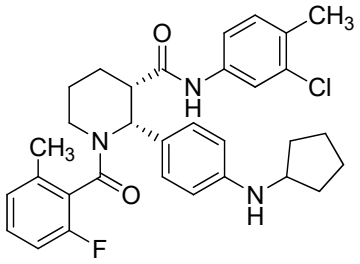
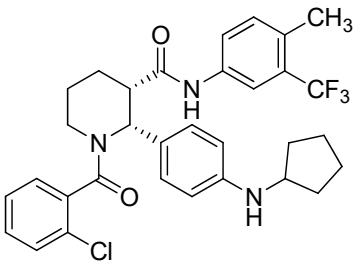


IA



IB



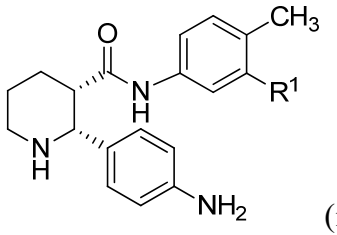
IC

The preparation of compound IA has been provided as shown in Fig. 4, and involves a lengthy synthesis including a classical resolution of isomers (see, for example, the conversion of **6** to **7**).

[0012] There exists a need in the art for more efficient methods of preparation of compounds IA, IB and IC. The present disclosure provides such methods, as well as intermediates in the synthetic pathways.

BRIEF SUMMARY

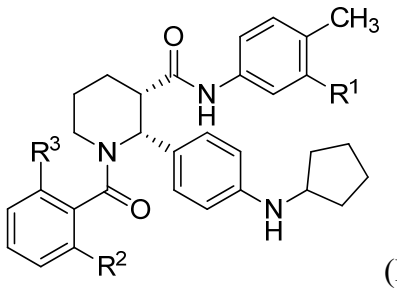
[00012a] In one aspect of the present disclosure, there is provided the compound having the formula (ii-4):



(ii-4)

wherein R^1 is Cl or CF_3, or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities.

[00012b] In another aspect of the present disclosure, there is provided a method of preparing a compound having formula (I):


(I)

or a salt thereof, wherein

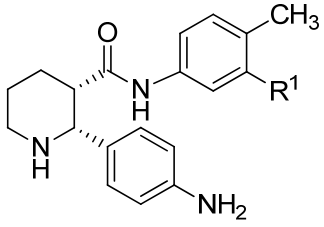
R^1 is Cl or CF_3;

R^2 is F or Cl; and

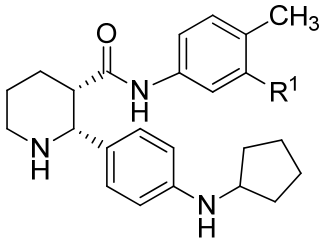
R^3 is H or CH_3;

and wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, said method comprising:

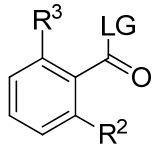
(a) contacting a compound having the formula (ii-4):


(ii-4)

wherein R^1 is Cl or CF_3; or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities, with cyclopentanone and a reducing agent to form a compound having the formula (ii-5):


(ii-5) ; and

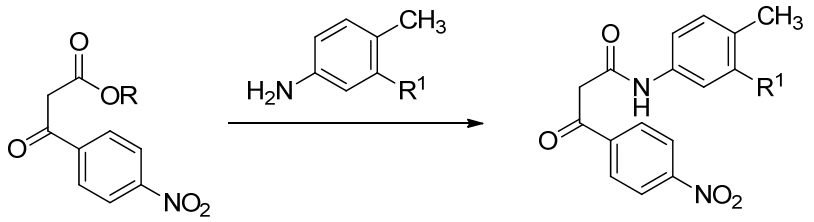
(b) contacting said compound of formula (ii-5) with a compound having the formula:



wherein LG is a leaving group, R^2 is F or Cl; and R^3 is H or CH_3; in the presence of a base to form a compound of formula (I) which is substantially free of enantiomeric or diastereomeric impurities.

