PROCESS FOR PREPARING AZABICYCLIC COMPOUNDS

CROSS-REFERENCE TO RELATED APPLICATIONS

[001] This application claims priority to provisional application U.S. Serial No. 61/243,477 filed on September 17, 2009. The entire contents of the aforementioned application are incorporated herein.

TECHNICAL FIELD OF THE INVENTION

[002] The present invention relates to a process for preparing azabicylic compounds that are useful in the synthesis of pharmaceutical compounds and salts thereof.

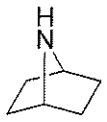
BACKGROUND OF THE INVENTION

[003] 7-azabicyclo[2.2.1]heptanes are useful intermediates in the synthesis of pharmaceutical compounds and salts thereof. For example, see U.S. patent nos. 6,117,889 and 6,060,473, each of which is hereby incorporated by reference in its entirety.

SUMMARY ~~OF THE INVENTION~~

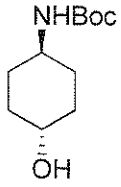
[004] What is disclosed herein is a process for preparing azabicyclic compounds that are useful intermediates for preparing pharmaceutical compounds and salts thereof.

[004a] In one aspect, there is provided a process for preparing Compound 7,



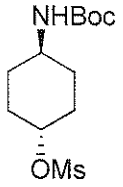
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or a pharmaceutically acceptable salt thereof, comprising contacting *trans*-4-aminocyclohexanol with Boc anhydride to produce Compound A



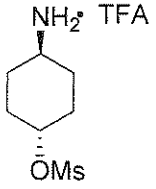
A ;

contacting Compound A with methanesulfonyl chloride to produce Compound B



B ;

contacting Compound B with trifluoroacetic acid to produce Compound C



C ; and

contacting Compound C with hydroxide to produce Compound 7.

DETAILED DESCRIPTION OF THE INVENTION

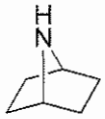
[005] **Definitions**

[006] Compounds and processes disclosed herein include those described generally above, and are further illustrated by the classes, subclasses, and species disclosed herein. As used herein, the following definitions shall apply unless otherwise indicated.

[007] The term "modulating" as used herein means increasing or decreasing by a measurable amount.

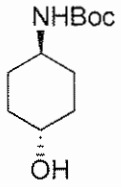
[008] For purposes of this invention, the chemical elements are identified in accordance with the Periodic Table of the Elements, CAS version, Handbook of Chemistry and Physics, 75th Ed. Additionally, general principles of organic chemistry are described in "Organic Chemistry", Thomas Sorrell, University Science Books, Sausalito: 1999, and "March's Advanced Organic Chemistry", 5th Ed., Ed.: Smith, M.B. and March, J., John Wiley & Sons, New York: 2001, the entire contents of which are hereby incorporated by reference.

[009] As described herein, compounds of the invention may optionally be substituted with one or more substituents, such as are illustrated generally above, or as exemplified by particular classes, subclasses, and species of the invention. It will be appreciated that the



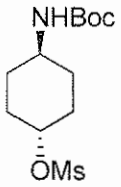
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or a pharmaceutically acceptable salt thereof, comprising contacting trans-4-aminocyclohexanol with Boc anhydride to produce ~~a~~ e<u>C</u>ompound ~~of formula~~ A



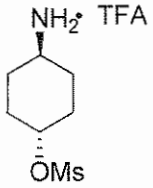
A ;

contacting ~~a~~ e<u>C</u>ompound ~~of formula~~ A with methanesulfonyl chloride to produce ~~a~~ e<u>C</u>ompound ~~of formula~~ B



B ;

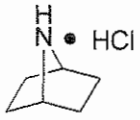
contacting ~~a~~ e<u>C</u>ompound ~~of formula~~ B with trifluoroacetic acid to produce ~~a~~ e<u>C</u>ompound ~~of formula~~ C



C ; and

contacting ~~a~~ e<u>C</u>ompound ~~of formula~~ C with hydroxide to produce ~~a~~ e<u>C</u>ompound ~~of formula~~ 7.

[015] In some embodiments, the invention includes a method of producing ~~a~~ e<u>C</u>ompound ~~of formula~~ 7a,



7a

comprising contacting ~~a~~ e<u>C</u>ompound ~~of formula~~ 7 with hydrochloric acid.

[016] In one embodiment, *trans*-4-aminocyclohexanol is contacted with Boc anhydride in the presence of a solvent and optionally in the presence of a base.

[017] In another embodiment, the solvent comprises water, dichloromethane, THF, 2-methyltetrahydrofuran, ethanol, methanol, isopropanol, DMF, DMSO, or combinations thereof.

[018] In one embodiment, the solvent is a mixture.

[019] In a further embodiment, the solvent is a mixture comprising water and dichloromethane.

