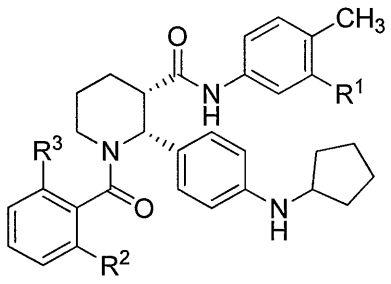


(ii-4)

(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] There is further provided herein is a method of preparing a compound having formula (I):

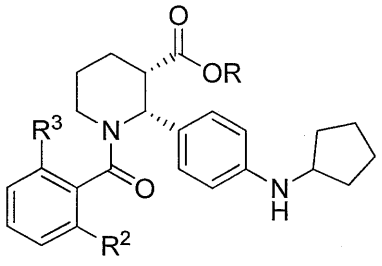


(I)

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):

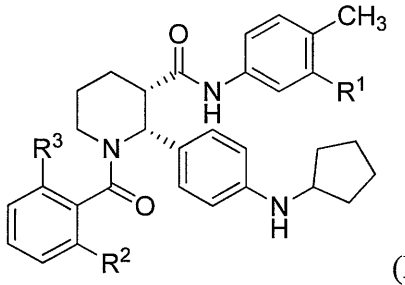
wherein LG is a leaving group; R^2 is F or Cl; and R^3 is H or CH_3; in the presence of a base to form a compound of formula (i-4):



(i-4); and

(b) converting said 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.

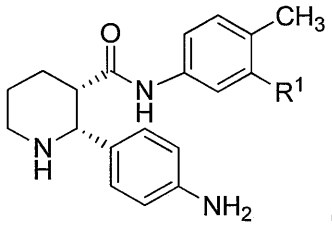
[0016] There is also provided herein is another method of preparing a compound having formula (I):



(I)

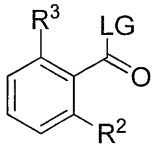
or a salt thereof, wherein R^1 is Cl or CF_3; R^2 is F or Cl; and R^3 is H or CH_3; and wherein the compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, the method comprising:

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



(ii-4)

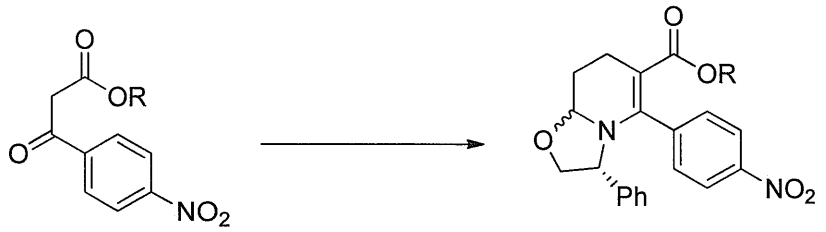
or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities, with cyclopentanone and a reducing agent under conditions sufficient to form a compound having the formula (ii-5):



wherein LG is a leaving group; under conditions sufficient to form a compound of formula (I) which is substantially free of enantiomeric or diastereomeric impurities.

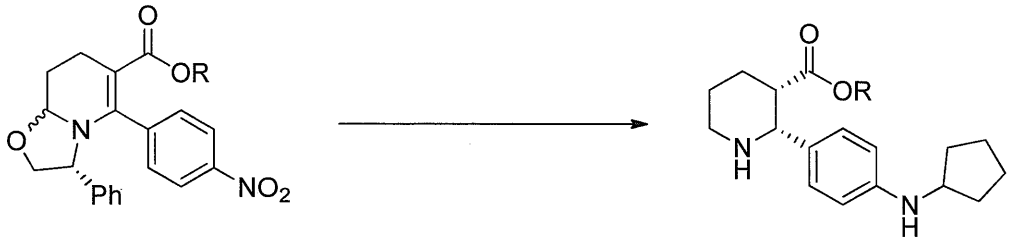
[0016a] In a further aspect of the present disclosure, there is provided a process for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or rotamer thereof, comprising any two, three or four of the steps (a), (b), (c), and (d), or optionally steps (d1) and (d2), which steps can be contiguous in the synthetic scheme or non-contiguous:

(a) reacting an ester of 3-(4-nitrophenyl)-3-oxo-propanoate (i-1) wherein R is selected from the group consisting of C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, with (*R*)-(−)-2-phenylglycinol, and acrolein diethyl acetal, to produce compound (i-2);



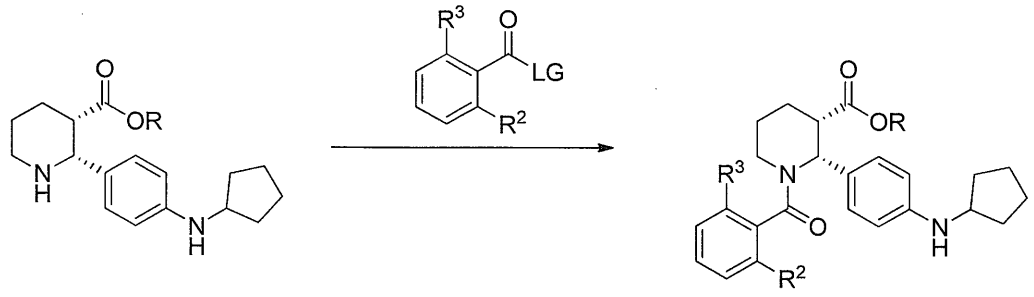
(i-1) (i-2)

(b) hydrogenating or reducing (i-2) to produce an intermediate amine and converting the intermediate amine to (i-3) with cyclopentanone and a reducing agent;



(i-2) (i-3)

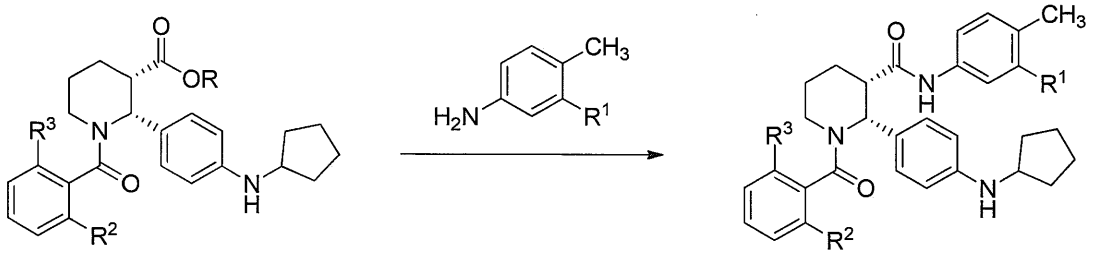
(c) combining (i-3) with either 2-fluoro-6-methylbenzoyl chloride or 2-chlorobenzoyl chloride in the presence of a first base to provide (i-4);



(i-3) (i-4)

wherein R^2 is fluoro, R^3 is methyl, and LG is chloro, or R^2 is chloro, R^3 is hydrogen, and LG is chloro;

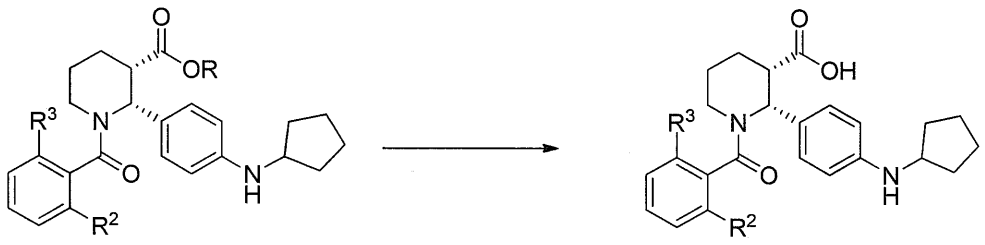
(d) combining (i-4) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline in the presence of a metal reagent to provide a compound of formula (I);



