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(71) Applicants: **GBR LABORATORIES PVT. LTD.** [IN/IN]; HNO 5-7-209/2, Sripuram Colony, BN Reddy Nagar, Vanasthalipuram, Hyderabad 500070, Telangana (IN). **RACHANA PHARMA TECH** [IN/IN]; Flat No 404, B-block, Surya Towers, Road No - 2, Snehapuri Colony, Nacharam, Hyderabad 500076, Telangana (IN).

(72) Inventors: **REDDY, G. Nithun**; HNO 5-7-209/2, Sripuram Colony, BN Reddy Nagar, Vanasthalipuram, Hyderabad 500070, Telangana (IN). **REDDY, G. Samhitha**; HNO 5-7-209/2, Sripuram Colony, BN Reddy Nagar, Vanasthalipuram, Hyderabad 500070, Telangana (IN). **REDDY, G. Madaalasa**; HNO 5-7-209/2, Sripuram Colony, BN Reddy Nagar, Vanasthalipuram, Hyderabad 500070, Telangana (IN). **RAMANI, M**; Flat No 404, B-block, Surya Towers, Road No - 2, Snehapuri Colony, Nacharam, Hyderabad 500076, Telangana (IN). **REDDY, G. Pratap**; E7, Fortune Indra Villae, Survey No - 11, Guttala Begumpath, Serilingampally Mandal, Shaikpet, Hyderabad 500081, Telangana (IN).

(74) Agent: **MAHURKAR, Anand Gopalkrishna**; KRISHNA & SAURASTRI ASSOCIATES LLP, 74/F, Venus, Worli Sea Face, Mumbai – 400 018, Maharashtra (IN).

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(54) Title: PROCESS FOR SYNTHESIS OF GLYCOPYRRONIUM BROMIDE

(57) Abstract: Provided herein are processes for preparation of glycopyrronium bromide comprising reaction of N-methylpyrrolidin-3-ol with compounds of Formula I or Formula II followed by additional steps.

PROCESS FOR SYNTHESIS OF GLYCOPYRRONIUM BROMIDE

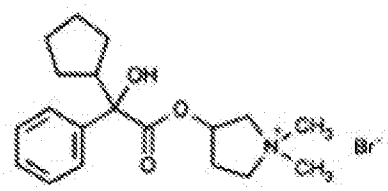
This application claims priority to Indian Provisional Patent Application No. 201741006245 filed on 22 February 2017, which is incorporated herein in its entirety.

FIELD OF INVENTION

This disclosure is related to a process for synthesis of glycopyrronium bromide.

BACKGROUND OF THE INVENTION

Glycopyrronium bromide (or glycopyrrolate) is a quaternary ammonium salt with the following chemical name: 3[(cyclopentylhydroxyphenylacetyl)oxy]-1,1-dimethyl pyrrolidinium bromide. The structural formula is shown below



The compound is an anticholinergic agent which is formulated for intramuscular or intravenous injection. Glycopyrronium bromide is indicated for use as a preoperative antimuscarinic to reduce salivary, tracheobronchial, and pharyngeal secretions; to reduce the volume and free acidity of gastric secretions; and to block cardiac vagal inhibitory reflexes during induction of anesthesia and/or intubation. When indicated, it is used intraoperatively to counteract surgically or drug induced or vagal reflexes associated arrhythmias. Glycopyrrolate protects against the peripheral muscarinic effects (e.g., bradycardia and excessive secretions) of cholinergic agents such as neostigmine and pyridostigmine given to reverse the neuromuscular blockade due to non-depolarizing muscle relaxants.

There is a need in the art for efficient methods of synthesis of pharmaceutical grade glycopyrronium bromide.

SUMMARY OF THE INVENTION

Provided herein are processes for preparation of glycopyrronium bromide comprising, in a first step, a reaction of N-methylpyrrolidin-3-ol with a compound of Formula I or Formula II as described herein followed by a coupling reaction with a suitable organo-magnesium reagent as described herein.