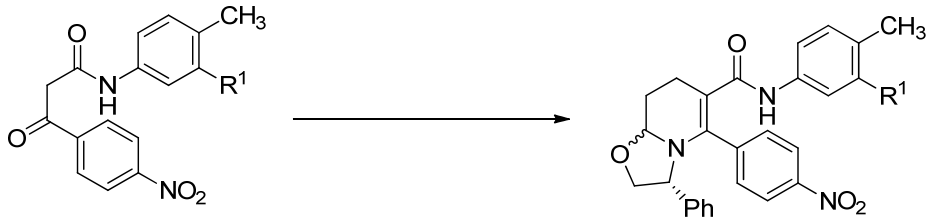
[00012c] In a further aspect of the present disclosure, there is provided a method for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt thereof, said method comprising:

(a') reacting an ester of 3-(4-nitrophenyl)-3-oxo-propanoate (i-1, or ii-1, wherein R is selected from the group consisting of C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline under conditions sufficient to provide a compound of formula (ii-2);



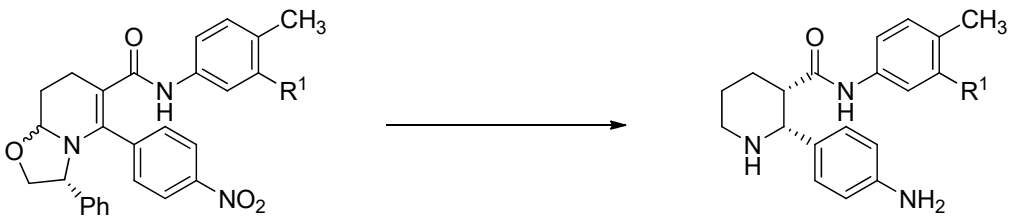
(i-1, ii-1) (ii-2)

(b') reacting (ii-2), (*R*)-(−)-2-phenylglycinol, and acrolein diethyl acetal or an equivalent thereof, to produce compound (ii-3);



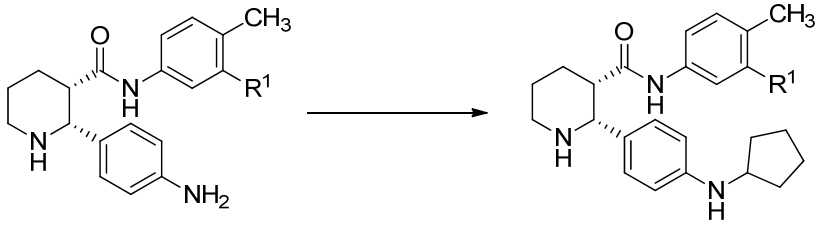
(ii-2) (ii-3)

(c') reducing (ii-3) under conditions sufficient to produce an intermediate diamine (ii-4) that is substantially free of enantiomeric or diastereomeric impurities;



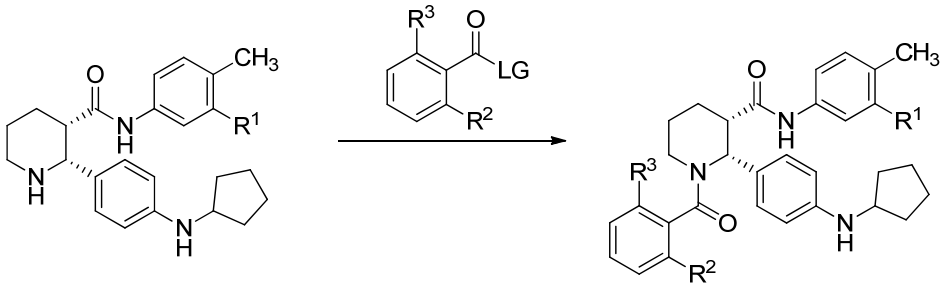
(ii-3) (ii-4)

(d') converting (ii-4) to (ii-5) with cyclopentanone and a reducing agent; and



(ii-4) (ii-5)

(e') combining (ii-5) with either 2-fluoro-6-methylbenzoyl chloride or 2-chlorobenzoyl chloride to provide (I);



(ii-5) (I)

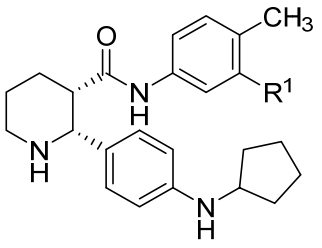
wherein

R^1 is C1 or CF_3;

R^2 is F or C1; and

R^3 is H or CH_3.

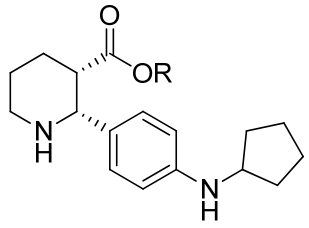
[00012d] In another aspect of the present disclosure, there is provided the compound having the formula (ii-5):



(ii-5)

wherein R^1 is Cl or CF_3, or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities.