(i-4) (I)

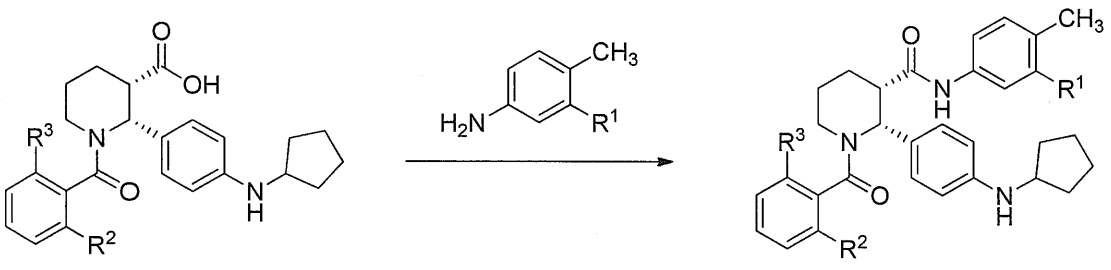
wherein, R^1 is C1 or CF_3;

(d)(1) converting of the ester (i-4) to a carboxylic acid (i-5):



(i-4) (i-5)

(d)(2) combining (i-5) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline in the presence of a coupling reagent and a second base to provide a compound of formula (I)



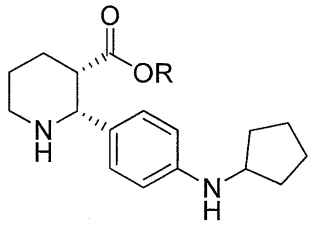
(i-5) (I)

wherein R^1 is C1 or CF_3; and wherein R^2 is chloro and R^3 is hydrogen, or R^2 is fluoro and R^3 is methyl.

[0017] Still other processes are provided as described below having two, three, or four or more synthetic transformations resulting in the preparation of compounds IA, IB and/or IC, or their pharmaceutically acceptable salts.

WHAT IS CLAIMED IS:

1. A compound having the formula (i-3):

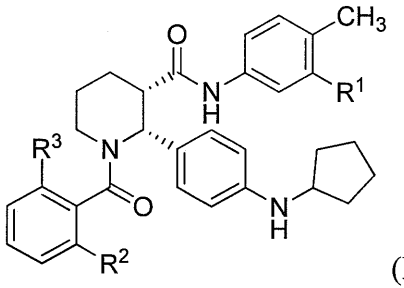


(i-3)

wherein R is selected from the group consisting of H, C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, or a salt thereof, said compound being substantially free of enantiomeric or diastereomeric impurities.

2. A compound of claim **1**, in salt form as a bis L-DTTA salt.

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



(I)

or a salt thereof, wherein

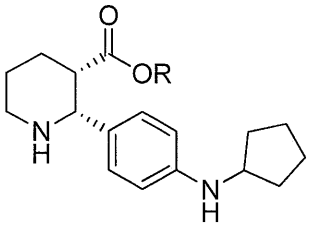
R^1 is Cl or CF_3;

R^2 is F or Cl; and

R^3 is H or CH_3;

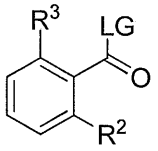
and wherein said compound of formula (I) is substantially free of enantiomeric or diastereomeric impurities, said method comprising:

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

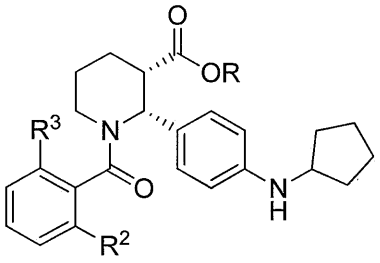


(i-3)

wherein R is selected from the group consisting of H, 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:



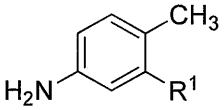
wherein LG is a leaving group; R^2 is F or Cl; and R^3 is H or CH_3; in the presence of a base to form a compound of formula (i-4):



(i-4); and

(b) converting said 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.