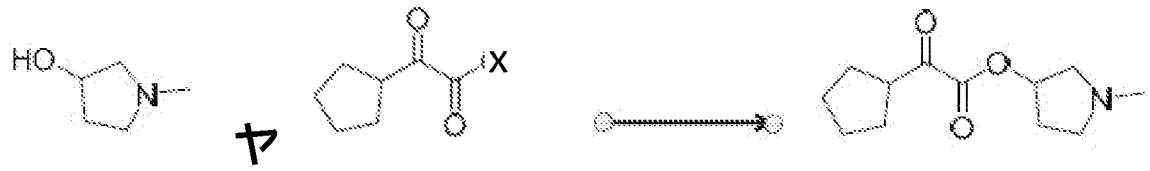
DETAILED DESCRIPTION OF THE INVENTION

All materials used herein were commercially purchased as described herein or prepared from commercially purchased materials as described herein.

Previously known methods for synthesis of glycopyrronium bromide comprised a reaction of alpha-cyclopentylphenylacetyl chloride with N-methylpyrrolidin-3-ol. By contrast, described herein are processes wherein the synthesis of glycopyrronium bromide is achieved by initially coupling N-methylpyrrolidin-3-ol with either 2-oxo-2-phenyl acetic acid derivatives or 2-oxo-2-cyclopentyl acetic acid derivatives followed by a Grignard reaction, as described in more detail in the Examples section.

In one aspect, provided herein is a process for preparation of glycopyrronium bromide comprising

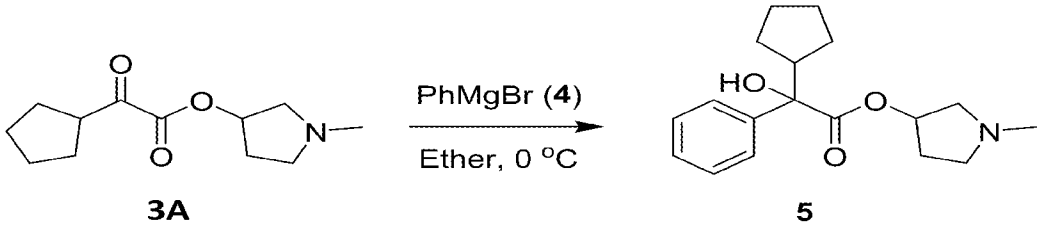
(i) reacting N-methylpyrrolidin-3-ol with a compound of Formula I to obtain a compound of structure 3A:



Formula I わ

wherein X is H, OH, OMe or Cl; and

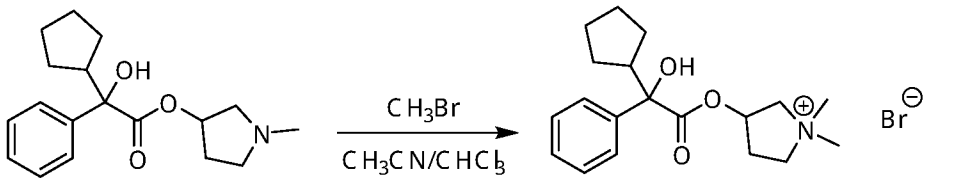
(ii) reacting the compound of structure 3A with phenyl magnesium bromide to obtain a compound of structure 5



3A 5

Scheme 1 describes certain non-limiting reaction conditions for the reaction of a compound of Formula I with N-methylpyrrolidin-3-ol. Other suitable coupling protocols will be apparent to one of skill in the art and are contemplated within the scope of embodiments described herein.

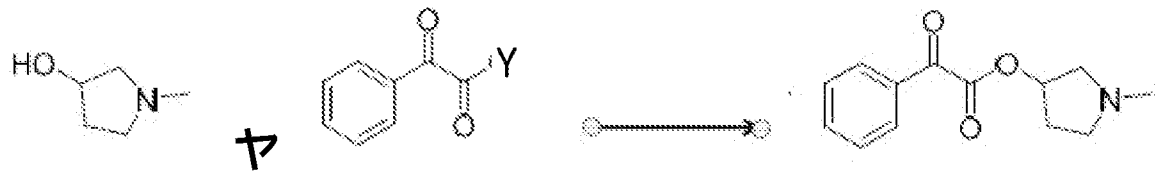
In one group of embodiments, said process further comprises reacting the compound of structure 5 with methyl bromide to obtain a compound of structure 6



