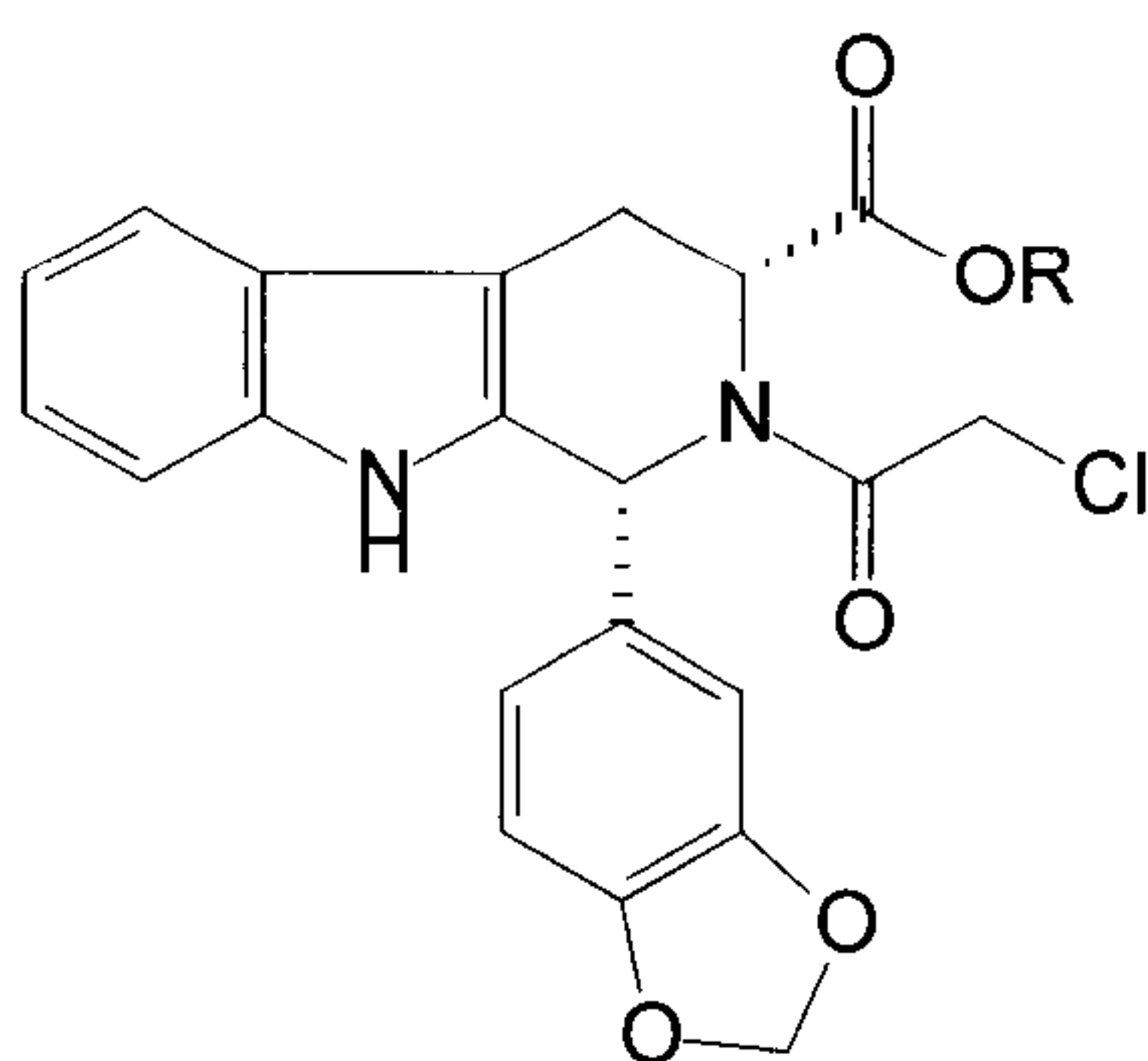
[0053] The compound of Formula (3), or a salt thereof, for use in the
30 isomerization may be enriched in the *cis*-isomer or it may comprise
approximately equal amounts of *cis*- and *trans*-isomers. Preferably, the

compound of Formula (3), or a salt thereof, is enriched in the *cis*-isomer prior to the isomerization step.

[0054] Following the isomerization reaction, the compound of Formula (3), or a salt thereof, preferably has a diastereomeric composition $\geq 90\%$ *cis*-isomer. More preferably, the compound of Formula (3) has a diastereomeric composition of $\geq 95\%$, and even more preferably $\geq 97\%$ *cis*-isomer. The diastereomeric composition of the compound of Formula (3), or a salt thereof, may be further enriched in the *cis*-isomer by suitable purification methods such as recrystallization. Preferably, a suitable solvent for recrystallization is selected from the group of acetonitrile and alcohols, such as isopropanol and methanol. More preferably, the solvent is acetonitrile.

[0055] Conversion of the *cis*-isomer of the compound of Formula (3) to Tadalafil (1) in step (ii) may be conducted according to any method known in the art, for example, the methods reported in WO 95/19978 A1, WO 2004/011463 A1, WO 2005/068464 A2 and WO 2007/052283 A1. Preferably, the *cis*-isomer of the compound of Formula (3) is converted to Tadalafil (1) by a process comprising:

- (a) reacting the *cis*-isomer of the compound of Formula (3), or a salt thereof, with chloroacetyl chloride to provide a compound of Formula (2):



(2); and

- (b) reacting the compound of Formula (2) with methylamine to provide Tadalafil of Formula (1),
wherein R is a C1-C4 alkyl group.

[0056] The reaction of the compound of Formula (3) with chloroacetyl chloride is preferably conducted in the presence of a suitable base selected, for example, from the group consisting of tertiary amines, metal carbonates and metal bicarbonates. Preferably, the base is triethylamine.

5 [0057] The reaction of the compound of Formula (3) with chloroacetyl chloride is preferably conducted in a solvent. Exemplary solvents for the reaction include ethers, esters and chlorinated hydrocarbons. Preferably, the solvent is selected from tetrahydrofuran, ethyl acetate and dichloromethane. Most preferably, the solvent is tetrahydrofuran.

10 [0058] The reaction of the compound of Formula (3) with chloroacetyl chloride may be conducted at any suitable temperature, and it preferably conducted at a reduced temperature, for example, at a temperature in the range of about -10 °C to about 10 °C. Most preferably, the reaction is conducted at a temperature in the range of about -5 °C to about 5 °C.

15 [0059] Reaction of the compound of Formula (2) with methylamine may be conducted in any suitable solvent, and is preferably selected from among ethers, amides, sulfoxides, alcohols and mixtures thereof. Preferably, the solvent is selected from the group consisting of tetrahydrofuran, N,N-dimethylformamide, dimethylsulfoxide, methanol, ethanol and mixtures
20 thereof. Most preferably, the solvent for the reaction of the compound of Formula (2) with methylamine is a mixture of dimethylsulfoxide and methanol.