4. A method in accordance with claim **3**, wherein step (b) includes contacting said compound of formula (i-4) with an aniline having the formula:

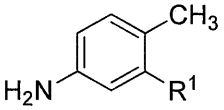


wherein R^1 is Cl or CF_3; in the presence of a metal reagent.

5. A method in accordance with claim **3**, wherein step (b) includes

(b)(1) hydrolyzing said compound of formula (i-4) where R is C_{1-8} alkyl, aryl, and aryl-C_{1-4} alkyl to a compound of formula (i-4) where R is H; and

(b)(2) contacting the compound of formula (i-4) where R is H with an aniline having the formula:



wherein R^1 is Cl or CF_3; in the presence of a coupling reagent and a second base to provide said compound of formula (I).

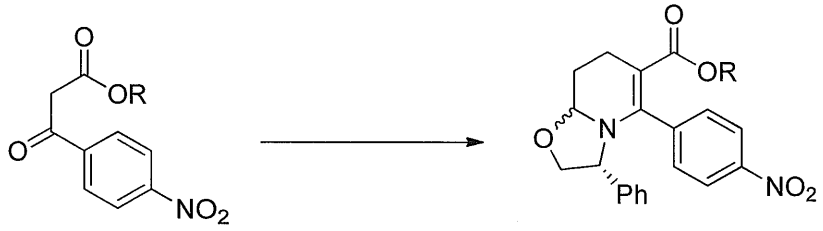
6. A method of any of claims **3**, **4** or **5**, wherein R^1 is CF_3, R^2 is F, and R^3 is CH_3.

7. A method of any of claims **3**, **4** or **5**, wherein R^1 is CF_3, R^2 is Cl, and R^3 is H.

8. A method of any of claims **3**, **4** or **5**, wherein R^1 is Cl, R^2 is F, and R^3 is CH_3.

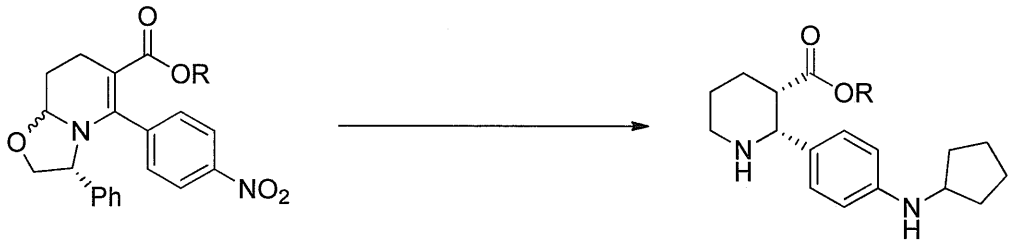
9. A process for the preparation of compounds of formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or rotamer thereof, comprising any two, three or four of the steps (a), (b), (c), and (d), or optionally steps (d1) and (d2), which steps can be contiguous in the synthetic scheme or non-contiguous:

(a) reacting an ester of 3-(4-nitrophenyl)-3-oxo-propanoate (i-1) wherein R is selected from the group consisting of C_{1-8} alkyl, aryl and aryl-C_{1-4} alkyl, with (*R*)-(−)-2-phenylglycinol, and acrolein diethyl acetal, to produce compound (i-2);



