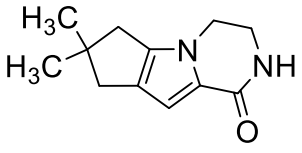
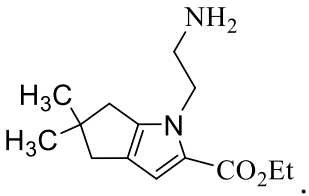
[0003] The US 2013/0116235 publication further discloses a useful five-step process for the preparation of tricyclic lactam compounds used as intermediates in the preparation of 2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one and having the structure:



.

In the final step, the above-reference tricyclic lactam compound is generated by ring closure from the following compound:



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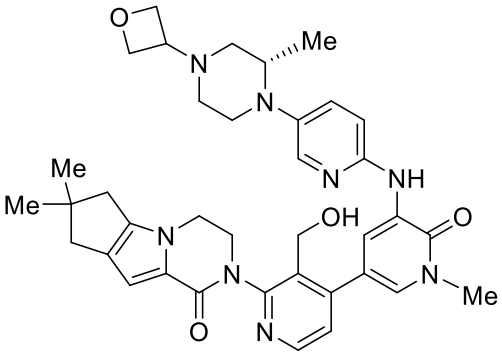
The multistep process requires two chromatographic purification steps and the overall yield based on the starting material was low.

[0004] A need therefore exists for improved method for preparing 2-{3'-hydroxymethyl-1-methyl-5-[5-((S)-2-methyl-4-oxetan-3-yl-piperazin-1-yl)-pyridin-2-ylamino]-6-oxo-1,6-dihydro-[3,4']bipyridinyl-2'-yl}-7,7-dimethyl-3,4,7,8-tetrahydro-2H,6H-cyclopenta[4,5]pyrrolo[1,2-a]pyrazin-1-one and intermediate compounds therefore.

SUMMARY

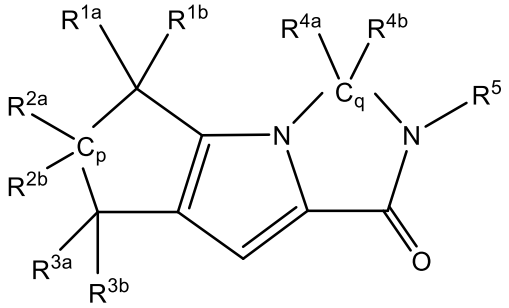
[0005] The disclosure is directed to a method of preparing compound 200, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof:



200

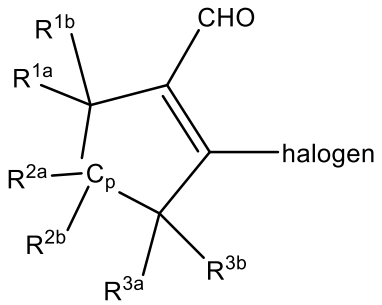
.

[0011] The disclosure is also directed to a method for preparing a tricyclic lactam of formula 400, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof:

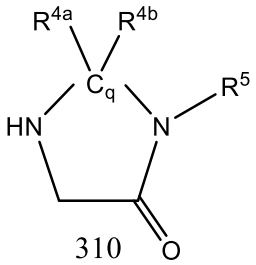


400 .

[0012] The method comprises forming a reaction mixture comprising an organic solvent, an organic base, and the compounds of formulas 300 and 310:



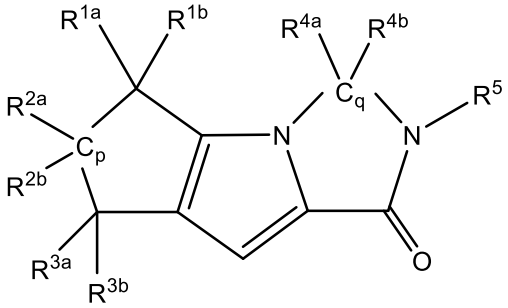
300 and



310 .

[0013] The reaction mixture is reacted to form a reaction product mixture comprising the tricyclic lactam of formula 400. R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a} and R^{4b} are independently selected from H, and C_{1-6} alkyl. R^5 is selected from H, C_{1-6} alkyl, cycloalkyl, aryl, substituted aryl, benzyl, substituted benzyl, heteroaryl, substituted heteroaryl. p is 1, 2, 3 or 4; and q is 1, 2, 3 or 4.

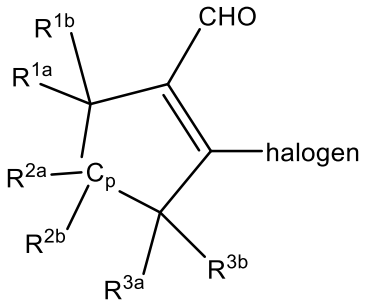
[0013a] In one aspect, the present disclosure is directed to a method for preparing a tricyclic lactam of formula 400, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,



400

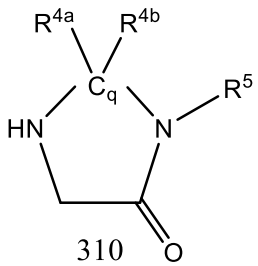
,

the method comprising forming a reaction mixture comprising an organic solvent, an organic base, and formulas 300 and 310



300

and



310

and reacting the reaction mixture to form a reaction product mixture comprising the tricyclic lactam of formula 400,

wherein:

R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a} and R^{4b} are independently selected from H and C_{1-6} alkyl;

R^5 is selected from H, C_{1-6} alkyl, cycloalkyl, aryl, substituted aryl, benzyl, substituted benzyl, heteroaryl, and substituted heteroaryl;

p is 1,2, 3 or 4; and

q is 1, 2, 3 or 4.

BRIEF DESCRIPTION OF THE DRAWINGS

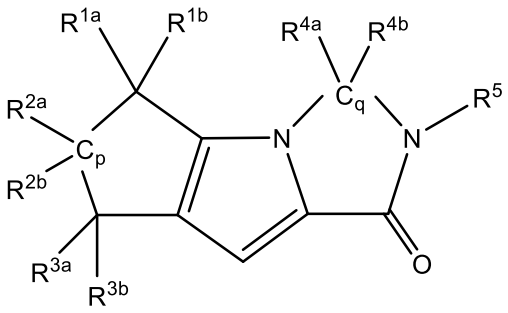
[0014] Figure 1 shows a method for the preparation of compounds 170, 182, 190 and 200.

[0015] Figure 2 shows a method for the preparation of compounds 170 and 182, and another method for the preparation of compounds 190 and 200.

[0016] Figure 3 shows a method for the preparation of compounds 70, 90, 40, 154, 153, 140, 141 and 180.

WHAT IS CLAIMED IS:

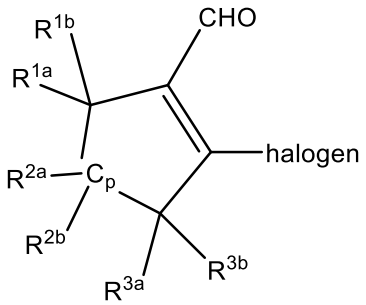
1. A method for preparing a tricyclic lactam of formula 400, stereoisomers thereof, geometric isomers thereof, tautomers thereof, and salts thereof,



400

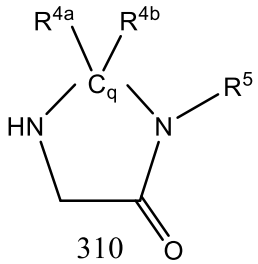
,

the method comprising forming a reaction mixture comprising an organic solvent, an organic base, and formulas 300 and 310



300

and



310

and reacting the reaction mixture to form a reaction product mixture comprising the tricyclic lactam of formula 400,

wherein:

R^{1a}, R^{1b}, R^{2a}, R^{2b}, R^{3a}, R^{3b}, R^{4a} and R^{4b} are independently selected from H and C_{1-6} alkyl;

R^5 is selected from H, C_{1-6} alkyl, cycloalkyl, aryl, substituted aryl, benzyl, substituted benzyl, heteroaryl, and substituted heteroaryl;

p is 1,2, 3 or 4; and

q is 1, 2, 3 or 4.

2. The method of claim 1 wherein p is 1 or 2, and q is 1 or 2.

3. The method of claim 1 or claim 2 wherein the organic base is a tri- C_{1-6} alkyl amine.

4. The method of claim 1 or claim 2, wherein the organic base is selected from 4-methylmorpholine and N-ethyldiiopropylamine.

5. The method of any one of claims 1 to 4 wherein the solvent is a polar aprotic solvent.

6. The method of claim 5 wherein the solvent is selected from N-methylpyrrolidone and dimethylformamide.

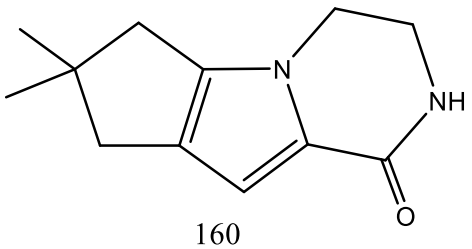
7. The method of any one of claims 1 to 6 wherein halogen is Cl.

8. The method of any one of claims 1 to 7 wherein p is 1 and q is 2.

9. The method of any one of claims 1 to 8 wherein R^{1a}, R^{1b}, R^{3a}, R^{3b}, R^{4a}, R^{4b} and R^{5} are H, and R^{2a} and R^{2b} are $-CH_3$.

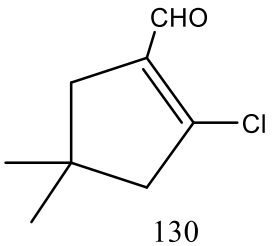
10. The method of any one of claims 1 to 9 wherein the reaction mixture comprises from about 0.25 to about 2 moles per liter, from about 0. 5 to about 1.5 moles per liter or from about 0.5 to about 1 moles per liter of formula 300; between 1 and 2 equivalents, or from about 1.1 to about 1.5 equivalents base; and between 0.7 and 1 equivalents, from about 0.75 to about 0.95 equivalents, or from about 0.8 to about 0.9 equivalents of formula 310.

11. The method of any one of claims 1 to 10 wherein the tricyclic lactam of formula 400 is species formula 160 of the structure:



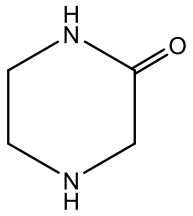
160 ,

formula 300 is the species of formula 130 of the structure:



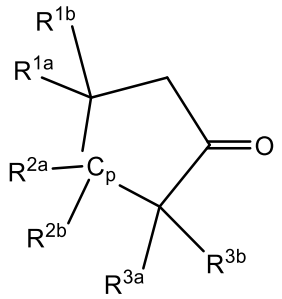
130 , and

formula 310 is piperazine-2-one of formula 10:



10 .

12. The method of any one of claims 1 to 11 wherein formula 300 is prepared by forming a reaction mixture comprising a polar aprotic solvent, a non-polar solvent, phosphorous oxychloride and formula 320:



320

and reacting the reaction mixture to form a reaction product mixture comprising formula 300.

13. The method of claim 12 wherein the polar aprotic solvent is dimethylformamide, the non-polar solvent is dichloromethane, the mole ratio of phosphorous oxychloride to formula 320 is from about 1.5:1 to about 2.7:1 or from about 1.8:1 to about 2.4:1, and the mole ratio of the polar aprotic solvent to formula 320 is from about 1.5:1 to about 3.5:1 or from about 2:1 to about 3:1.

14. The method of claim 12 or claim 13 wherein compound 320 is the subgenus compound 321 wherein

R^{1a} and R^{1b} are each independently selected from the group consisting of H and C_{1-6} alkyl;

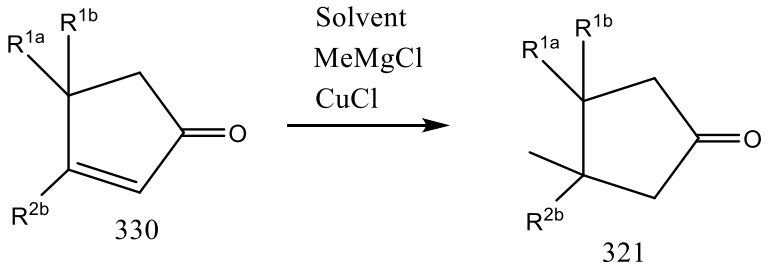
R^{2a} is $-CH_3$;

R^{2b} is selected from the group consisting of H and C_{1-6} alkyl;

R^{3a} and R^{3b} are each H;

p is 1; and

wherein compound 321 is prepared by forming a reaction mixture comprising a polar aprotic solvent, methyl magnesium chloride, copper (I) chloride and compound 330 and reacting the reaction mixture to form a reaction product mixture comprising compound 321 according to the following reaction scheme:

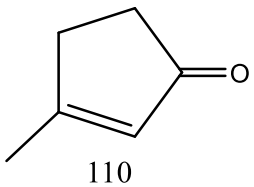


.

15. The method of any one of claims 12 to 14 wherein

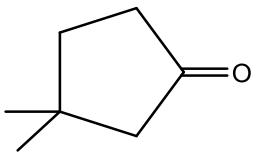
R^{1a}, R^{1b}, R^{3a} and R^{3b} are H, p is 1, and R^{2a} and R^{2b} are $-CH_3$,

wherein compound 321 is the species of compound 120 prepared by forming a reaction mixture comprising a polar aprotic solvent, methyl magnesium chloride, copper (I) chloride and compound 110:



110

and reacting the reaction mixture to form a reaction product mixture comprising compound 120



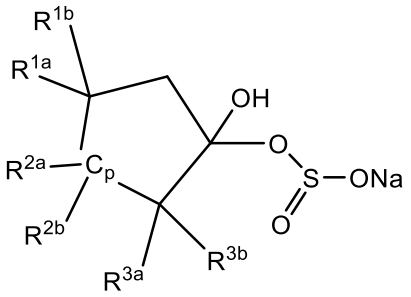
120

.

16. The method of claim 15 wherein the solvent is tetrahydrofuran, the mole ratio of methyl magnesium chloride to compound 110 in the reaction mixture is between 1:1 and 2:1, or from about 1.1:1 to about 1.4:1, and the mole ratio of copper (I) chloride to compound 110 in the reaction mixture is from about 0.1:1 to about 0.5:1, or from about 0.15:1 to about 0.25:1.

17. The method of any one of claims 12 to 16 further comprising purifying compound 320, the purification comprising:

(i) forming a first reaction mixture comprising crude compound 320, an organic solvent that is not miscible with water, and an aqueous solution of sodium bisulfite, and reacting the first reaction mixture to form a first reaction product mixture comprising the solid ketone bisulfite adduct of compound 340:



340

(ii) isolating solid compound 340 from the first reaction product mixture,

(iii) forming a second reaction mixture comprising isolated compound 340, water, a low boiling solvent that is not miscible with water, and sodium bicarbonate, and reacting the second reaction mixture to form a second reaction product mixture comprising a first phase comprising dichloromethane and the predominant amount of purified compound 320 is in solution in the first phase, and a second phase comprising water, and

(iv) separating the first phase comprising the purified compound 320 from the aqueous phase.

18. The method of claim 17 wherein:

(i) crude compound 320 is in solution in organic solvent that is not miscible with water, the ratio of water volume to the crude compound 320 weight in the first reaction mixture is from about 1:1 L/kg to about 10:1 L/kg, from about 1.5:1 L/kg to about 4:1 L/kg, or from about 2:1 L/kg to about 3:1 L/kg, and the equivalent ratio of sodium bisulfite to compound 320 in the first reaction mixture is from about 2:1 to about 5:1 or from 3:1 to about 5:1;

(ii) the second reaction mixture comprises a ratio of water volume to isolated solid 340 weight of from about 5:1 L/kg to about 15:1 L/kg, or from about 7.5:1 L/kg to about 10.5:1 L/kg, the ratio of water volume to the low boiling solvent volume that is not miscible with water in the second reaction mixture is from

about 1:1 to about 3:1 or from about 1.5:1 to about 2.5:1, and the equivalent ratio of sodium bicarbonate to compound 340 in the second reaction mixture is between 1:1 and 2:1, or from about 1.25:1 to about 1.75:1, and

(iii) the yield of purified compound 320 is at least 60% based on compound 330 and the purity of purified compound 330 is at least 98% or at least 99%.

19. The method of claim 17 or claim 18 wherein the organic solvent that is not miscible with water in the first reaction mixture is a hexane, and wherein the low boiling solvent that is not miscible with water in the second reaction mixture is dichloromethane.

20. The method of any one of claims 1 to 11 wherein,

R^{1a} and R^{1b} are each independently selected from the group consisting of H and C_{1-6} alkyl;

R^{2a} is $-CH_3$;

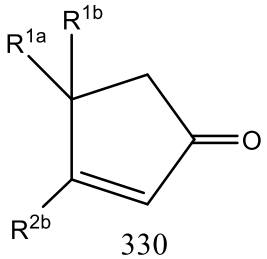
R^{2b} is selected from the group consisting of H and C_{1-6} alkyl;

R^{3a} and R^{3b} are each H;

p is 1; and

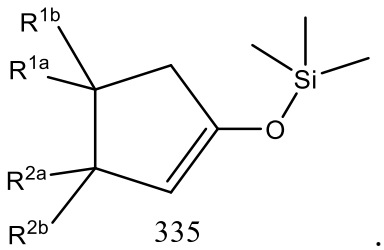
wherein compound 300 is prepared by:

(i) forming a first reaction mixture comprising a first polar aprotic solvent, methyl magnesium chloride, copper (I) chloride, lithium chloride, chlorotrimethylsilane, and compound 330:



330

and reacting compound 330 to form a first reaction product mixture comprising compound 335 where R^{2a} is $-CH_3$



335

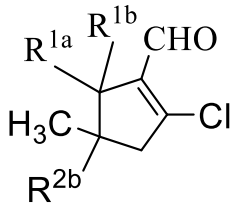
;

(ii) quenching the first reaction product mixture with methanol as a first quenching agent;

(iii) further quenching with a second quenching agent in aqueous solution and adding a non-polar water-immiscible solvent to the quenched reaction product mixture;

(iv) separating the phases and collecting the organic phase comprising the predominant amount of compound 335 and concentrating the organic phase to obtain compound 335 in solution;

(v) forming a second reaction mixture comprising a second polar aprotic solvent, phosphorous oxychloride, and the solution of compound 335, and reacting the second reaction mixture to form a second reaction product mixture comprising compound 301 of the structure



301 ;

(vi) quenching the second reaction product mixture with a third quenching agent in aqueous solution; and

(vii) separating the phases and collecting the organic phase comprising the predominant amount of compound 301 in solution.

21. The method of claim 20 wherein the first polar aprotic solvent is tetrahydrofuran, the second quenching agent is ammonium chloride, the non-polar water-immiscible solvent is toluene, the second polar aprotic solvent is dimethylformamide, and the third quenching agent is potassium phosphate.

22. The method of claim 20 or claim 21 wherein:

(i) the first reaction mixture comprises: from about 0.25 to about 2, or from about 0.5 to about 1.1 moles per liter of compound 330; a stoichiometric excess of methylmagnesium chloride as compared to compound 330, a mole ratio of methylmagnesium chloride to compound 330 of between 1:1 and 1.5:1, or from about 1.1:1 to about 1.3:1; a stoichiometric excess of

chlorotrimethylsilane as compared to compound 330, a mole ratio of chlorotrimethylsilane to compound 330 of between 1:1 and 1.2:1, or from about 1.01:1 to about 1.1:1; a mole ratio of copper (I) chloride to compound 330 of from about 0.05:1 to about 0.2:1, or from about 0.05:1 to about 0.15:1; and a mole ratio of lithium chloride to compound 330 of from about 0.05:1 to about 0.2:1, or from about 0.07:1 to about 0.15:1,

(ii) the second reaction mixture comprises: from about 0.5 to about 2 moles per liter or from about 0.7 to about 1.3 moles per liter compound 335; and a mole ratio of phosphorous oxychloride to compound 335 of from about 1.5:1 to about 3.1:1, or from about 2.1:1 to about 2.6:1, and

(iii) the yield of compound 300 based on compound 330 is at least 70% or at least 75%, and the purity of compound 301 is at least 85% or at least 88%.

23. The method of any one of claims 20 to 22 wherein R^{1a} and R^{1b} are each H and R^{2b} is $-CH_3$.