[0013] In one example, provided herein is a compound useful in the preparation of several C5aR antagonists, having the formula (i-3):

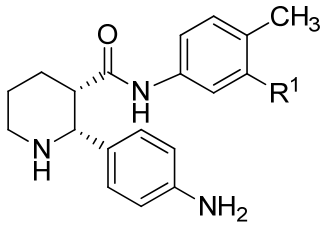


(i-3)

(2R,3S)

wherein R is selected from H, C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, or a salt thereof, which is substantially free of enantiomeric or diastereomeric impurities (the (2R,3R), (2S,3R) and (2S,3S) isomers).

[0014] In another example, provided herein is a compound useful in the preparation of several C5aR antagonists, the compound having the formula (ii-4):

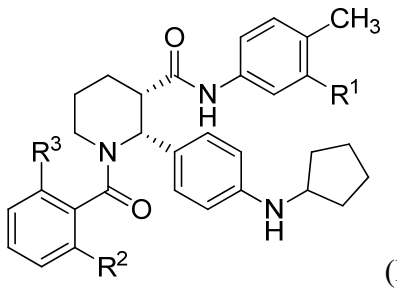


(ii-4)

(2R,3S)

or a salt thereof, wherein R^1 is Cl or CF_3, and wherein the compound is substantially free of enantiomeric or diastereomeric impurities (the corresponding (2R,3R), (2S,3R) and (2S,3S) isomers).

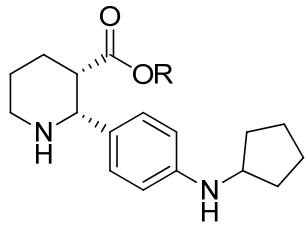
[0015] In yet another example, provided herein is a method of preparing a compound having formula (I):



(I)

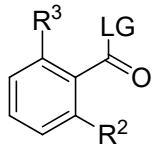
or a salt thereof, wherein R^1 is Cl or CF_3; R^2 is F or Cl; and R^3 is H or CH_3; and wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, the method comprising:

(a) contacting a compound having the formula (i-3):

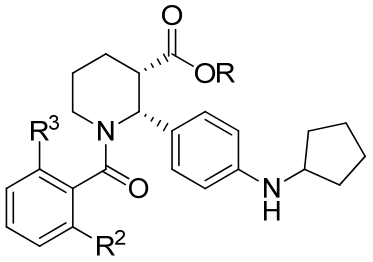


(i-3)

wherein R is selected from C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, which is substantially free of enantiomeric or diastereomeric impurities, or a salt thereof, with a compound having the formula:



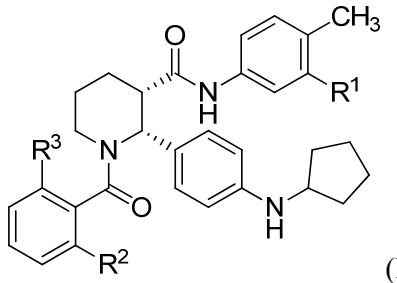
wherein LG is a leaving group; under conditions sufficient to form a compound of formula (i-4):



(i-4); and

(b) converting the compound of formula (i-4) to said compound of formula (I) wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities.

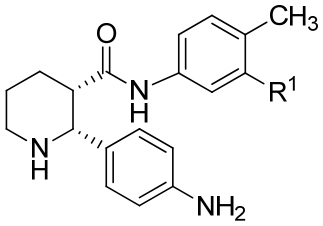
[0016] In still another example, provided herein is another method of preparing a compound having formula (I):



(I)

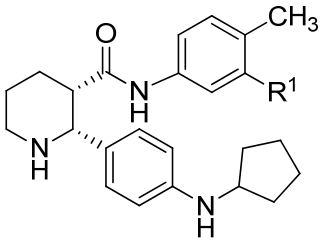
or a salt thereof, wherein R^1 is Cl or CF_3; R^2 is F or Cl; and R^3 is H or CH_3; and wherein the compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, the method comprising:

(a) contacting a compound having the formula (ii-4):



(ii-4)

or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities, with cyclopentanone and a reducing agent under conditions sufficient to form a compound having the formula (ii-5):

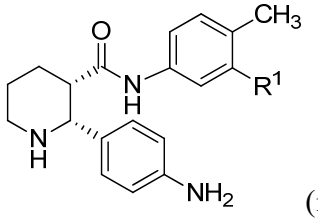


(ii-5) ; and

(b) contacting said compound of formula (ii-5) with a compound having the formula:

WHAT IS CLAIMED IS:

1. The compound having the formula (ii-4):



(ii-4)

wherein R^1 is Cl or CF_3, or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities.