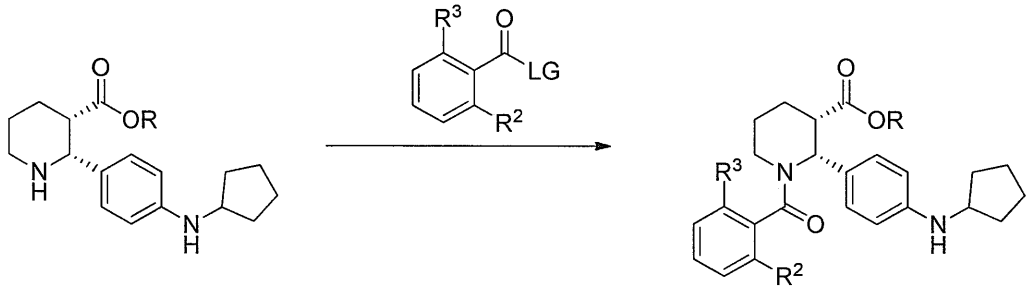
(i-1) (i-2)

(b) hydrogenating or reducing (i-2) to produce an intermediate amine and converting the intermediate amine to (i-3) with cyclopentanone and a reducing agent;



(i-2) (i-3)

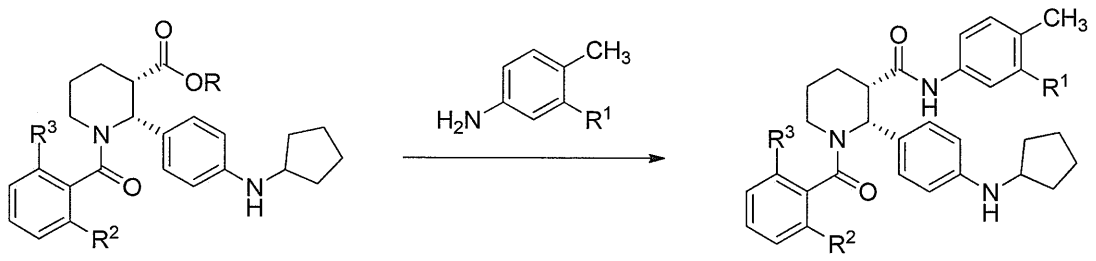
(c) combining (i-3) with either 2-fluoro-6-methylbenzoyl chloride or 2-chlorobenzoyl chloride in the presence of a first base to provide (i-4);



(i-3) (i-4)

wherein R^2 is fluoro, R^3 is methyl, and LG is chloro, or R^2 is chloro, R^3 is hydrogen, and LG is chloro;

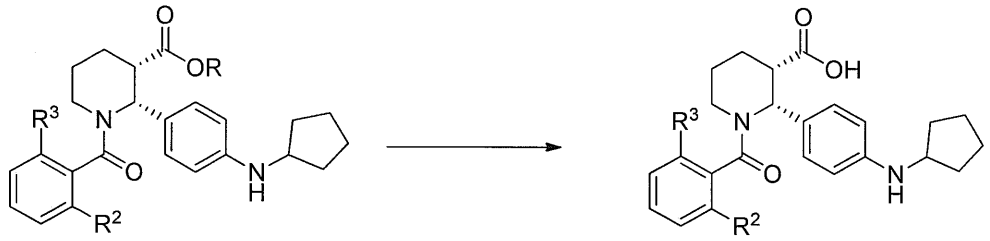
(d) combining (i-4) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline in the presence of a metal reagent to provide a compound of formula (I);



(i-4) (I)

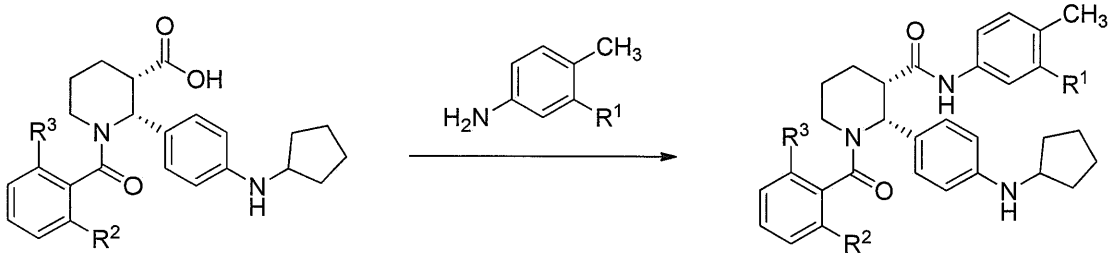
wherein, R^1 is C1 or CF_3;

