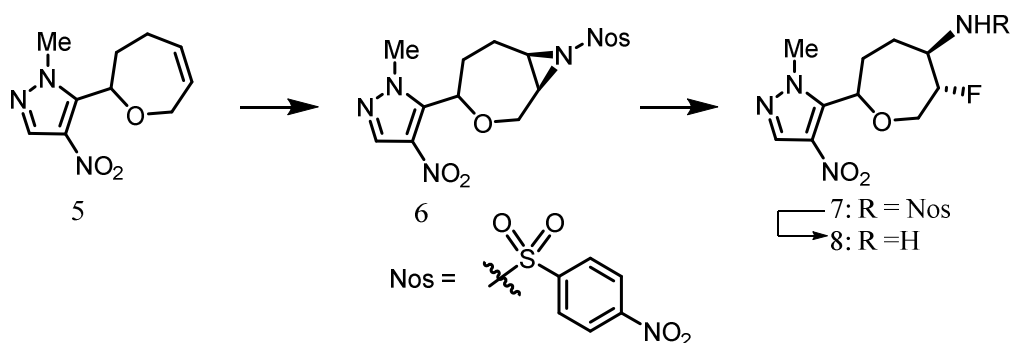


[0005] Other PIM inhibitors have been reported. (W. Blackaby *et al.*, WO2014/048939; X. Wang *et al. J. Med. Chem.* **2019** 62:2140-2153; L.S. Chen *et al. Blood* **2011** 118(3):693; Dakin, L. A. *et al. Bioorg. Med. Chem. Lett.* **2012** 22(14):4599-4604 and Burger, M. T. *et al., J. Med Chem.* **2015** 58(21):8373-8386.

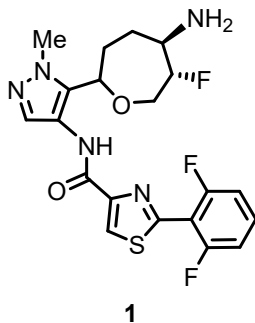
BRIEF SUMMARY

[0006] The present process is an improved process for the preparation of substituted oxepane derivatives comprising the steps of treating a 2,3,4,7-tetrahydrooxepine of formula **5** with sodium chloro((4-nitrophenyl)sulfonyl)amide and *N*-bromosuccinimide to afford the aziridine **6** which can be subjected to HF mediated ring opening to afford **7** which can be cleaved to afford fluoro-amino oxepane **8**.

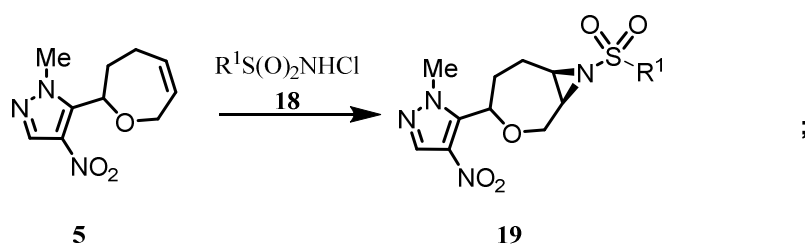


[0007] Protection of the nascent primary amine, reduction of the nitro group, condensation with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid with 1-1'-carbonyl diimidazole (CDI) and subsequent deprotection of the amine affords **1**.

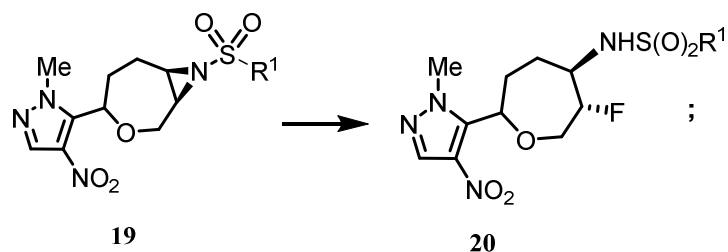
[0007a] In one aspect, the present disclosure provides a process for the preparation of N-((5-((5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (**1**) comprising the steps of:



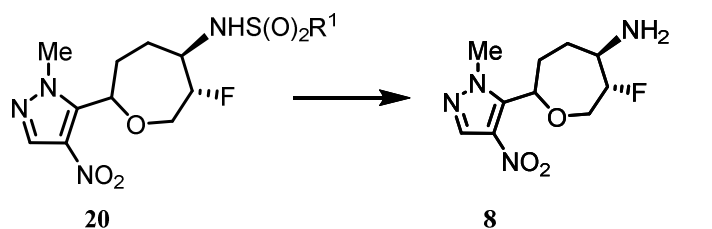
(i). treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5**) with an *N*-chlorosulfonamide (**18**) [wherein R¹ is nitrophenyl or *tert*-butyl](#), and a bromine source to afford the aziridine **19**



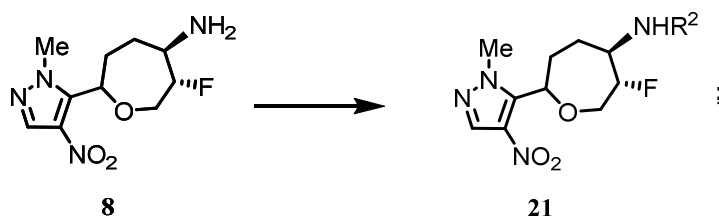
(ii) treating **19** with a nucleophilic fluoride source to afford **20**



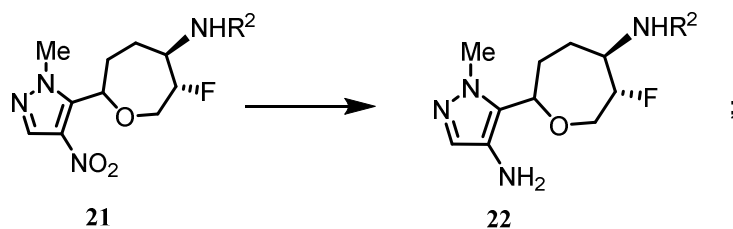
(iii) contacting **20** with a first cleavage reagent selected from a thiol and strong base or trifluoromethyl sulfonic acid to afford **8**



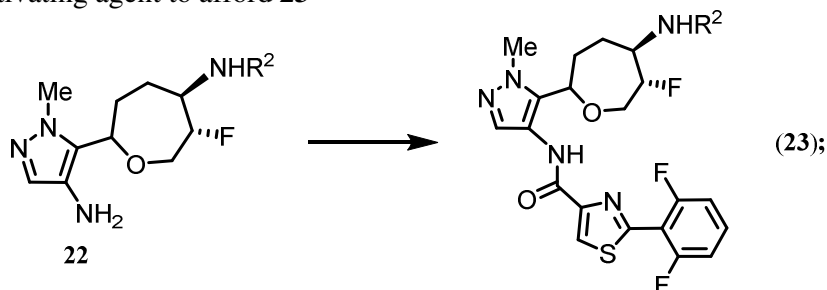
(iv) introducing a amine protecting group to afford **21**, [wherein R² is Boc, Fmoc or Cbz](#)



(v) reducing **21** to afford **22**

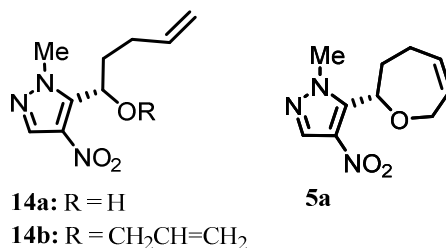


(vi) condensing **22** with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid in the presence of an activating agent to afford **23**



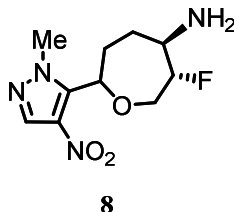
(vii) treating **23** with a second cleavage reagent to afford **1**.