5 6

In another aspect, provided herein is a process for preparation of glycopyrronium bromide comprising

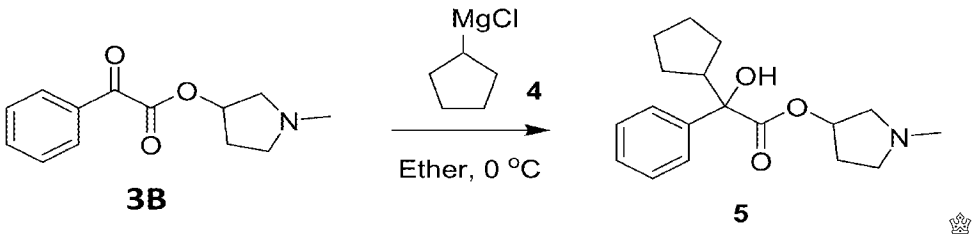
(i) reacting N-methylpyrrolidin-3-ol with a compound of Formula II to obtain a compound of structure 3B:



Formula II わ

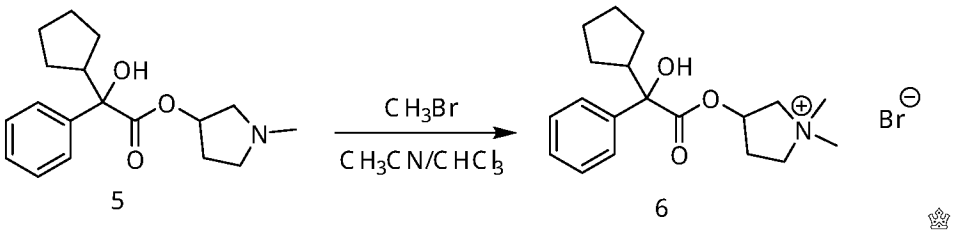
wherein Y is H, OH, OMe or Cl; and

(ii) reacting the compound of structure 3B with cyclopentyl magnesium chloride to obtain a compound of structure 5



Scheme 2 describes certain non-limiting reaction conditions for the reaction of a compound of Formula II with N-methylpyrrolidin-3-ol. Other suitable coupling protocols will be apparent to one of skill in the art and are contemplated within the scope of embodiments described herein.

In one group of embodiments, the process described above further comprises reacting the compound of structure 5 with methyl bromide to obtain a compound of structure 6

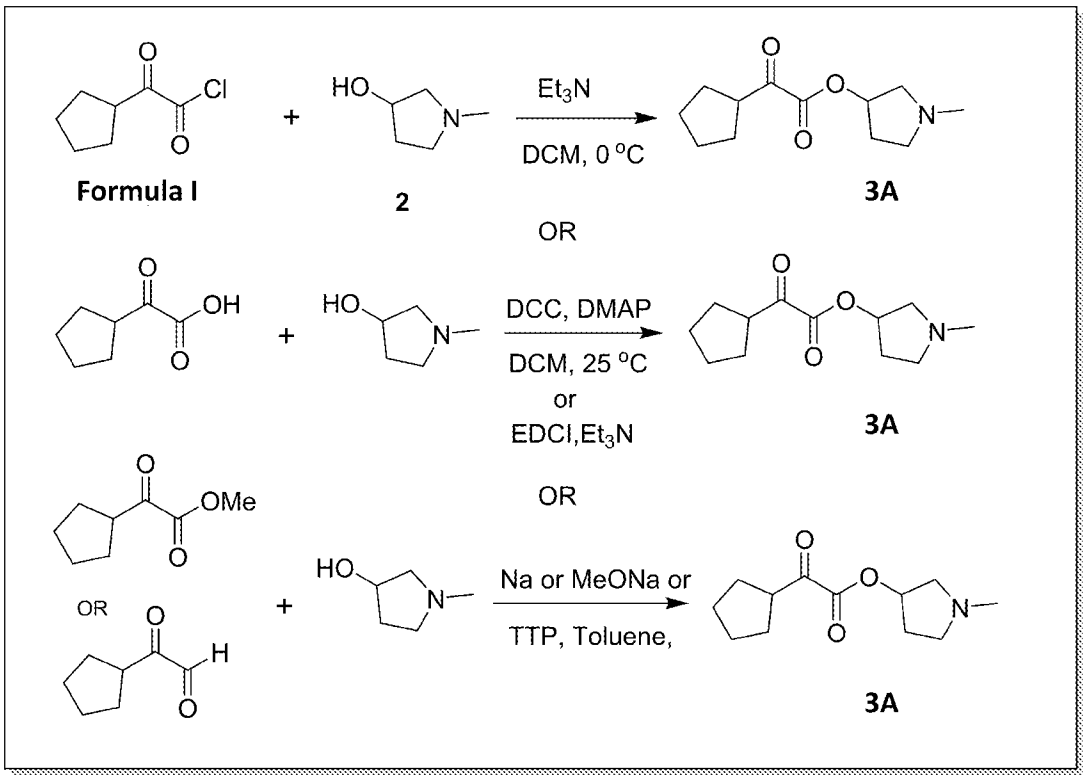


EXAMPLES

EXAMPLE 1

Scheme 1

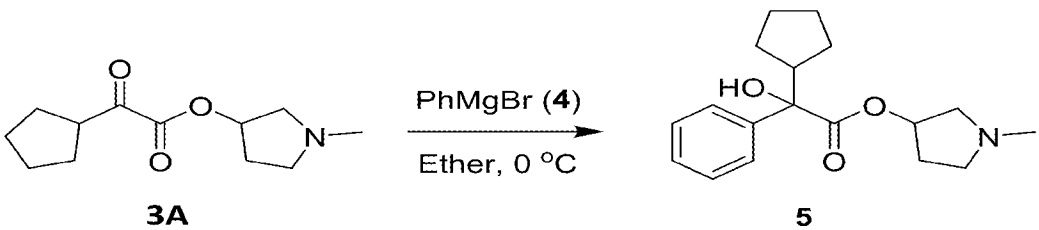
STEP I



To a stirred solution of N-methylpyrrolidin-3-ol (2, 1 equiv) and Et_3N (1.2 equiv) in dichloromethane was added a solution of 2-cyclopentyl-2-oxoacetyl chloride (1, 1.1 equiv) in DCM at 0 °C under nitrogen atmosphere for 20 min. The resulting solution was allowed to stir at room temperature over 10h. After completion, the mixture was quenched with water and extracted with diethyl ether to afford the pure product (3A).

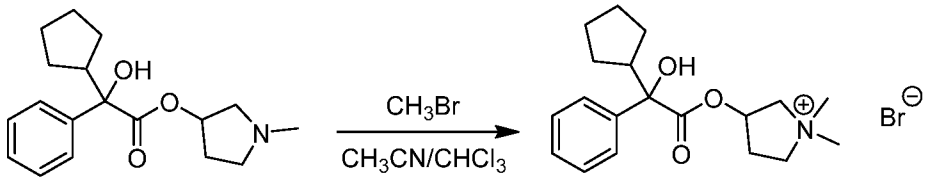
Similarly, the product 3A is also obtained by reaction of 2 with other reagents, phenyl oxalic acid, methyl phenyl oxalate, and phenyl hemi-oxaldehyde respectively as shown in Scheme 1.

STEP II



To a mixture of bromobenzene (2.2 equiv) and Mg metal (2.2 equiv) in THF (15 mL) was stirred over a period of 30 min at 0 · C. To this mixture, a solution of 1-methylpyrrolidin-3-yl 2-cyclopentyl-2-oxoacetate (3, 1 equiv) in THF was added in portions over a period of 30 min. Up on completion, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was separated and concentrated in vacuo. The resulting residue was purified by column chromatography to afford the pure product (5).

STEP III



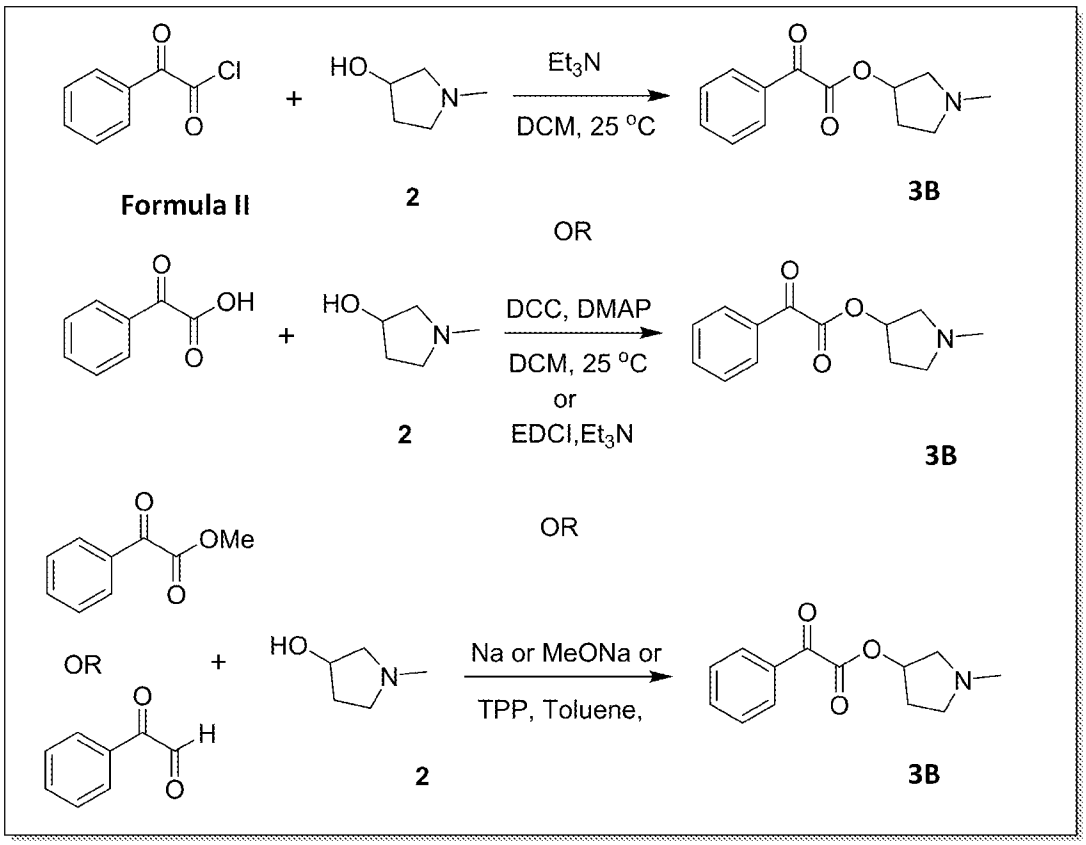
5 6

To a solution of compound 5 (1 equiv) in acetonitrile and chloroform mixture (10 mL, 2:3) was added methyl bromide (4 equiv). The mixture was stirred at room temperature for 72h. The solvents were evaporated, and the resulting residue was washed with diethyl ether to afford the pure product (6) as a white solid.

EXAMPLE 2

Scheme 2

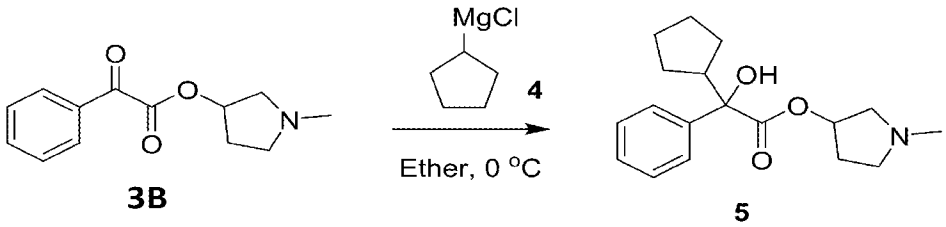
STEP I



To a stirred solution of N-methylpyrrolidin-3-ol (2, 1 equiv) and Et_3N (1.2 equiv) in dichloromethane was added a solution of 2-oxo-2-phenylacetyl chloride (1.1 equiv) in dichloromethane at 0 °C under nitrogen atmosphere for 15 min. The resulting solution was allowed to stir at room temperature over 12h. After completion, the mixture was quenched with water and extracted with diethyl ether to afford the pure product (3B).

Similarly, the product 3B is also obtained by reaction of 2 with other reagents, phenyl oxalic acid, methyl phenyl oxalate, and phenyl hemi-oxaldehyde respectively as shown in Scheme 2.

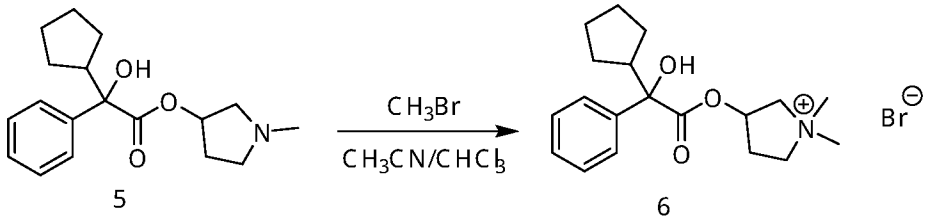
STEP II



3B 5

To a mixture of cyclopentyl bromide (4, 2.2 equiv) and Mg metal (2.2 equiv) in THF (15 mL) was stirred over a period of 30 min at 0 ·C. To this mixture, a solution of 1-methylpyrrolidin-3-yl-2-oxo-2-phenylacetate (3B, 1 equiv) in THF was added in portions over a period of 30 min. Up on completion, the reaction mixture was poured into ice water and extracted with ethyl acetate. The organic layer was separated and concentrated in vacuo. The resulting residue was purified by column chromatography to afford the pure product (5).

STEP III



5 6

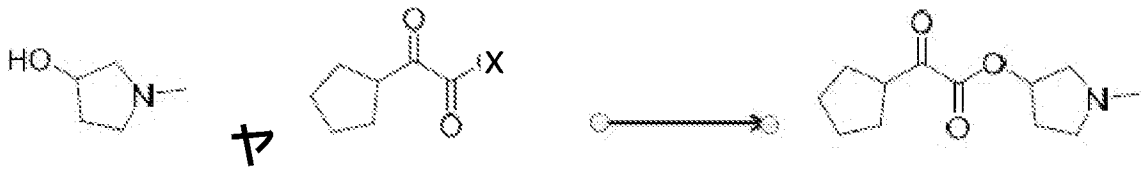
To a solution of compound 5 (1 equiv) in acetonitrile and chloroform mixture (10 mL, 2:3) was added methyl bromide (4 equiv). The mixture was stirred at room temperature for 75h. The solvents were evaporated, and the resulting residue was washed with diethyl ether to afford the pure product (6) as a white solid.

The invention has been described in detail with reference to preferred embodiments thereof. However, it will be appreciated by those skilled in the art that changes may be made in these embodiments without departing from the principles and nature of the invention, the scope of which is defined in the appended claims and their equivalents.

Claims :

1. A process for preparation of glycopyrronium bromide comprising

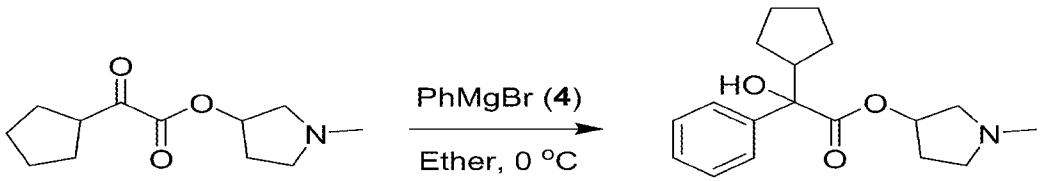
(i) reacting N-methylpyrrolidin-3-ol with a compound of Formula I to obtain a compound of structure 3A:



Formula I

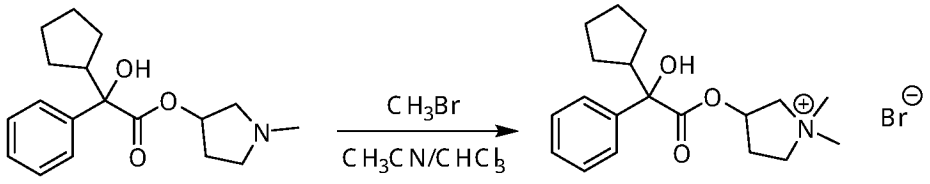
wherein X is H, OH, OMe or Cl; and

(ii) reacting the compound of structure 3A with phenyl magnesium bromide to obtain a compound of structure 5



3A 5

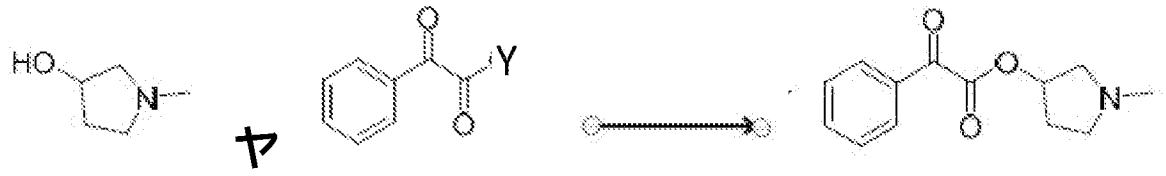
2. The process of claim 1, further comprising reacting the compound of structure 5 with methyl bromide to obtain a compound of structure 6



5 6

3. A process for preparation of glycopyrronium bromide comprising

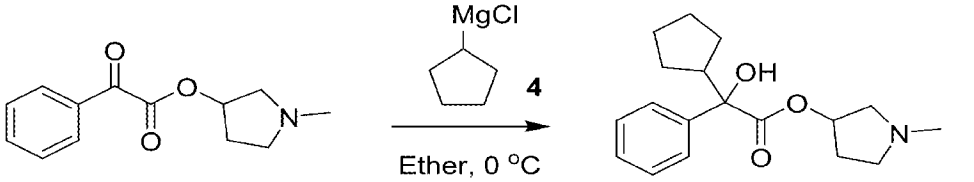
(i) reacting N-methylpyrrolidin-3-ol with a compound of Formula II to obtain a compound of structure 3B:



Formula II わ

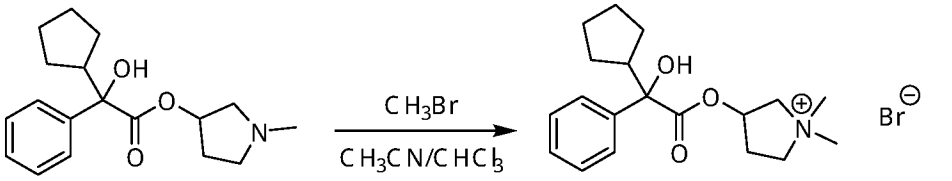
wherein Y is H, OH, OMe or Cl; and

(ii) reacting the compound of structure 3B with cyclopentyl magnesium chloride to obtain a compound of structure 5



3B 5

4. The process of claim 3, further comprising reacting the compound of structure 5 with methyl bromide to obtain a compound of structure 6



5 6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2018/050083

A. CLASSIFICATION OF SUBJECT MATTER
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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)

C07CD207/12

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)

TotalPatent One

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2956062 A (LUNSFORD CARL D [US]) 11 October 1960 (11/10/1960) Examples 1-10	1-4
Y	US 2009/0005577 A1 (KRAIOUCHKINE N [US]) 01 January 2009 (01/01/2009) paragraph [0017]-[0019], [0021], [0034], [0047]-[0049], [0057]	1-4
Y	CN 103159659 A (DUN W ET AL [CHN]) 19 June 2013 (19/06/2013) Claim 1, paragraph [0007]	1-4

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01-05-2018	01-05-2018

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