(d)(1) converting of the ester (i-4) to a carboxylic acid (i-5):



(i-4) (i-5)

(d)(2) combining (i-5) with 3-chloro-4-methylaniline or 3-trifluoromethyl-4-methylaniline in the presence of a coupling reagent and a second base to provide a compound of formula (I)



(i-5) (I)

wherein R^1 is C1 or CF_3; and wherein R^2 is chloro and R^3 is hydrogen, or R^2 is fluoro and R^3 is methyl.

10. The process of claim **3** or **9**, 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.

11. The process of claim **3** or **9**, wherein LG halogen.

12. The process of claim **4** or **9**, wherein the metal reagent is selected from the group consisting of an organoalumininum reagent, an alkyllithium compound, a Grignard reagent, an organozinc reagent, sodium hydride, and sodium potassium or lithium HMDS salts.

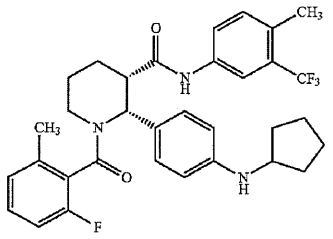
13. The process of claim **4** or **9**, wherein the metal reagent is an organoaluminum reagent.

14. The process of claim **4** or **9**, wherein the metal reagent is $Al(Me)_3$ or trimethylaluminum complexed with DABCO (DABAL-Me_3).

15. The process of claim **9**, wherein the compound of formula (I) is produced with a purity of greater than about 95% (w/w).

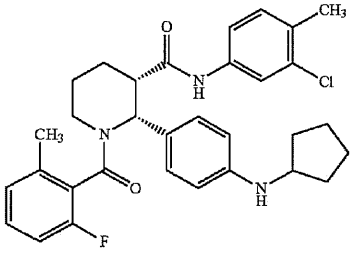
16. The process of claim **9**, wherein the compound of formula (I) is produced with purity of greater than 99% (w/w).

17. The process of claim **9**, wherein the compound of formula (I) is represented by a compound of formula IA



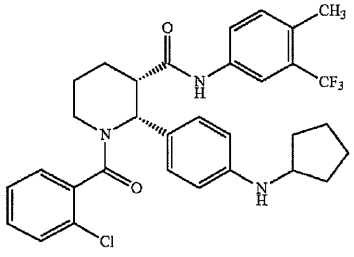
(IA).

18. The process of claim **9**, wherein the compound of formula (I) is represented by a compound of formula IB



(IB).

19. The process of claim **9**, wherein the compound of formula (I) is represented by a compound of formula IC



(IC).

20. The process of claim **9**, wherein the process comprises the four steps (a), (b), (c), and (d), and optionally steps (d1) and (d2).

21. The process of claim **3**, 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 ($NaHCO_3$).

22. The process of claim **5** or **9**, wherein the coupling reagent is *O*-(7-Azabenzotriazole-1-yl)-*N,N,N,N',N'*-tetramethyluronium hexafluorophosphate (HATU) or methanesulfonyl chloride (MsCl).

23. The process of claim **5** or **9**, wherein the second base is N-methylmorpholine or *N,N*-diisopropylethylamine.

24. The process of claim **9**, wherein the first 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 ($NaHCO_3$).

25. The process of claim **9**, wherein the reducing agent is selected from the group consisting of hydrogen gas with a metal catalyst, sodium sulfide, sodium dithionite, ammon050ium sulfide, lithium aluminum hydride, lithium borohydride, sodium borohydride, sodium cyanoborohydride and sodiumtriacetoxyborohydride.