[0007b] In one aspect, the present disclosure provides a process for the chiral synthesis of **5a** by oxidation of

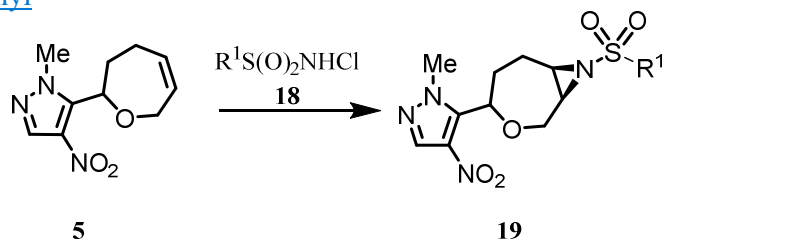


14 to afford 1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)pent-4-en-1-one (**16**) with the Dees-Martin reagent and chiral catalytic hydrogenation with chloro[*N*-(1*R*,2*R*)-1,2-diphenyl-2-[[3-(η^6 -phenyl)propyl]amino- κ N]ethyl]-4-methylbenzenesulfonamido- κ N]-ruthenium to afford **14a** which is alkylated with allyl bromide to afford **14b** and cyclized to (*S*)-1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5a**) with an olefin metathesis reaction.

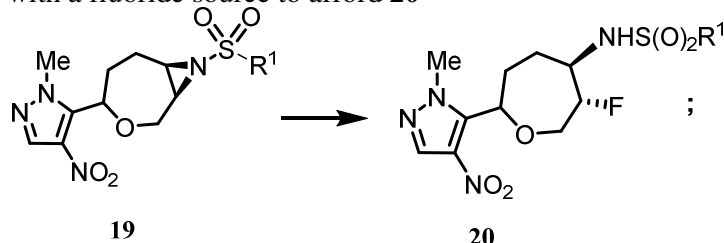
[0007cb] In another aspect, the present disclosure provides a process for the preparation of (3*S*,4*R*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-amine (**8**) comprising the steps:



(i) treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5**) with an *N*-chlorosulfonamide (**18**) and bromine source to afford the aziridine **19**, wherein **R¹** is 4-nitrophenyl



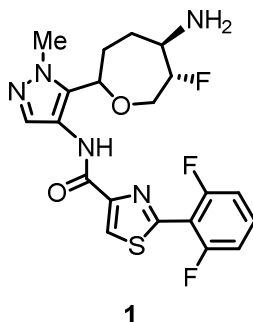
(ii) treating **19** with a fluoride source to afford **20**



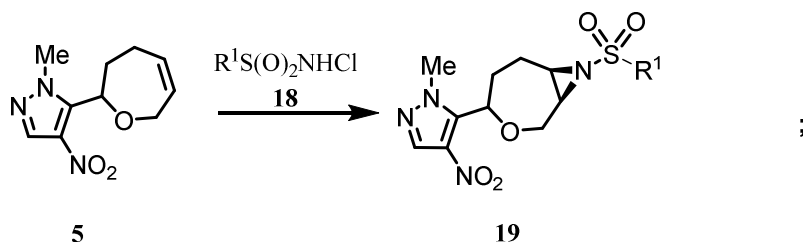
(iii) contacting **20** with a reagent selected from a thiol and a strong base or trifluoromethyl sulfonic acid to afford **8**

We claim:

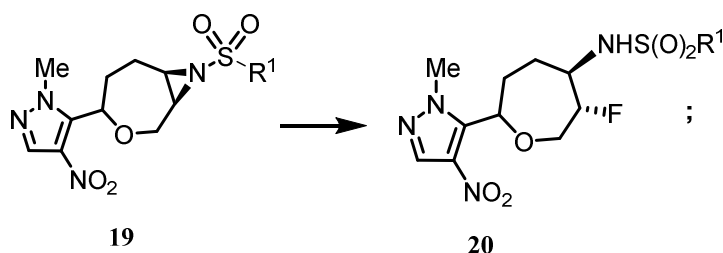
1. A process for the preparation of N-(5-((5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (**1**) comprising the steps of:



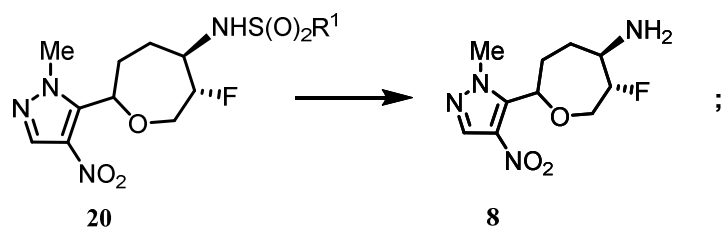
- (i). treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5**) with an *N*-chlorosulfonamide (**18**) [wherein R¹ is nitrophenyl or *tert*-butyl](#), and a bromine source to afford the aziridine **19**



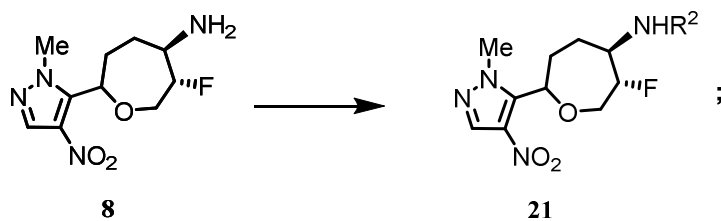
- (ii) treating **19** with a nucleophilic fluoride source to afford **20**



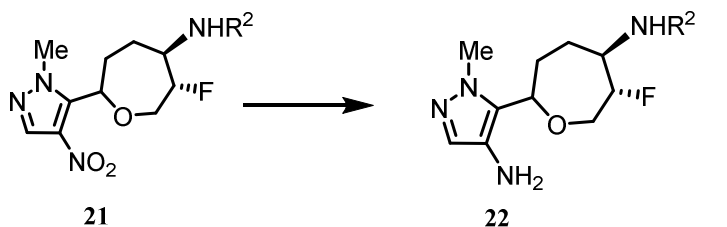
- (iii) contacting **20** with a first cleavage reagent selected from a thiol and strong base or trifluoromethyl sulfonic acid to afford **8**



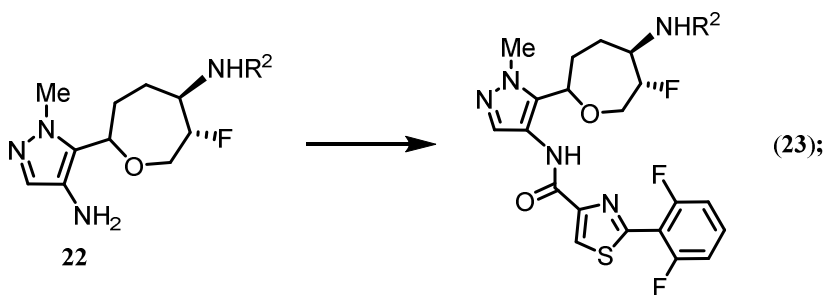
- (iv) introducing a amine protecting group to afford **21**, [wherein R² is Boc, Fmoc or Cbz](#)



(v) reducing **21** to afford **22**



(vi) condensing **22** with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid in the presence of an activating agent to afford **23**



(vii) treating **23** with a second cleavage reagent to afford **1**.

2. The process of claim 1 wherein;

(a) ~~R¹ is nitrophenyl or *tert*-butyl;~~

(ba) the bromine source is N-bromosuccinimide;

(eb) the nucleophilic fluoride source is triethylamine trihydrofluoride

(d) ~~R² is selected from the group consisting of Boc, Fmoc and Cbz;~~

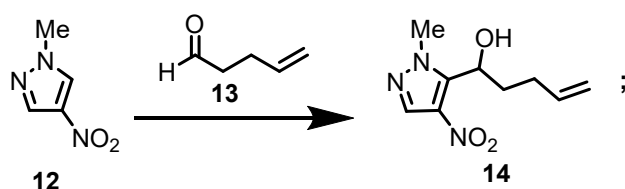
(ec) the first cleavage reagent is thioacetic acid and potassium *tert*-butoxide when R¹ is nitrophenyl and trifluoromethyl sulfonic acid when R¹ is *tert*-butyl;

(fd) the nitro reducing agent is hydrogen and Noblyst P8078;

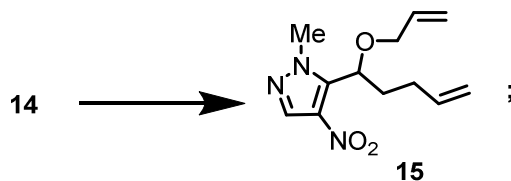
(ge) the second cleavage agent is trifluoroacetic acid, piperidine or catalytic hydrogenation.

3. The process of claim 2 wherein:

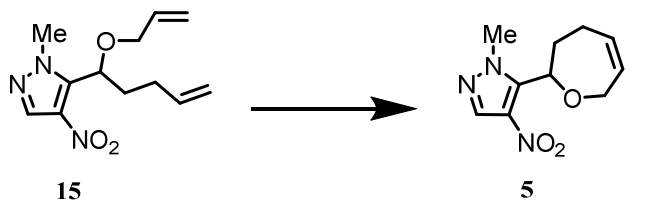
- (a) R¹ is *p*-nitrophenyl or *o*-nitrophenyl;
 - (b) R² is Boc;
 - (c) the first cleavage reagent is thioacetic acid and potassium *tert*-butoxide;
 - (e) the second cleavage agent is trifluoroacetic.
4. The process of claim 3 wherein R¹ is *p*-nitrophenyl.
 5. The process of claim 1 which process further comprises the steps of
 - (i) deprotonating N-methyl 4-nitro-1*H*-pyrazole (**12**) with lithium hexamethyldisilazane and reacting the resulting conjugate base with pent-4-enal (**13**) to afford **14**



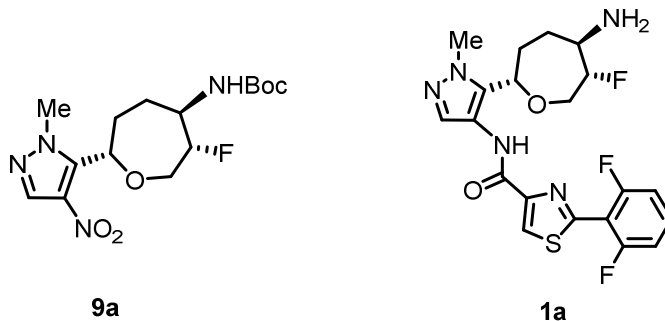
- (ii) alkylating the hydroxyl moiety with allyl bromide to afford **15**



- (iii) subjecting **15** to an olefin metathesis reaction to afford **5**

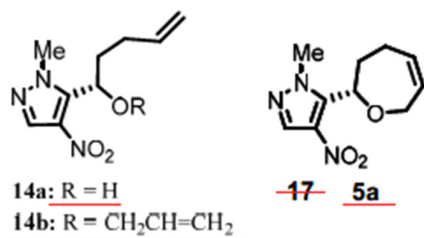


6. The process of claim 3 said process further comprising resolution of compound **9a** by chiral HPLC



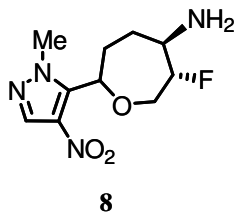
chromatography to afford **9a** that is further converted into 1a as described in claim 1.

7. The A process of claim 1 said process further comprising for the chiral synthesis of **17-5a** by oxidation of

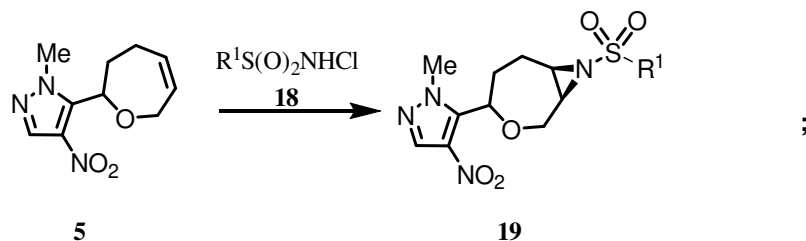


14 to afford 1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)pent-4-en-1-one (**16**) with the Dees-Martin reagent and chiral catalytic hydrogenation with chloro[*N*-[(1*R*,2*R*)-1,2-diphenyl-2-[[3-(η^6 -phenyl)propyl]amino- κN]ethyl]-4-methylbenzenesulfonamido- κN]-ruthenium to afford **14a** which is alkylated with allyl bromide to afford **14b** and cyclized to (*S*)-1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**17-5a**) with an olefin metathesis reaction which is further transformed to **1** as described in claim 1.

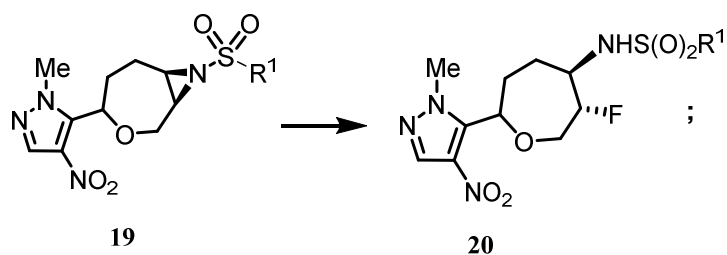
8. A process for the preparation of (3*S*,4*R*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-amine (**8**) comprising the steps:



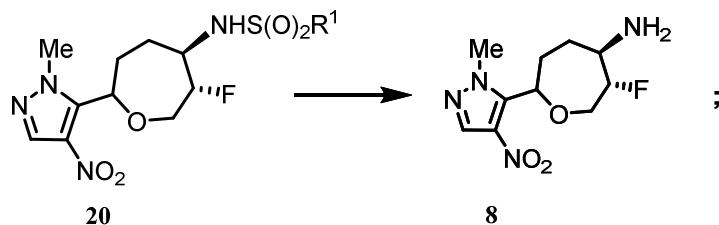
(i) treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5**) with an *N*-chlorosulfonamide (**18**) and bromine source to afford the aziridine **19**, wherein R¹ is 4-nitrophenyl



(ii) treating **19** with a fluoride source to afford **20**



(iii) contacting **20** with a reagent selected from a thiol and a strong base or trifluoromethyl sulfonic acid to afford **8**



9. The process of claim 6 wherein the N-chlorosulfonamide is sodium chloro(*p*-nitrophenyl)sulfonyl)amide, and ~~the cleavage reagent,~~ the cleavage reagent is thioacetic acid and potassium *tert*-butoxide.

10. The process of claim 6 wherein the N-chlorosulfonamide is sodium chloro(*o*-nitrophenyl)sulfonyl)amide, and ~~the cleavage reagent,~~ the cleavage reagent is thioacetic acid and potassium *tert*-butoxide.

11. The process [for the preparation of N-\(5-\(\(5*R*,6*S*\)-5-amino-6-fluorooxepan-2-yl\)-1-methyl-1*H*-pyrazol-4-yl\)-2-\(2,6-difluorophenyl\)thiazole-4-carboxamide according to ~~of~~ claim \[6-1\]\(#\) wherein the N-chlorosulfonamide \(\[18\]\(#\)\) is sodium chloro\(*tert*-butylsulfonyl\)amide and the \[first\]\(#\) cleavage reagent \[is\]\(#\) trifluoromethylsulfonic acid.](#)

* * * * *