[020] In one embodiment, a base is present and the base comprises sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, or combinations thereof.

[021] In another embodiment, ~~a~~ eCompound ~~of formula~~ A is contacted with methanesulfonyl chloride in the presence of a solvent and optionally in the presence of a base.

[022] In one embodiment, the solvent comprises tetrahydrofuran.

[023] In another embodiment, a base is present and the base comprises a tertiary amine base.

[024] In a further embodiment, the base is triethylamine.

[025] In one embodiment, ~~the~~ eCompound ~~of formula~~ B is contacted with trifluoroacetic acid in the presence of a solvent.

[026] In a further embodiment, the solvent is dichloromethane.

[027] In another embodiment, ~~the~~ eCompound ~~of formula~~ B is contacted with trifluoroacetic acid under neat conditions.

[028] In one embodiment, ~~the~~ Ceompound ~~of formula~~ C is contacted with hydroxide in the presence of a solvent.

[029] In a further embodiment, the hydroxide is present as sodium hydroxide or potassium hydroxide and the solvent comprises water.

[030] In one embodiment, the process further comprises distillation of the reaction mixture and recovery of ~~a~~ eCompound ~~of formula~~ 7 in a pure form.

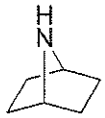
[031] In one embodiment, the process further comprises recrystallizing Compound 7a from acetonitrile.

[032] In another embodiment, the process further comprises recrystallizing Compound 7a from a mixture of methanol and 2-methyltetrahydrofuran.

[033] In one embodiment, the ratio of methanol to 2-methyltetrahydrofuran is about 1:1.

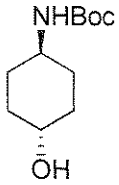
WHAT IS CLAIMED IS:

1. A process for preparing Compound 7,



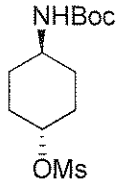
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or a pharmaceutically acceptable salt thereof, comprising contacting *trans*-4-aminocyclohexanol with Boc anhydride to produce ~~a~~ eCompound ~~of formula~~ A



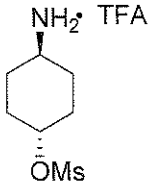
A ;

contacting ~~a~~ eCompound ~~of formula~~ A with methanesulfonyl chloride to produce ~~a~~ eCompound ~~of formula~~ B



B ;

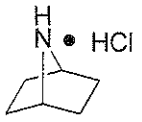
contacting ~~a~~ eCompound ~~of formula~~ B with trifluoroacetic acid to produce ~~a~~ eCompound ~~of formula~~ C



C ; and

contacting ~~a~~ eCompound ~~of formula~~ C with hydroxide to produce ~~a~~ eCompound ~~of formula~~ 7.

2. The process of claim 1, further comprising a process for producing ~~a~~ eCompound ~~of formula~~ 7a,



7a

comprising contacting compound 7 with HCl.

3. The process of claim 1, wherein *trans*-4-aminocyclohexanol is contacted with Boc anhydride in the presence of a solvent and optionally in the presence of a base.
4. The process of claim 3, wherein the solvent comprises water, dichloromethane, THF, 2-methyltetrahydrofuran, ethanol, methanol, isopropanol, DMF, DMSO, or combinations thereof.
5. The process of claim 4, wherein the solvent is a mixture.
6. The process of claim 5, wherein the solvent is a mixture comprising water and dichloromethane.
7. The process of claim 3, wherein a base is present and the base comprises sodium bicarbonate, potassium bicarbonate, sodium carbonate, potassium carbonate, or combinations thereof.
8. The process of claim 1, wherein ~~a e~~Compound ~~of formula~~ A is contacted with methanesulfonyl chloride in the presence of a solvent and optionally in the presence of a base.
9. The process of claim 8, wherein the solvent comprises tetrahydrofuran.
10. The process of claim 8, wherein a base is present and the base comprises a tertiary amine base.
11. The process of claim 10, wherein the base is triethylamine.
12. The process of claim 1, wherein ~~the e~~Compound ~~of formula~~ B is contacted with trifluoroacetic acid in the presence of a solvent.
13. The process of claim 12, wherein the solvent is dichloromethane.
14. The process of claim 1, wherein ~~the e~~Compound ~~of formula~~ B is contacted with trifluoroacetic acid under neat conditions.
15. The process of claim 1, wherein ~~the e~~Compound ~~of formula~~ C is contacted with hydroxide in the presence of a solvent.
16. The process of claim 15, wherein the hydroxide is present as sodium hydroxide or potassium hydroxide and the solvent comprises water.
17. The process of claim 1, further comprising distillation of the reaction mixture and recovery of ~~a e~~Compound ~~of formula~~ 7 in a pure form.