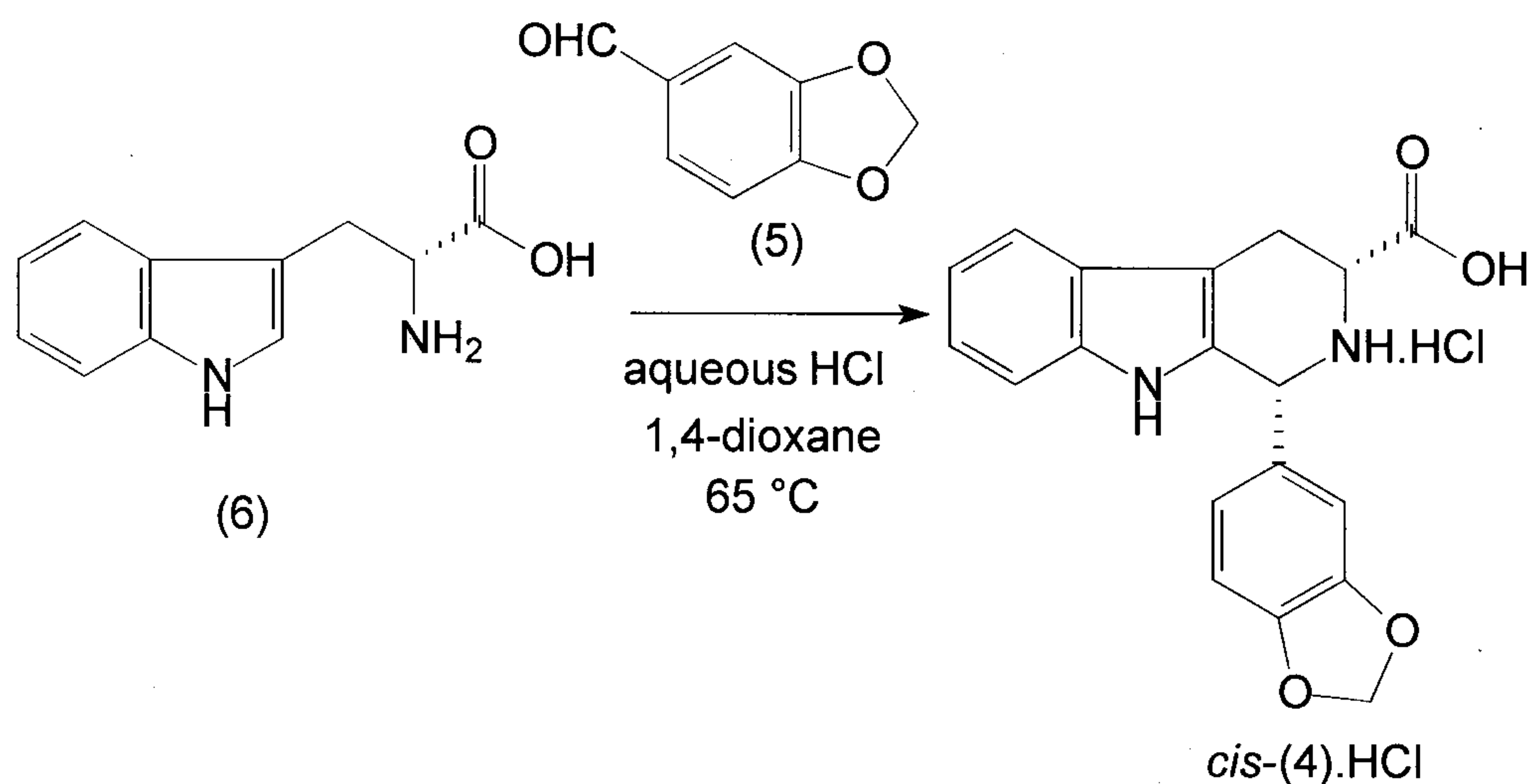
[0060] In the reaction of the compound of Formula (2) with methylamine, the methylamine may be provided as an aqueous or alcoholic solution. Preferably, methylamine is provided as an aqueous solution.

25 [0061] The reaction of the compound of Formula (2) with methylamine may be conducted at any suitable temperature, and preferably at an elevated temperature. More preferably, the reaction is conducted at a temperature in the range of about 40 °C to about 60 °C. Most preferably, the reaction is conducted at a temperature of about 40 °C to about 45 °C.

EXAMPLES

[0062] The following examples are illustrative of some of the embodiments of the invention described herein. It will be apparent to the skilled reader that various alterations to the described processes in respect of the reactants, reagents and conditions may be made when using the processes of the present invention without departing from the scope or intent thereof.

Comparative Example 1: Preparation of (1R, 3R)-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylic acid hydrochloride using conditions analogous to Example 3 of WO 2009/121791 A1

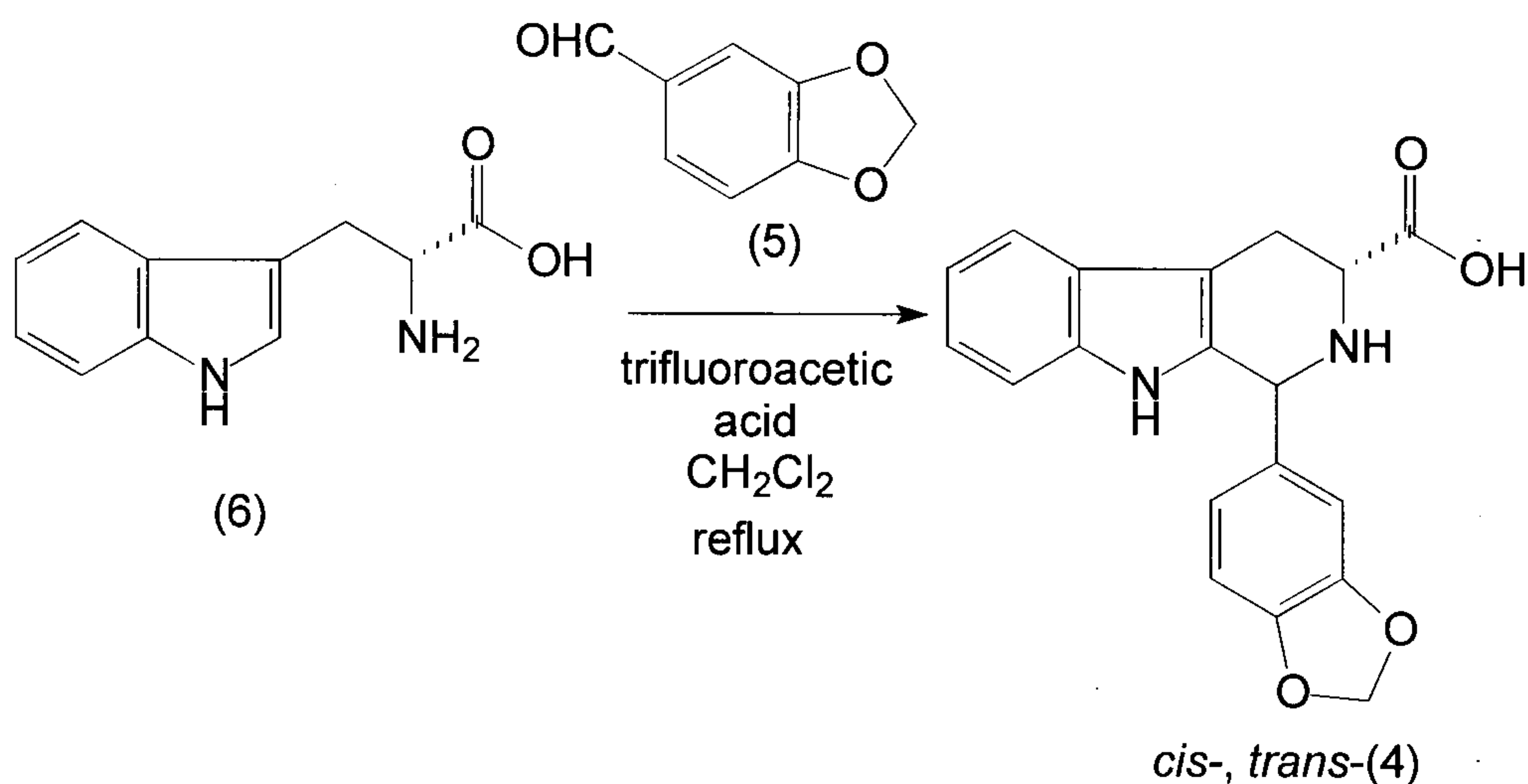


[0063] To a stirring suspension of D-tryptophan (6) (4.0 g, 19.6 mmol) in 1,4-dioxane (45 mL) purged with nitrogen was added piperonal (5) (3.3 g, 21.7 mmol), followed by continued stirring at ambient temperature for 5 minutes. To the resulting suspension was charged concentrated (37 wt%) HCl (2.4 g, 24.3 mmol) resulting briefly in a clear solution which became a thick beige solid mass that was stirred uniformly with vigorous stirring. Thinning of this solid mass was observed as it was heated to 60-65 °C and maintained for 104 hours. Reaction completion was verified by ¹H NMR (*cis/trans* diastereomeric ratio of 82/18). Two unknown impurities, appearing as singlets in the ¹H NMR (conducted in d₆-DMSO) at 10.95 ppm and 10.85 ppm, were observed with an estimated molar % with respect to the compound of Formula (4) of 39%). The reaction mixture was cooled to room temperature, filtered, and the filter cake was washed with 1,4-dioxane (2 X 10

mL). The filter cake was air dried for 1 week to afford 2.8 g (39% yield) of (1R,3R)-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido[3,4-b]indole-3-carboxylic acid (*cis*-(4)) hydrochloride as a yellow solid.

5

Comparative Example 2: Preparation of 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylic acid using conditions analogous to Example 1 of WO 2007/100387 A2



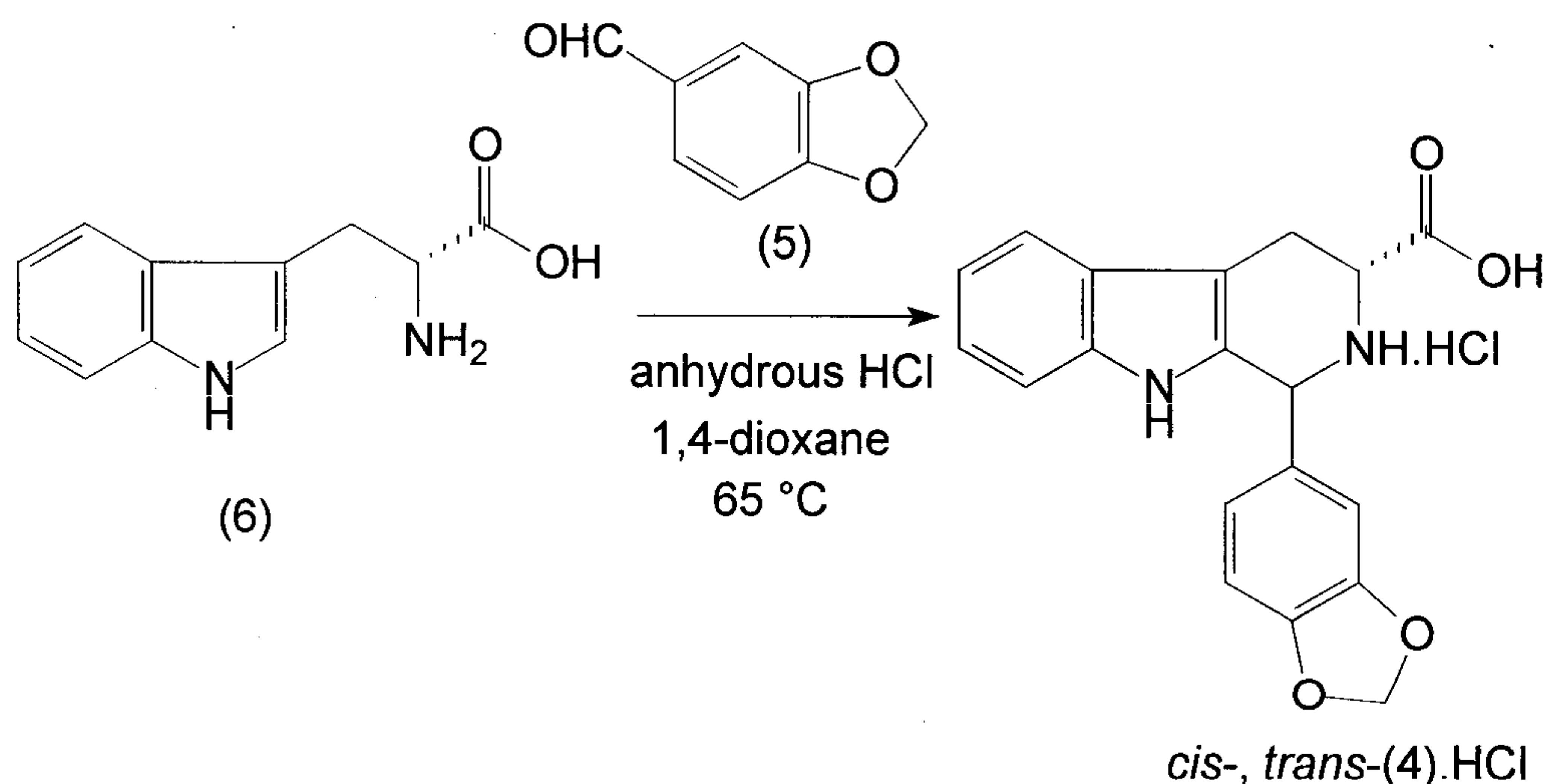
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[0064] To a stirring suspension of D-tryptophan (6) (10.0 g, 49.0 mmol) in dichloromethane (100 mL) purged with nitrogen was added piperonal (5) (8.8 g, 58.7 mmol), with stirring continued at ambient temperature for 5 minutes. The suspension was cooled to 2 °C and trifluoroacetic acid (9.2 g, 81.0 mmol) was added over 10 minutes. Upon heating to reflux, the thick suspension thinned considerably and changed to a hazy orange solution composed of an upper orange phase and a small lower red phase. Maintenance at reflux eventually caused the reaction mixture to become a clear orange solution. Following 17 hours at reflux, reaction completion was verified by ¹H NMR (diastereomeric ratio 47/53 *cis*/*trans*). Upon cooling the reaction mixture to room temperature, the product precipitated (¹H NMR showed the solids to have a diastereomeric ratio of 45/55 *cis*/*trans*). The slurry was reheated to 28 °C and dichloromethane (100 mL) was added, followed by saturated sodium bicarbonate solution (7 wt%, 50 mL), producing a thick suspension having pH of 3.5. Additional saturated sodium bicarbonate solution was added to obtain a neutral pH along followed by methanol (40 mL). A jelly-like solid evolved, which interfered with phase separation. Additional trifluoroacetic acid was

20

added to re-adjust the pH to 3.5. Due to the failure of the two phases to separate, the reaction mixture was filtered to remove the jelly-like solid. A test showed that this jelly solid was very soluble in methanol. As a result, methanol (300 mL) was added to dissolve the solid. Additional saturated sodium bicarbonate solution was added to neutralize the clear methanol solution. Dichloromethane (500 mL) was charged to form two phases. The phases were separated, the aqueous phase was extracted with dichloromethane (200 mL) twice and the organic layers were combined and concentrated to dryness to afford 13.7 g (84% yield) of 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylic acid as a yellow solid having a diastereomeric ratio of 40/60 *cis/trans* as determined by NMR.

Example 1: Preparation of 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylic acid hydrochloride (Formula (4)·HCl)

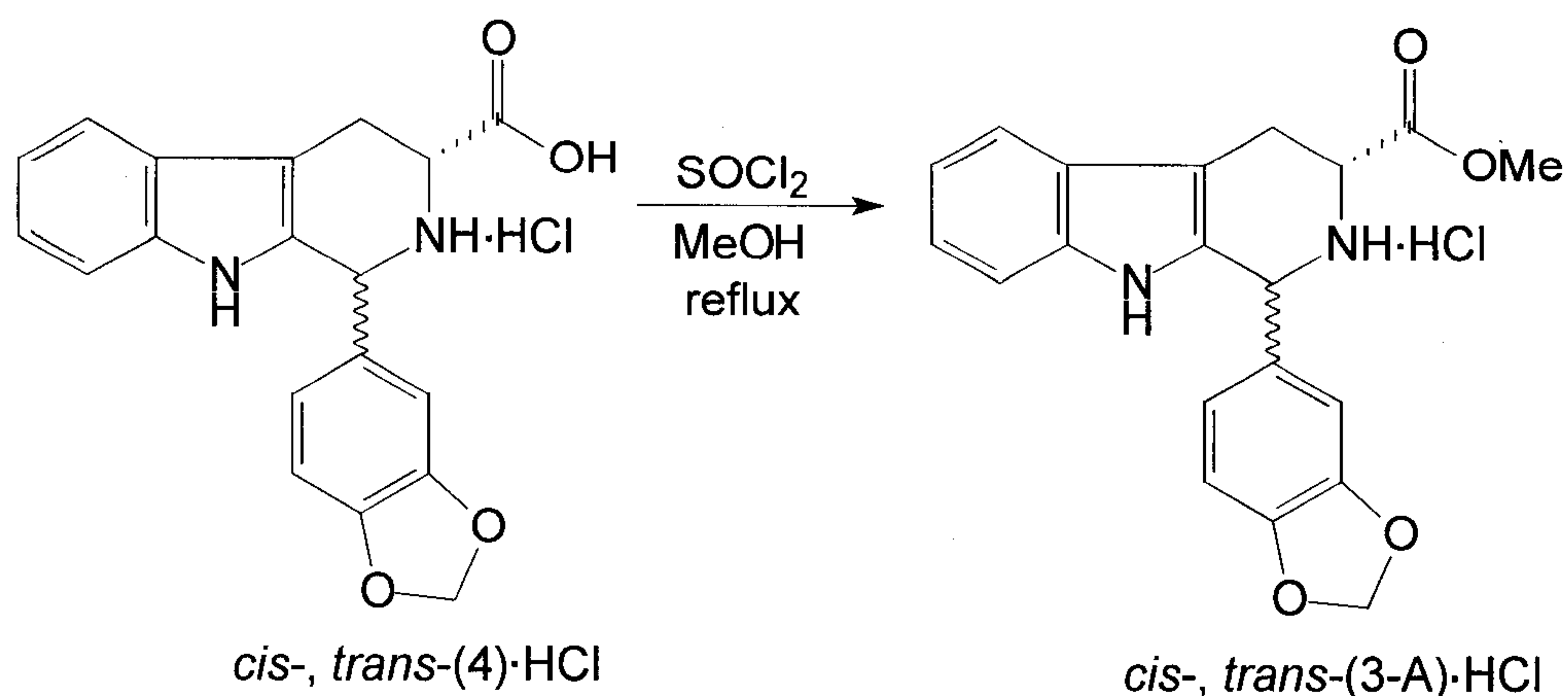


[0065] To a stirring suspension of D-tryptophan (6) (4.0 g, 19.6 mmol) in 1,4-dioxane (40 mL) purged with nitrogen was added piperonal (5) (3.3 g, 21.7 mmol), with stirring being continued at ambient temperature for 5 minutes. To the resulting suspension was charged an anhydrous solution of 4 M HCl in dioxane (7.4 g (1.05 g/mL), 28.0 mmol, SIGMA-ALDRICH®) resulting in an almost clear solution, which became a thick red solid mass that was stirred uniformly with momentary vigorous stirring. Upon heating to 65 °C, this suspension began to thin, and changed from red to purple, and

eventually to beige, after 2 hours at 65 °C. Following 27 hours at 65 °C, reaction completion was verified by ¹H NMR in d₆-DMSO (diastereomeric ratio of 60/40 *cis/trans*). Two unknown impurities appearing as singlets in ¹H NMR at 10.95 ppm and 10.85 ppm were observed (molar % two impurities with respect to product (4) 18 %). The reaction mixture was cooled to room temperature, 1,4-dioxane (10 mL) was charged and the suspension was stirred for 3 hours. The slurry was then filtered, with the filter cake being washed with 1,4-dioxane (3 X 10 mL) and dried under high vacuum at 45-50 °C for 26 hours to afford 6.2 g (85% yield) of 1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylic acid (Formula (4)) hydrochloride as a white solid having a diastereomeric ratio of 59/41 *cis/trans*.

[0066] Thus, the embodiment of the invention exemplified in Example 1 from improvements in yield and purity of the process of the art exemplified in Comparative Example 1, and also provides an improved, and simplified, work-up procedure when compared to the process exemplified in Comparative Example 2. These benefits make the process exemplified in Example 1 more amenable to commercial manufacture than the processes described in the prior art.

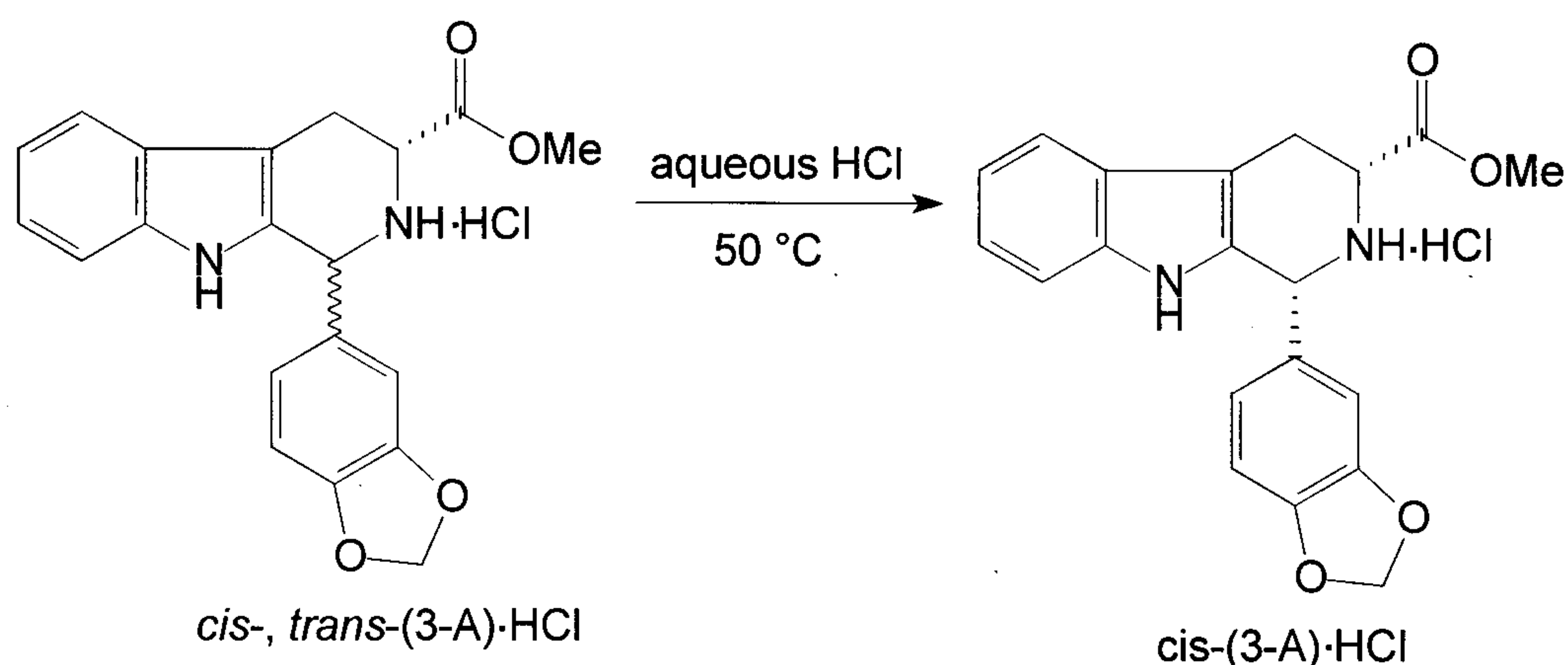
Example 2: Preparation of methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylate hydrochloride (Formula (3-A)·HCl)



[0067] To a cooled (0 °C) and stirring solution of the compound of Formula (4) (37.3 g, 86.7 mmol corrected for 13.3 wt % dioxane) in methanol (930 mL) was added thionyl chloride (22.1 g, 186 mmol) dropwise over a period of 30

minutes, with the resulting solution being heated to reflux and maintained for 16 hours. Upon verification of reaction completion by ^1H NMR, the reaction mixture (ca. 1000 mL) containing methyl-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylate (Formula (3-A)) hydrochloride was cooled to ambient temperature and used in Example 4 without isolation.

Example 3: Preparation of methyl-(1*R*, 3*R*)-1,2,3,4-tetrahydro-1-(3,4-methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylate hydrochloride (*cis*-isomer Formula (3-A)·HCl)



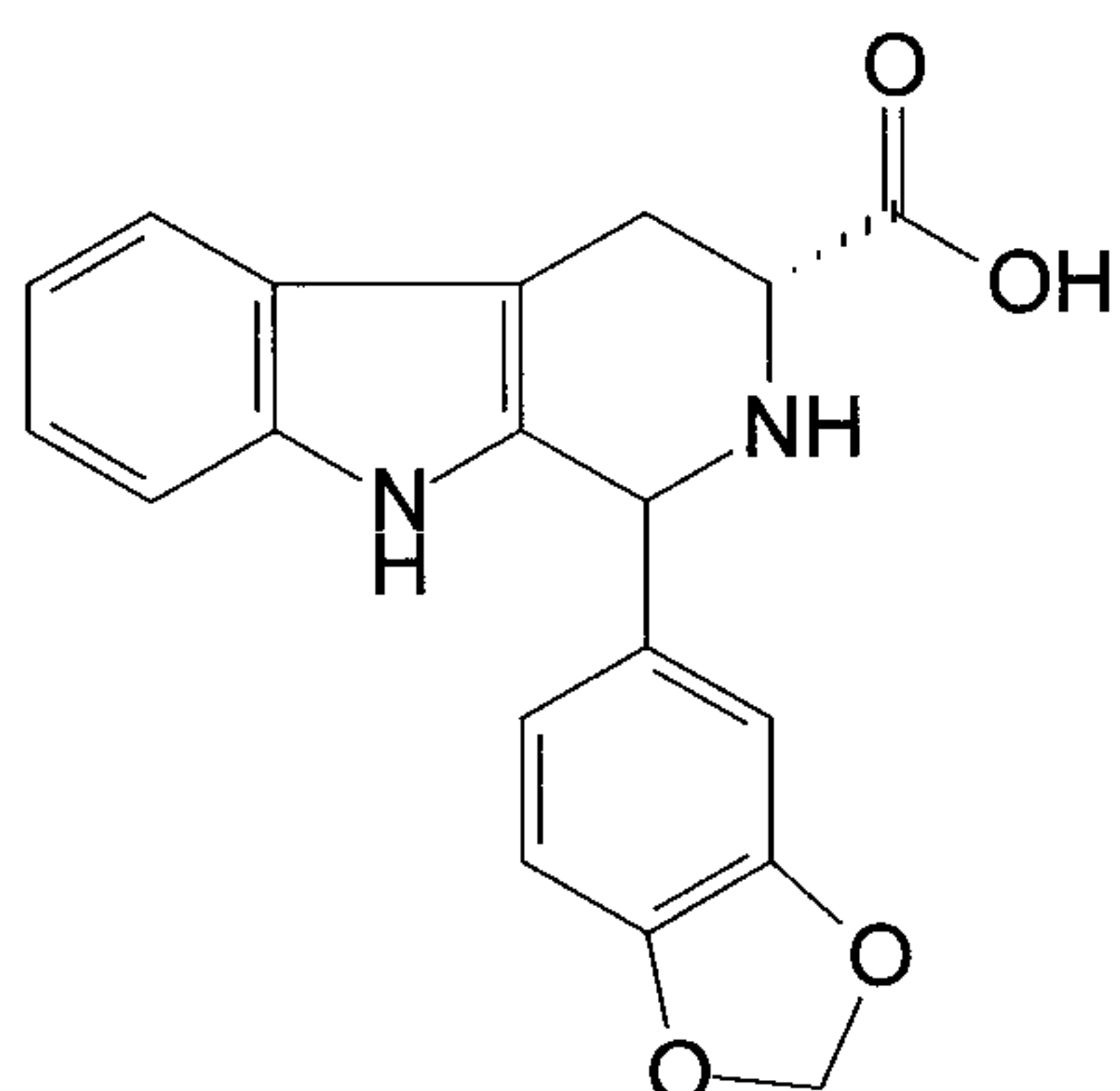
[0068] A portion (500 mL) of the methanolic solution containing a mixture of the *cis*- and *trans*-isomers of the hydrochloride salt of the compound of Formula (3A) from Example 2 (43.4 mmol) was concentrated to 40-50 mL. Deionized water (300 mL) was charged and the reaction mixture was concentrated to around 2 volumes (^1H NMR analysis indicated ca. 0.02 wt % of residual MeOH). The reaction mixture was charged with deionized water to 8 volumes followed by 0.2 M HCl (3.2 volumes, 0.30 eq), and then heated at 50 °C for 21 hours. ^1H NMR showed a diastereomeric ratio of 92/8 *cis*/*trans*. The reaction mixture was cooled to room temperature over 1-2 hours and maintained for 20 hours, and then further cooled to 0 °C over 1-2 hours and maintained at 0 °C for 2 hours. The resulting solid was filtered, washed with cold (0 °C) deionized water (19 mL) followed by methyl *t*-butyl ether (2 X 40 mL) and dried under high vacuum at 45-50 °C for 24 hours to afford 15.8 g (94% yield from (4)) of methyl-(1*R*, 3*R*)-1,2,3,4-tetrahydro-1-(3,4-

methylenedioxyphenyl)-9H-pyrido [3,4-b]indole-3-carboxylate (Formula (3-A)) hydrochloride as a pale yellow solid having a diastereomeric ratio of 97/3 *cis/trans* (a diastereomeric composition of 97 % *cis*-isomer). HPLC purity of the sample was: 95 % (a/a).

- 5 [0069] Therefore, as demonstrated in these exemplary embodiments of the invention, the new reaction conditions used in the processes of the present invention provide increases in yield and purity when compared to analogous reactions known in the art. Further, these embodiments of the invention are more amenable to use on a commercial scale. Owing to the high yield and
- 10 purity of the products obtained using the processes of the invention, these combined benefits make it practical to produce the compound of Formula (3) on a commercial scale, which, in turn, allows for the use of processes for the preparation of Tadalafil that avoid the use of amide coupling agents, such as DCC and HOBt, in the final steps. The use of such reagents is associated
- 15 with increased cost, the generation of by-products such as DCU (dicyclohexylurea), and safety risks.

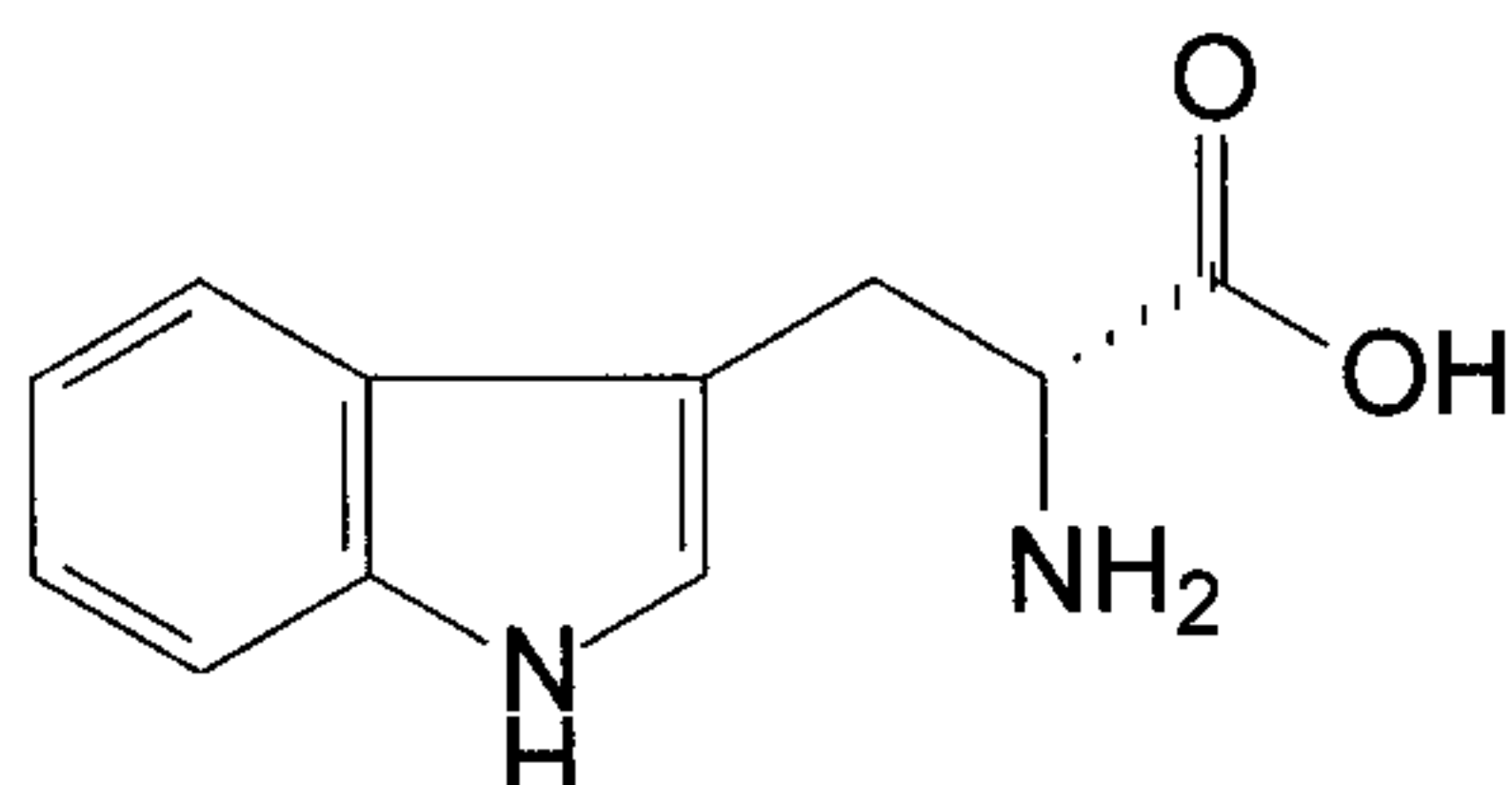
What is claimed is:

1. A process for the preparation of a compound of Formula (4):



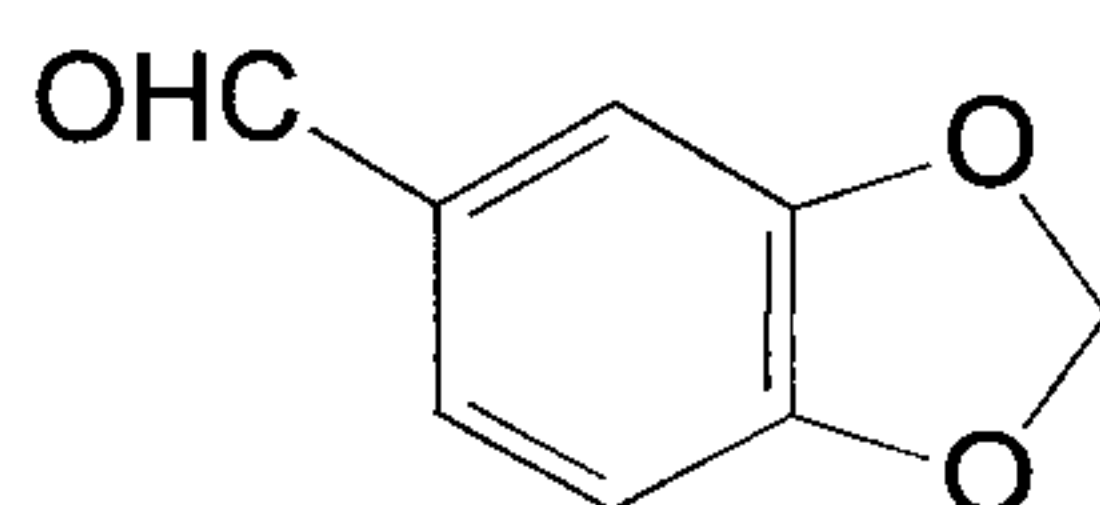
(4),

or a salt thereof, the process comprising condensing, under substantially anhydrous conditions in the presence of an inorganic acid (HX) and an organic solvent (S1), a compound of Formula (6):



(6),

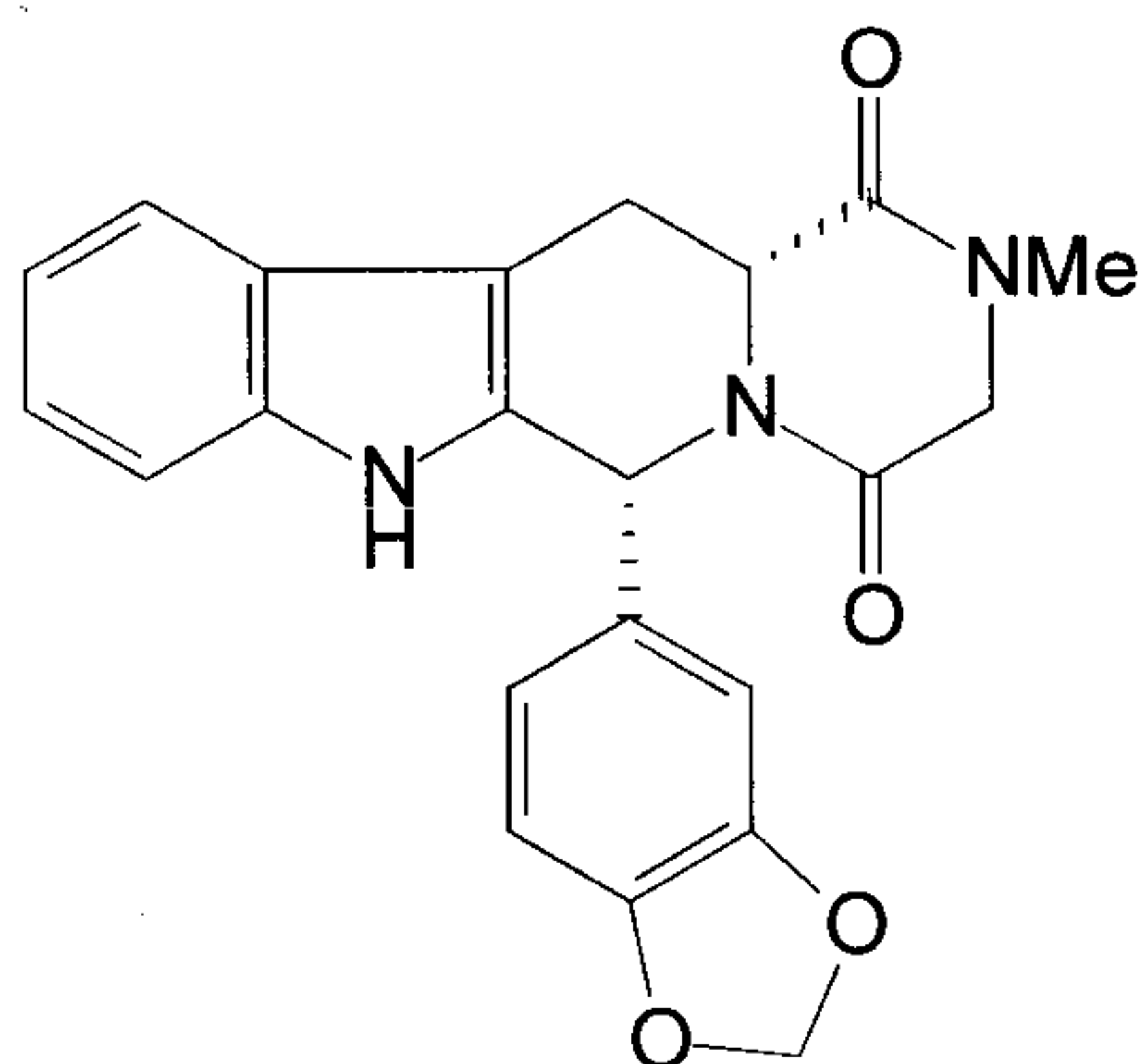
or a salt thereof, and a compound of Formula (5):



(5).

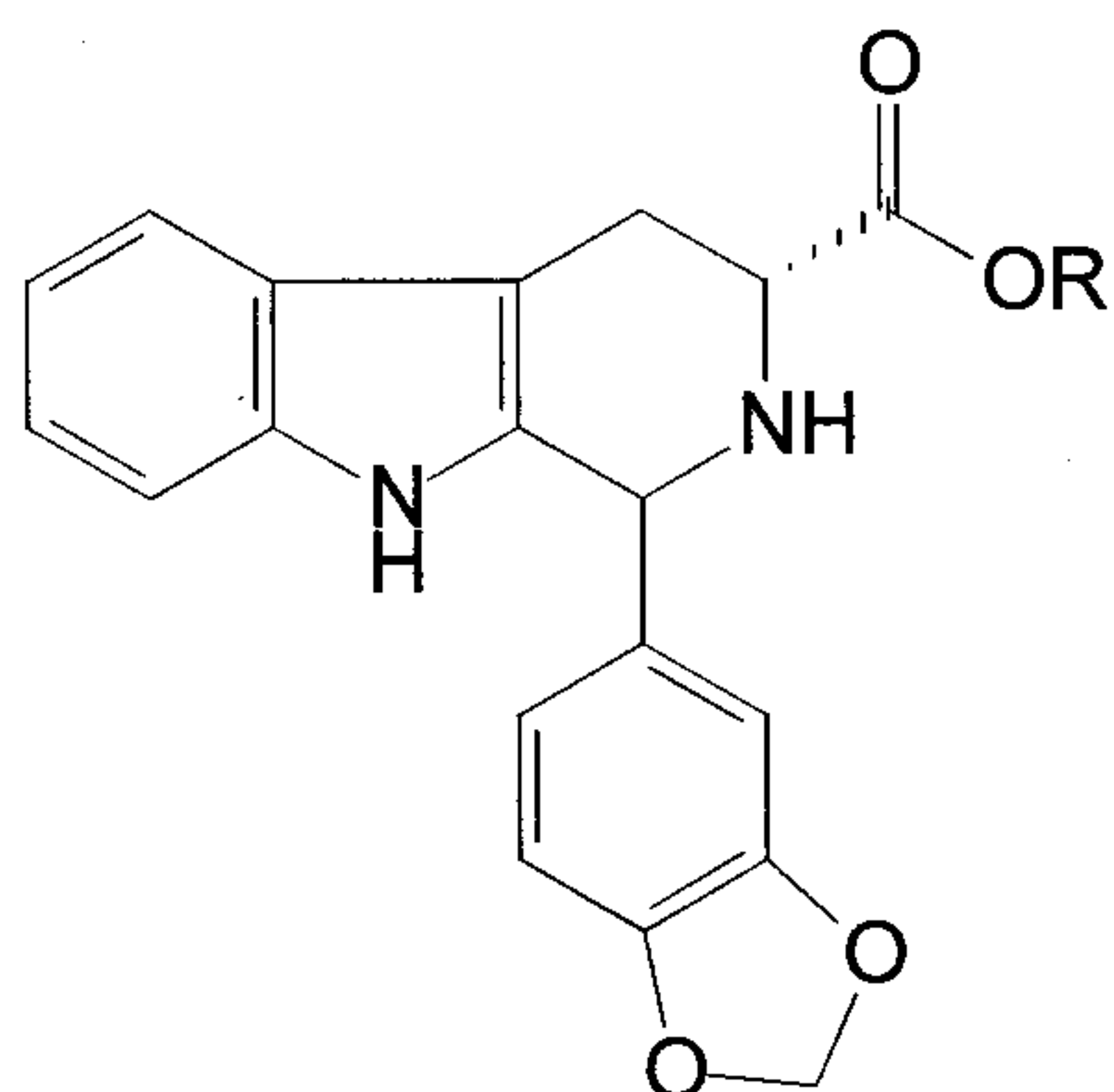
2. The process of claim 1, wherein the substantially anhydrous conditions refers to an initial water content for the process of less than about 3 wt%.
3. The process of claim 2, wherein the substantially anhydrous conditions refers to an initial water content for the process of less than about 1 wt%.
4. The process of any one of claims 1 to 3, wherein the inorganic acid (HX) is selected from the group consisting of hydrogen halides, sulfuric acid, nitric acid, and phosphoric acid.

5. The process of claim 4, wherein the inorganic acid (HX) is hydrogen chloride.
6. The process of any one of claims 1 to 5, wherein the organic solvent (S1) is an ether selected from the group consisting of 1,4-dioxane, tetrahydrofuran, methyl *t*-butyl ether and 2-methyl tetrahydrofuran.
7. The process of claim 6, wherein the organic solvent (S1) is 1,4-dioxane.
8. The process of claim 7, wherein the process is conducted at a temperature of about 55 °C to about 75 °C.
9. The process of any one of claims 1 to 8, wherein the compound of Formula (4) is provided as a salt with acid (HX).
10. The process of any one of claims 1 to 9, wherein the diastereomeric ratio of the compound of Formula (4), or a salt thereof, is enriched in the *cis*-isomer relative to the *trans*-isomer.
11. The process of claim 10, wherein the diastereomeric ratio of the compound of Formula (4), or a salt thereof, is enriched in up to about 90% of the *cis*-diastereomer.
12. The process of any one of claims 1 to 11, wherein the compound of Formula (4), or a salt thereof, is further converted to the compound of Formula (1) (Tadalafil):



(1).

13. The process of any one of claims 1 to 11, wherein the compound of Formula (4), or a salt thereof, is further subjected to esterification in the presence of an alcohol (ROH) and a carboxylic acid activating agent, to provide a compound of Formula (3):



(3),

5 or a salt thereof,
wherein R is a C1-C4 alkyl group.

14. The process of claim 13, wherein the carboxylic acid activating agent is selected from the group consisting of hydrogen chloride, oxalyl chloride, thionyl chloride, alkyl chloroformate and 1,1'-carbonyldiimidazole.

10 15. The process of claim 14, wherein the carboxylic acid activating agent is thionyl chloride or hydrogen chloride.

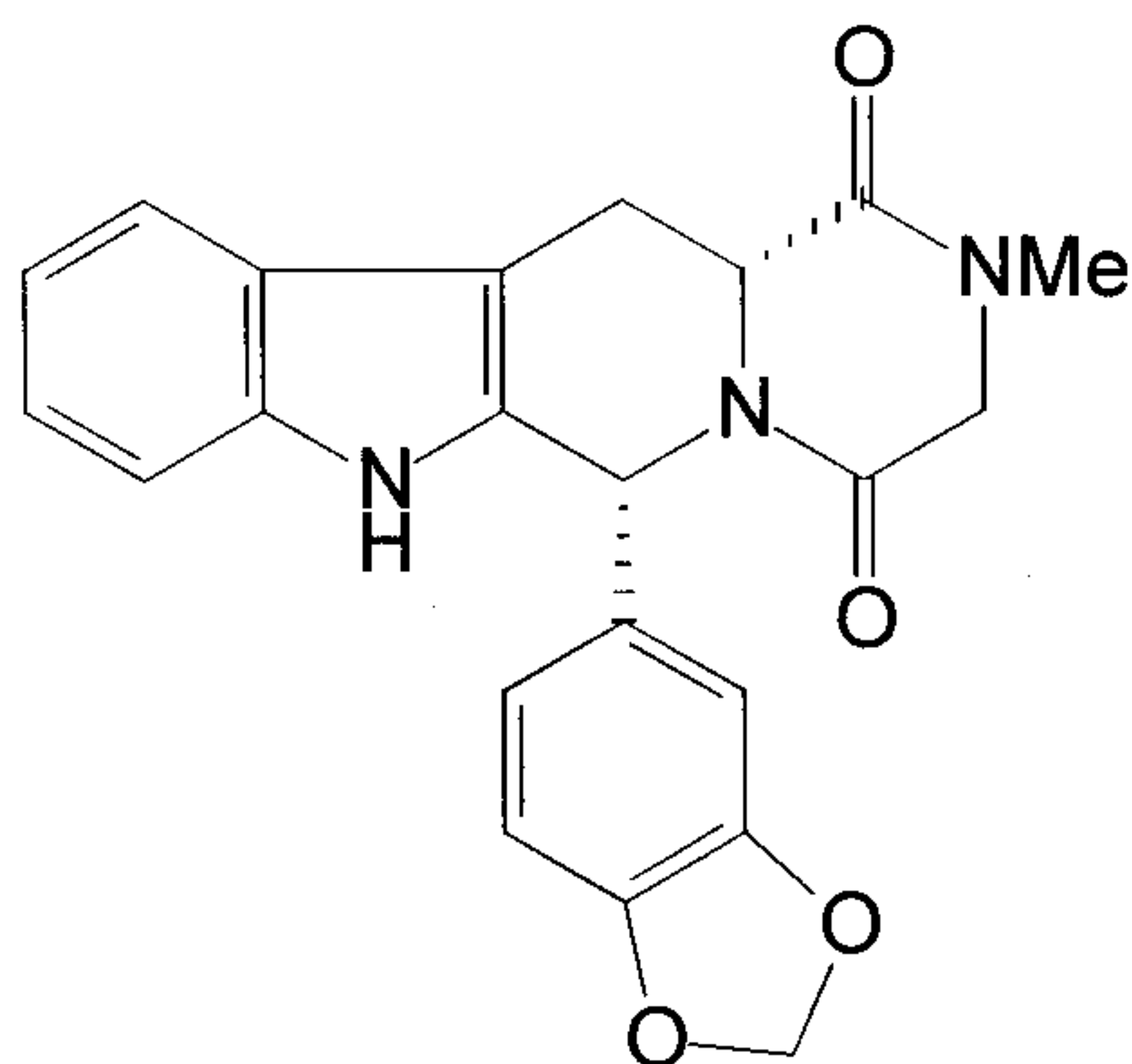
16. The process of any one of claims 13 to 15, wherein the esterification is conducted at a temperature of about 55 °C to about 75 °C.

15 17. The process of any one of claims 13 to 16, wherein the compound of Formula (3) is provided as a salt.

18. The process of any one of claims 13 to 17, wherein the diastereomeric ratio of the compound of Formula (3), or a salt thereof, and the compound of Formula (4), or a salt thereof, are each enriched in the *cis*-isomer relative to the *trans*-isomer.

20 19. The process of any one of claims 13 to 18, wherein the esterification of the compound of Formula (4) to the compound of Formula (3) is conducted under substantially anhydrous conditions.

20. The process of any one of claims 13 to 19, wherein the compound of Formula (3), or a salt thereof, is further converted to the compound of Formula (1)



(1),

by a process comprising:

5 (i) heating the compound of Formula (3), or a salt thereof, in the presence of aqueous acid (HA) to isomerize the *trans*-isomer to the *cis*-isomer of the compound of Formula (3), or a salt thereof; and

(ii) converting the *cis*-isomer of the compound of Formula (3), or a salt thereof, to the compound of Formula (1).

10 21. The process of claim 20, wherein the acid (HA) is hydrochloric acid.

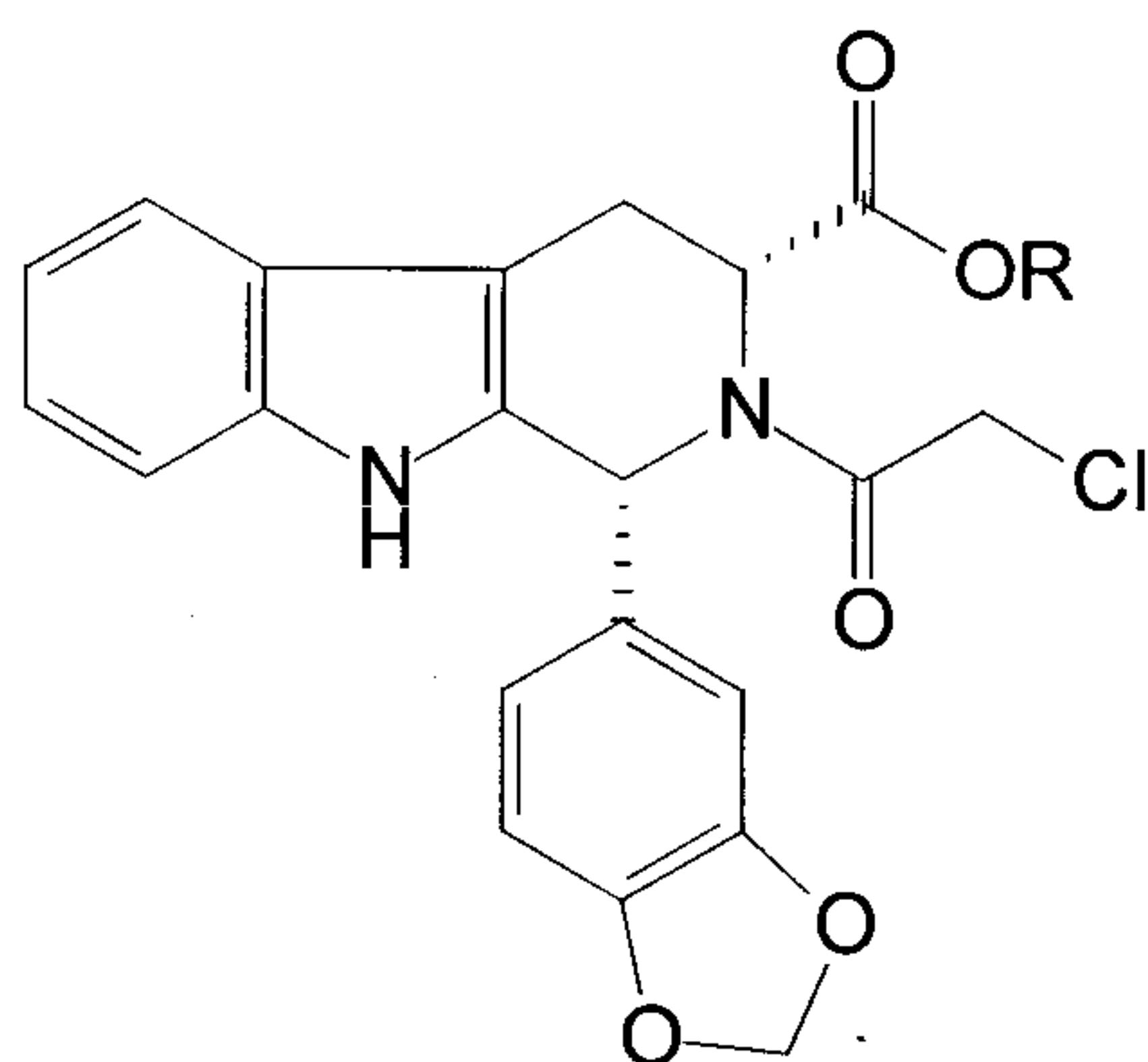
22. The process of claim 20 or 21, wherein, following step (i), the compound of Formula (3), or a salt thereof, has a diastereomeric composition of $\geq 90\%$ *cis*-isomer.

15 23. The process of any one of claims 20 to 22, wherein the heating during step (i) is conducted over less than about 25 hours.

24. The process of any one of claims 20 to 23, wherein converting the *cis*-isomer of the compound of Formula (3) to the compound of Formula (1) comprises:

20 (a) reacting the *cis*-isomer of the compound of Formula (3), or a salt thereof, with chloroacetyl chloride to provide a compound of Formula (2):

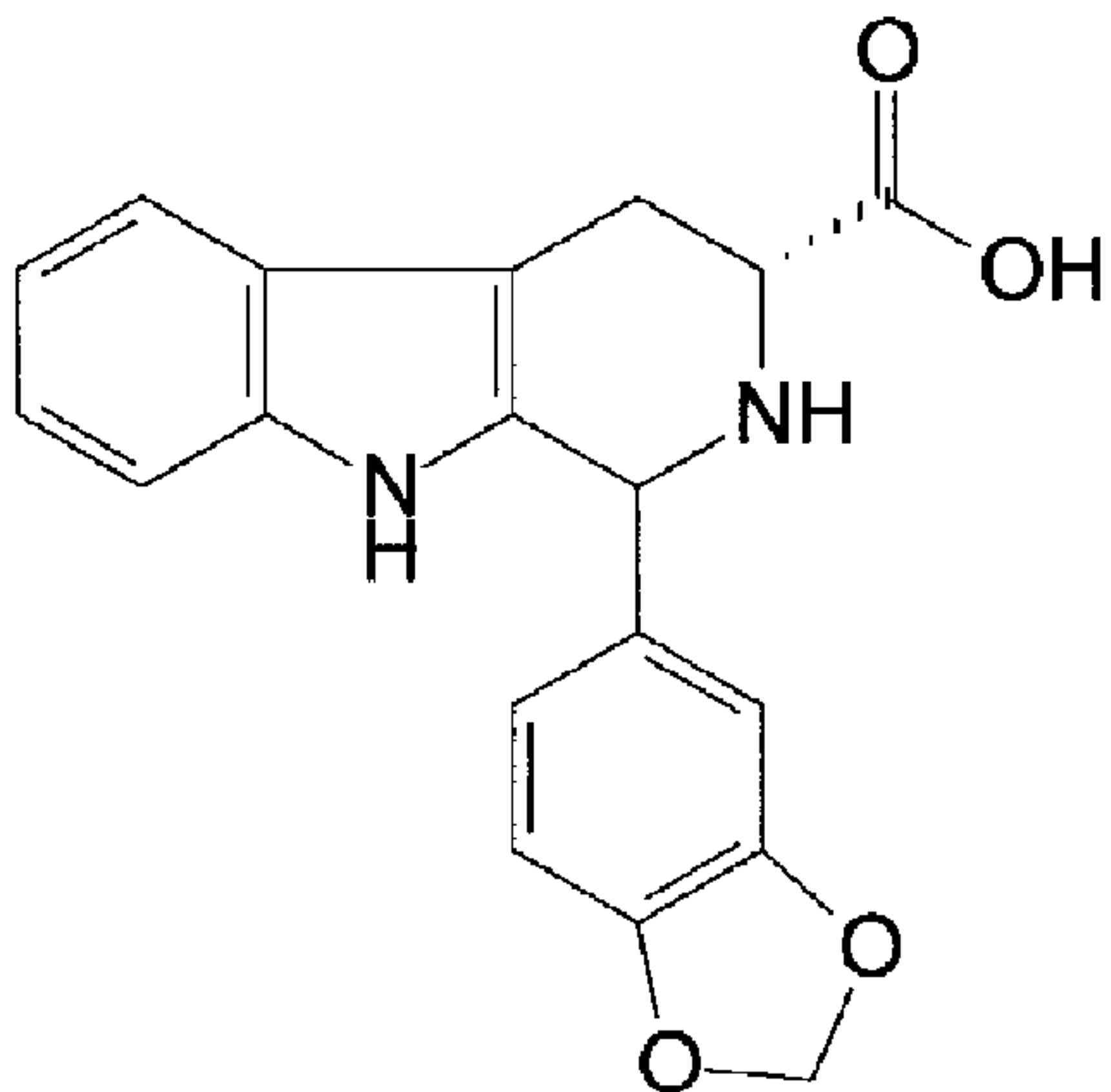
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(2); and

(b) reacting the compound of Formula (2) with methylamine to provide the compound of Formula (1),
wherein R is a C1-C4 alkyl group.

25. The process of any one of claims 13 to 24, wherein R is methyl.



(4)