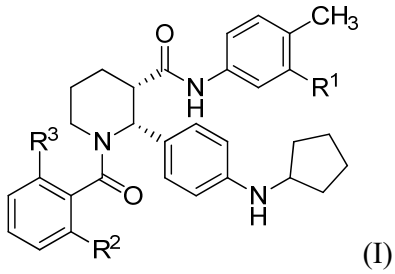
2. The compound of claim 1, in salt form as a L-DTTA salt ((-)-O,O'-di-p-toluoyl-L-tartaric acid salt).

3. The compound of claim 1, wherein R^1 is CF_3.

4. The compound of claim 1, wherein R^1 is Cl.

5. The compound of claim 1, in salt form as a bis L-DTTA salt ((-)-O,O'-di-p-toluoyl-L-tartaric acid salt).

6. A method of preparing a compound having formula (I):



(I)

or a salt thereof, wherein

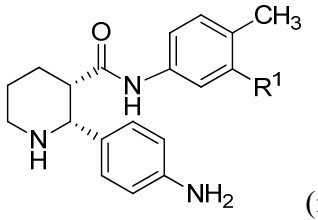
R^1 is Cl or CF_3;

R^2 is F or Cl; and

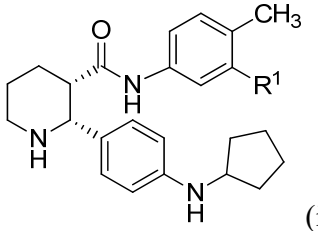
R^3 is H or CH_3;

and wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, said method comprising:

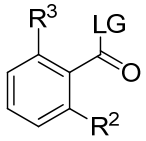
(a) contacting a compound having the formula (ii-4):


(ii-4)

wherein R^1 is Cl or CF_3; or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities, with cyclopentanone and a reducing agent to form a compound having the formula (ii-5):


(ii-5) ; and

(b) contacting said compound of formula (ii-5) with a compound having the formula:



wherein LG is a leaving group, R^2 is F or Cl; and R^3 is H or CH_3; in the presence of a base to form a compound of formula (I) which is substantially free of enantiomeric or diastereomeric impurities.

7. The method in accordance with claim 6, wherein R^1 is CF_3, R^2 is F, and R^3 is CH_3.

8. The method in accordance with claim 6, wherein R^1 is CF_3, R^2 is Cl, and R^3 is H.

9. The method in accordance with claim 6, wherein R^1 is Cl, R^2 is F, and R^3 is CH_3.

10. The method of any one of claims **6** to **9**, wherein the reducing agent is selected from the group consisting of hydrogen gas with a metal catalyst, sodium sulfide, sodium dithionite, ammonium sulfide, lithium aluminum hydride, lithium borohydride, sodium borohydride, sodium cyanoborohydride and sodiumtriacetoxyborohydride.

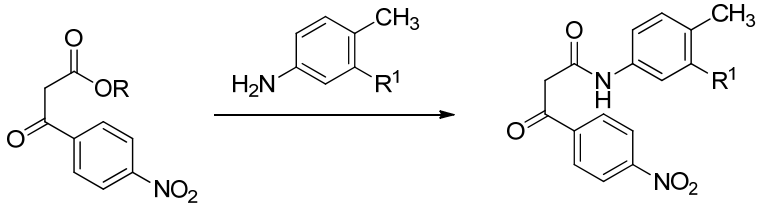
11. The method of any one of claims **6** to **10**, wherein LG is selected from the group consisting of halogen, hydroxyl, methanesulfonate (or mesylate), trifluoromethanesulfonate (triflate), benzenesulfonate, 4-methylbenzenesulfonate (tosylate),4-nitrobenzenesulfonate, 4- chlorobenzenesulfonate, and the carboxylate component of a mixed or symmetrical anhydride.

12. The method of any one of claims 6 to 10, wherein LG is halogen.

13. The method of any one of claims **6** to **12**, wherein the base is selected from the group consisting of triethylamine, N,N-diisopropylethylamine, DBU, N-methyl morpholine, potassium carbonate (K_2CO_3), potassium bicarbonate ($KHCO_3$), sodium carbonate, and sodium bicarbonate ($NaHCO_3$).

