

Docket No.: 3663-0111PUS1
(Patent)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Patent Application of:

Raymond MCCAGUE et al.

Application No.: 16/336,024

Confirmation No.: 3794

Filed: March 22, 2019

Art Unit: 1629

For: PROCESS

Examiner: SHIAO, REI
TSANG

AMENDMENT UNDER 37 C.F.R. § 1.111

MS AMENDMENT

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Commissioner:

In reply to the Office Action dated August 07, 2020, the following are respectfully submitted in connection with the above-identified application.

Amendments to the Specification

Amendments to the Claims.

Remarks.

BIRCH, STEWART, KOLASCH & BIRCH, LLP

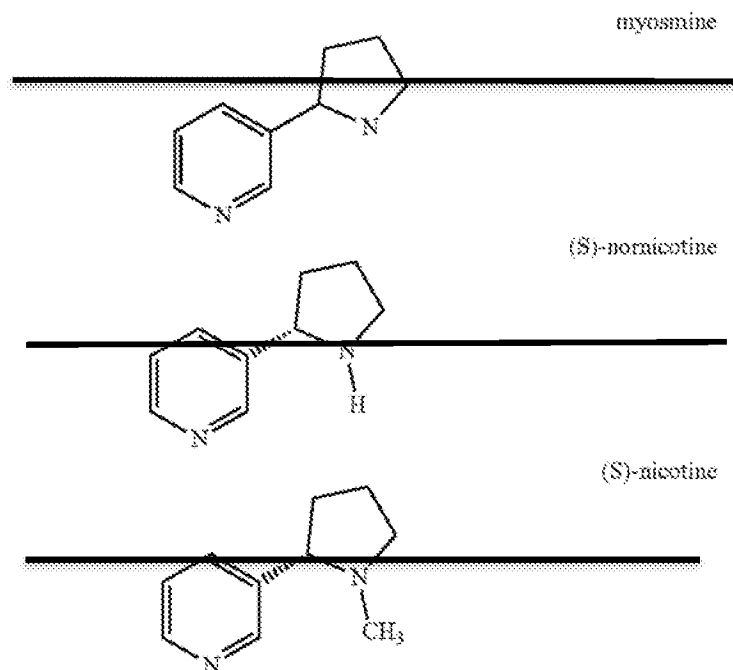
MAA/MAA/mkh

HANGSEN EXHIBIT 1014
Hangsen v. Zanoprima, IPR2023-00503

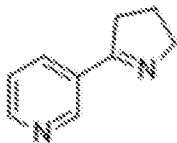
AMENDMENTS TO THE SPECIFICATION

Please amend the published Specification at paragraph [0013] as follows:

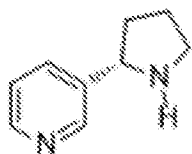
[0013] ~~As the skilled person will appreciate, myosmine, (S)-nornicotine and (S)-nicotine, have the following structures:~~



[0013] As the skilled person will appreciate, myosmine, (S)-nornicotine and (S)-nicotine, have the following structures:



myosmine



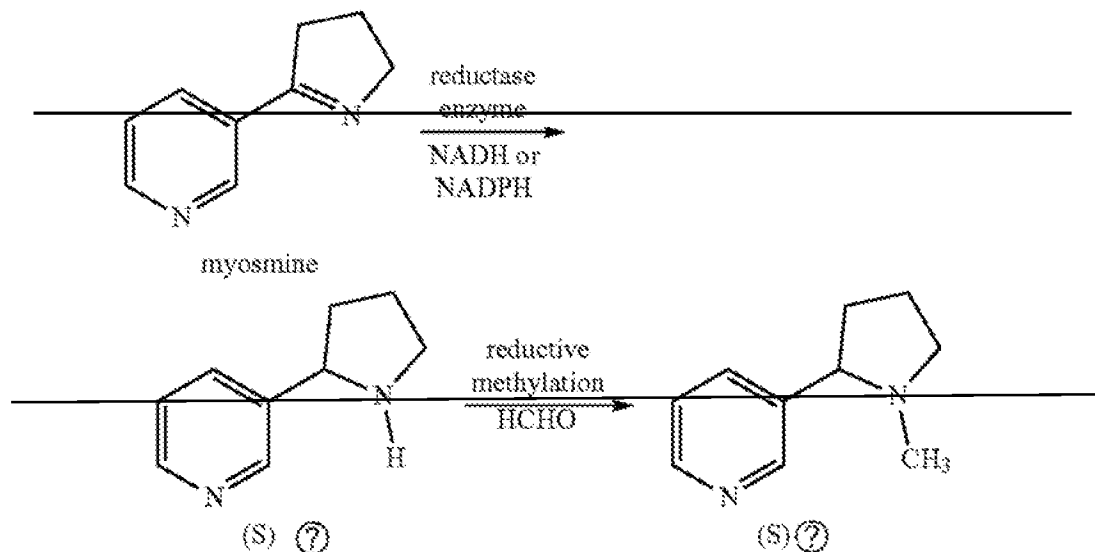
(S)-nornicotine



(S)-nicotine

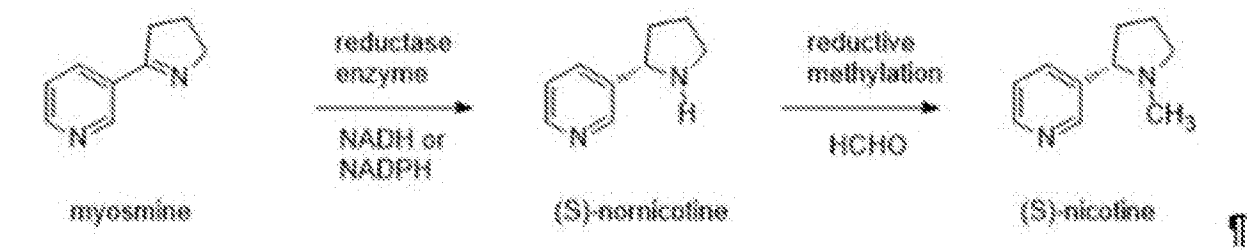
Please amend paragraph [0047] of the published application as follows.

~~[0047] A particularly preferred reaction scheme is displayed below as scheme 1:~~



? indicates text missing or illegible when filed

[0047] A particularly preferred reaction scheme is displayed below as scheme 1:



AMENDMENTS TO THE CLAIMS

1. **(Currently Amended)** A process of making (S)-nicotine comprising the steps of:
 (i) reducing myosmine with an enzyme with imine reductase activity to form (S)-nornicotine;
 and
 (ii) methylating the (S)-nornicotine formed from step (i) to form (S)-nicotine;
 wherein step (ii) is carried out by way of reductive methylation; and
 wherein in step (ii) the (S)-nornicotine is reductively methylated, using formaldehyde or a
 formaldehyde-based compound in the presence of a reductant.
2. **(Cancelled)**
3. **(Cancelled)**
4. **(Currently Amended)** The process of ~~claim 3,~~claim 1 wherein the formaldehyde is introduced as part of an aqueous solution.
5. **(Currently Amended)** The process of ~~claim 3,~~claim 1 wherein the formaldehyde-based compound is a dimer of formaldehyde, a polymer of formaldehyde, or an acetal of formaldehyde.
6. **(Currently Amended)** The process of ~~claim 2,~~claim 1, wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.
7. **(Currently Amended)** The process of ~~claim 2,~~claim 1, wherein the reductant is formic acid.
8. **(Previously Presented)** The process of claim 1, wherein the process is carried out without isolation of the (S)-nornicotine formed from step (i).

9. (Previously Presented) The process of claim 1, wherein in step (i) the (S)-nornicotine is formed as part of an aqueous solution, and wherein step (ii) comprises methylating the (S)-nornicotine contained within the aqueous solution.
10. (Original) The process according to claim 9, wherein in step (ii) the (S)-nornicotine is reductively methylated using formaldehyde introduced as part of an aqueous solution.
11. (Previously Presented) The process of claim 1, wherein the (S)-nicotine is obtained with an enantiomeric excess of at least 90%, preferably at least 95%, more preferably at least 98%, most preferably at least 99%.
12. (Previously Presented) A process for producing a pharmaceutical composition, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in the pharmaceutical composition together with one or more pharmaceutical excipients.
13. (Original) The process of claim 12, wherein the pharmaceutical composition is a transdermal patch, a lozenge, or an inhalation formulation.
14. (Previously Presented) A process for producing a formulation for an electronic cigarette device, comprising forming (S)-nicotine according to the process of claim 1, and including the (S)-nicotine in a solvent with one or more additives.
15. **(Cancelled)**
16. **(Cancelled)**
17. (Previously Presented) The process of claim 4, wherein the reductant is formic acid, sodium cyanoborohydride, or palladium/hydrogen.
18. **(Cancelled)**

19. (Previously Presented) The process of claim 4, wherein the reductant is formic acid.

20. **(Cancelled)**

REMARKS

Status of the Claims

Claims 1, 4-15, 17 and 19 are now present in this application. Claim 1 is independent.

Claims 2, 3, 15, 16, 18 and 20 have been canceled. Claims 1 and 4-7 have been amended. Claim 1 has been amended to include the features of claims 2 and 3. Claims 4-7 have been amended to revise the dependency in view of the amendments to claim 1 and cancellation of claims 2 and 3.

No new matter has been added by way of this amendment. Reconsideration of this application, as amended, is respectfully requested.

Amendments to the specification

The specification as published, has been amended herein to correct printing errors introduced by the USPTO into paragraphs [0013] and [0047]. No new matter has been added with these corrections as the corrections reflect the specification as originally filed.

Priority under 35 U.S.C. § 119

Applicant thanks the Examiner for acknowledging Applicant's claim for foreign priority under 35 U.S.C. § 119. However, the Examiner states that the certified copy of the Priority Document has not been received.

Applicant respectfully submits that the certified copy of the Priority Document has been requested through the USPTO's Electronic Priority Document Exchange (PDX) Program. Upon review of the image file wrapper in PAIR, it appears that the USPTO retrieved the priority document on October 30, 2020. Acknowledgment of receipt of the certified Priority Document is therefore respectfully requested in the next Office Action.

Rejection under 35 U.S.C. § 112(a)

Claim 1 stands rejected under 35 U.S.C. § 112(a) as failing to comply with the enablement requirement.

The Examiner asserts that claim 1 lacks enablement for the feature "methylating the (S)-nornicotine" without limitation. This rejection is respectfully traversed.

Nevertheless, in the interests of advancing prosecution in a timely manner, claim 1 has been limited to require that the methylation step is carried out by way of reductive methylation, using formaldehyde or a formaldehyde-based compound in the presence of a reductant. The skilled person in the art would be readily familiar with formaldehyde-based reagents so as to practice claim 1 across its scope without undue burden.

In this regard, the formaldehyde-based compound is simply a compound that is capable of generating formaldehyde in-situ (see page 8, lines 7-12 of the specification as filed). Indeed, the person skilled in the art would readily understand from the specification that methylating using formaldehyde – either by direct addition or, by addition of a reagent that can generate formaldehyde in-situ – would provide particularly good results. Applicant further notes that although claim 5 gives a list of possible options for the formaldehyde-based compound, this list is non-exhaustive, and it is evident from page 8 of the application as filed that the compounds listed in claim 5 are possible, but (importantly) non-essential, embodiments of the invention. As such, the skilled person would understand based on their own technical knowledge, that alternative formaldehyde-based compounds further to those listed in claim 5 may be used to carry out the invention defined in amended claim 1 across its full scope.

As such, it is clear that the skilled person would find no undue burden in carrying out the amended claim across its full scope and claim 1 if thus fully enabled. Accordingly, reconsideration and withdrawal of this rejection are respectfully requested.

Rejection under 35 U.S.C. § 112(b)

Claim 15 stands rejected under 35 U.S.C. § 112(b) as being indefinite, for failure to set forth any steps involved in the method/process. Claim 15 has been cancelled, thus rendering this rejection moot.

Rejections under 35 U.S.C. § 103

Claims 1-20 are rejected under 35 U.S.C. 103 as being obvious over Arnold (US 2016/0115150) in view of Flora (Regulatory Toxicology and Pharmacology, 2016, 74:1-11).

A complete discussion of the Examiner's rejection is set forth in the Office Action, and is not being repeated here. Applicant traverses this rejection and withdrawal thereof is respectfully requested.

The present invention is directed to the stereoselective synthesis of (S)-nicotine. The process of the invention provides a convenient two-step process from the common intermediate myosmine that affords high enantiomeric selectivity for the (S) isomer of nicotine, while also achieving high chemical purity. The claimed combination of steps (i) and (ii) provide the effective and convenient production of (S)-nicotine, without having to resort to resolution of a racemic mix (see page 3, lines 7-17 of the application as filed).

Applicant submits that Arnold requires three chemical steps from myosmine to (S)-nicotine. Further, Arnold does not concern the stereoselective synthesis of (S)-nicotine, and is instead solely concerned with the production of a racemic mix. This is reiterated throughout the document, with each example producing R,S-nicotine i.e. the racemic mix. As such, Arnold concerns a fundamentally different synthetic route, which ultimately has a different aim than the present invention – i.e. the aim in Arnold is to produce a racemic mix, rather than achieve stereoselectivity.

This fundamental purpose of Arnold must be kept in mind when considering what the skilled person would learn from the reference regarding the achievement of a stereoselective route, such as that of claim 1. Applicant also notes the benefits afforded by the claimed invention compared to the process of Arnold – including high stereoselectivity for the (S) isomer of nicotine without having to go via resolution of a racemic mix, and the ability to achieve this using a convenient two-step process. Due to the ability to avoid having to go via a racemic mix, the present invention achieves much higher yields of (S)-nicotine – yield is a particular limitation of racemic processes, where the maximum yield of the (S) isomer from resolution of the racemic mix would be 50% at its absolute best.

Applicant further submits that Arnold at least fails to disclose or suggest step (i) of claim 1, that is, reduction of myosmine using an enzyme with imine reductase activity. In contrast, Arnold is solely concerned with routes that reduce myosmine using either a “hydrogenation catalyst”, or a borohydride compound. The Examiner states as follows regarding the disclosure of “hydrogenation catalyst” in Arnold as encompassing an enzyme:

Arnold's '150 disclose a process of making nicotine by reducing myosamine with a reducing agent selected from hydrogenation catalyst (e.g. enzyme) to form nornicotine, then methylating the nornicotine with formaldehyde and formic acid, see columns 5-6.

However, it is clear from Arnold (and from the common knowledge and use of terminology in the art) that “hydrogenation catalyst” refers to the well-recognized process of catalytic hydrogenation, which is carried-out using a metal catalyst, e.g. palladium) + hydrogen. Therefore, a “hydrogenation catalyst” is both taught in Arnold and recognized in the art as being distinct from an enzyme with imine reductase activity. In addition, even if this term were to be viewed as encompassing an enzyme, which Applicant does not concede, it remains that there is no specific disclosure of an enzyme with imine reductase activity in Arnold. All of the examples in Arnold use either a metal catalyst + hydrogen, or use a borohydride compound, with paragraph 26 providing an explicit preference for palladium on carbon.

No motivation or reason is given in Arnold to explore alternative reductants, and there is certainly no motivation to dispense with the very clear direction in Arnold to use a metal catalyst + hydrogen or a borohydride compound, and instead use an enzyme with imine reductase activity. As such, there is nothing to point the skilled person towards the combination of steps (i) with (ii) as required by the claim.

Turning Flora et al, this document also does not concern the stereoselective synthesis of (S)-nicotine. Once again, the skilled person would therefore learn nothing regarding the achievement of a stereoselective route from this document. This document similarly does not encourage the skilled person to dispense with the metal catalyst + hydrogen/borohydride reduction process, and to arrive at the beneficial combination of steps (i) with (ii) as required by claim 1. As such, the present invention is not *prima facie* obvious over Arnold combined with Flora and withdrawal of the rejection is respectfully requested.

Conclusion

All of the stated grounds of rejection have been properly traversed, accommodated, or rendered moot. Applicant therefore respectfully requests that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. It is believed that a full and

complete response has been made to the outstanding Office Action, and as such, the present application is in condition for allowance.

For any outstanding matters in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD, Registration No. 40,069, at 703-205-8063 to discuss the present application. If unable to reach the above-identified contact, please call the general mailbox number 703-205-8007.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: October 30, 2020

Respectfully submitted,

By /MaryAnne ARMSTRONG, PhD/
MaryAnne Armstrong, PhD
Registration No.: 40,069
BIRCH, STEWART, KOLASCH & BIRCH, LLP
8110 Gatehouse Road
Suite 100 East
Falls Church, VA 22042