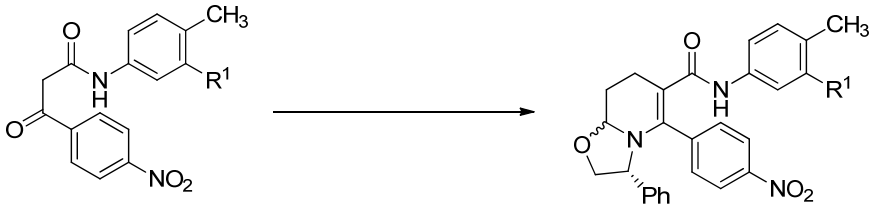
14. A method for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt thereof, said method comprising:

(a') reacting an ester of 3-(4-nitrophenyl)-3-oxo-propanoate (i-1, or ii-1, wherein R is selected from the group consisting of C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline under conditions sufficient to provide a compound of formula (ii-2);



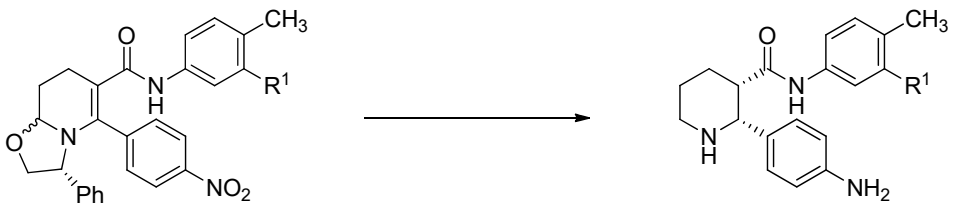
(i-1, ii-1) (ii-2)

(b') reacting (ii-2), (*R*)-(−)-2-phenylglycinol, and acrolein diethyl acetal or an equivalent thereof, to produce compound (ii-3);



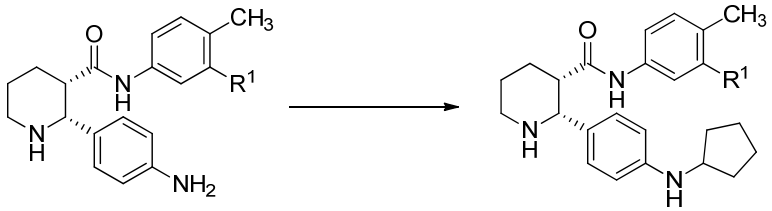
(ii-2) (ii-3)

(c') reducing (ii-3) under conditions sufficient to produce an intermediate diamine (ii-4) that is substantially free of enantiomeric or diastereomeric impurities;



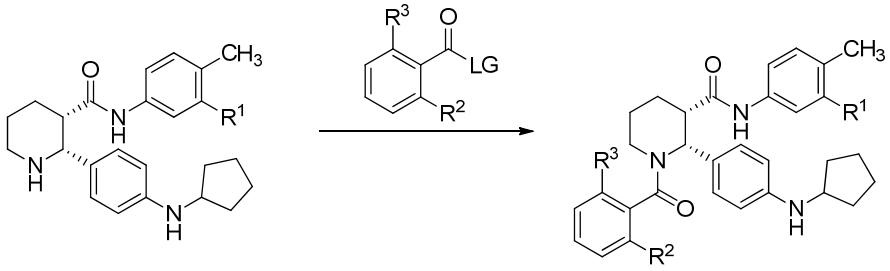
(ii-3) (ii-4)

(d') converting (ii-4) to (ii-5) with cyclopentanone and a reducing agent; and



(ii-4) (ii-5)

(e') combining (ii-5) with either 2-fluoro-6-methylbenzoyl chloride or 2-chlorobenzoyl chloride to provide (I);



(ii-5) (I)

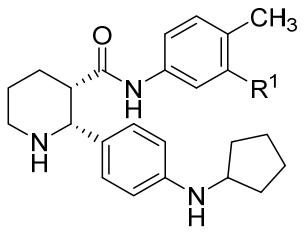
wherein

R^1 is C1 or CF_3;

R^2 is F or C1; and

R^3 is H or CH_3.

15. The compound having the formula (ii-5):



(ii-5)

wherein R^1 is Cl or CF_3, or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities.