

PROCESS FOR THE PREPARATION OF A MEDICAMENT CONTAINING AN OXEPANE RING.

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of priority to US Provisional Patent Application No. 62/934,382, filed November 12, 2019 and to US Provisional Patent Application No. 62/898,861, filed September 11, 2019, both of which are incorporated herein by reference in its entirety.

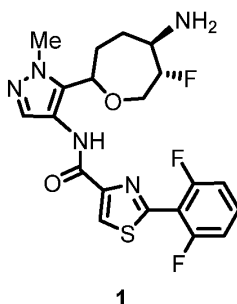
FIELD OF THE INVENTION

[0002] The present invention relates to a new process for the preparation of a PIM kinase inhibitor of formula 1. One object of the present invention is an improved process, which can be practiced efficiently and safely on commercial scale.

BACKGROUND OF THE INVENTION

[0003] Pim kinases are family of three highly related serine and threonine protein kinases encoded by the genes Pim-1, Pim-2, and Pim-3. The gene names are derived from the phrase Proviral Insertion, Moloney, frequent integration sites for murine moloney virus wherein the insertions lead to overexpression of Pim kinases and either *de novo* T-cell lymphomas, or dramatic acceleration of tumorigenesis in a transgenic Myc-driven lymphoma model (Cuypers et al. (1984) Cell, vol. 37 (1) pp. 141-50; Selten et al. (1985) EMBO J. vol. 4 (7) pp. 1793-8; van der Lugt et al. (1995) EMBO J. vol. 14 (11) pp. 2536-44; Mikkers et al. (2002) Nature Genetics, vol. 32 (1) pp. 153-9; van Lohuizen et al. (1991) Cell, vol. 65 (5) pp. 737-52). These experiments reveal synergy with the oncogene c-Myc, and suggest that inhibition of the Pim kinases may have therapeutic benefit.

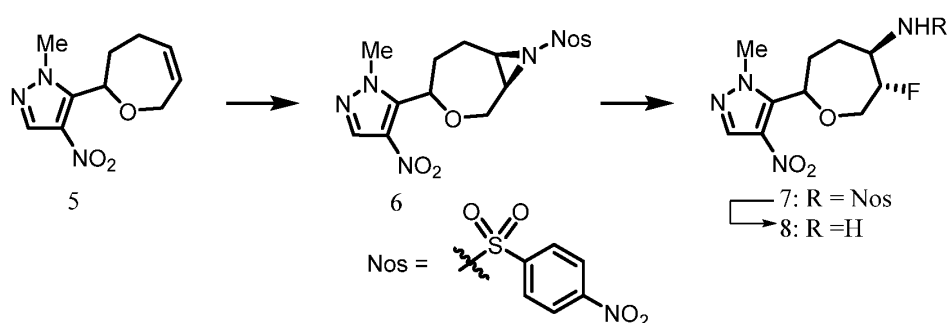
[0004] N-(5-((5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (I) is a highly selective inhibitor of Pim-1, Pim-2, and Pim-3. WO 2015/140189 discloses PIM inhibitors including 1 and related cyclic ether pyrazolyl compounds.



[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 OF THE INVENTION

[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**.

DETAILED DESCRIPTION OF THE INVENTION

[0008] The following definitions are set forth to illustrate and define the meaning and scope of the various terms used to describe the invention herein.

[0009] The phrase “a” or “an” entity as used herein refers to one or more of that entity; for example, a compound refers to one or more compounds or at least one compound. As such, the terms “a” (or “an”), “one or more”, and “at least one” can be used interchangeably herein.

[0010] As used in this specification, whether in a transitional phrase or in the body of the claim, the terms "comprise(s)" and "comprising" are to be interpreted as having an open-ended meaning. That is, the terms are to be interpreted synonymously with the phrases "having at least" or "including at least". When used in the context of a process, the term "comprising" means that the process includes at least the recited steps, but may include additional steps. When used in the context of a compound or composition, the term "comprising" means that the compound or

composition includes at least the recited features or components, but may also include additional features or components.

[0011] The term “optional” or “optionally” as used herein means that a subsequently described event or circumstance may, but need not, occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “optionally substituted” means that the optionally substituted moiety may incorporate a hydrogen or a substituent.

[0012] The term "about" is used herein to mean approximately, in the region of, roughly, or around. When the term "about" is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term "about" is used herein to modify a numerical value above and below the stated value by a variance of 20%.

[0013] As used herein, the term “treating”, “contacting” or “reacting” when referring to a chemical reaction means to add or mix two or more reagents under appropriate conditions to produce the indicated and/or the desired product. It should be appreciated that the reaction which produces the indicated and/or the desired product may not necessarily result directly from the combination of two reagents which were initially added, i.e., there may be one or more intermediates which are produced in the mixture which ultimately leads to the formation of the indicated and/or the desired product.

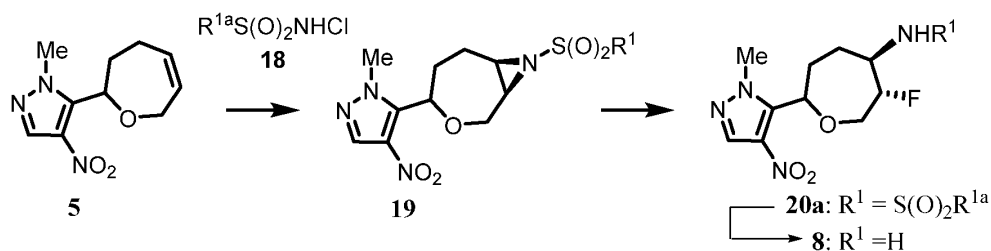
[0014] The term protecting group (PG) refers to any substituent conventionally used to hinder the reactivity of a functional group. As used herein refers to a chemical group that (a) efficiently combines with a reactive group in a molecule; (b) prevents a reactive group from participating in an undesirable chemical reaction; and (c) can be easily removed after protection of the reactive group is no longer required. Protecting groups are used in synthesis to temporarily mask the characteristic chemistry of a functional group because it interferes with another reaction. Reagents and protocols for to introduce and remove protecting groups are well known and have been reviewed in numerous texts (*e.g.*, T. W. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, New York, 1999, and Harrison and Harrison et al., *Compendium of Synthetic Organic Methods*, Vols. 1-8 John Wiley and Sons, 1971-1996). One skilled in the chemical arts will appreciate that on occasion protocols must be optimized for a particular molecule and such optimization is well with the ability of one skilled in these arts.

[0015] Suitable amino protecting groups for R¹ are fluorenylmethyloxycarbonyl (Fmoc), carbobenzyloxy (Cbz), methoxybenzylcarbonyl (Moz), *tert*-butoxycarbonyl (Boc), trichloroethoxycarbonyl (Troc), 2-(trimethylsilyl)ethoxycarbonyl (Teoc) or vinyloxycarbonyl (Voc). A preferred amino protecting group, as defined for R¹ is Boc.

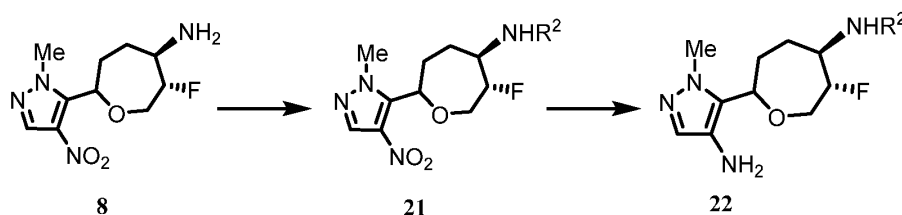
[0016] The term “halogen” refers to fluorine, chlorine, bromine and iodine.

- [0017] Conversion of olefins to aziridines with chloramine T, or other N-chloro arylsulfonamides in the presence of bromine sources (Other bromine sources can be employed. e.g., ZnBr₂, HgBr₂, FeBr₂, CuBr₂, NBS and phenyltrimethylammonium tribromide have been reported (Jeong, J.U. et al. *J. Am. Chem. Soc.* **1998** 120:6844; Ando, T. et al. *Tetrahedron Lett.* **1998** 39:309; Ando, T. et al. *Tetrahedron* **1998** 54:13485; Chang, M.-Y. et al. *Tetrahedron Lett.* **2014** 55:4767). One skilled in the art will appreciate that introduction of the aziridine can be accomplished with other sodium chloro(arylsulfonyl)amides. *ortho*-Nitrophenyl and *para*-nitrophenyl N-chloro arylsulfonamides can be used advantageously since they can be hydrolyzed with thiols and potassium *tert*-butoxide. N-chloro *tert*-butylsulfonamide affords aziridines substituted bearing a *t*-butylsulfonamide moiety which can be cleaved with trifluoromethylsulfonic acid. Ring opening of aziridines by nucleophilic fluorides to afford *beta*-fluoro amines have also been reported. (Hu, E. Eric, *Tetrahedron* **2004** 60:2701-2743; Champagne, P. R. et al. *Chemical Rev.* **2015** 113:9073-9174.)
- [0018] Reduction of a nitro group to an amine can be accomplished with a metal reducing agent such as Fe, Sn or Zn, in a reaction inert solvent, e.g. MeOH, EtOH, EtOAc, benzene, toluene, xylene, *o*-dichlorobenzene, DCM, DCE, THF, dioxane, or mixtures thereof. If desired, when the reducing reagent is Fe, Sn or Zn, the reaction is carried out under acidic conditions in the presence of water. The reduction may be carried out by hydrogenation in the presence of a metal catalyst, e.g. nickel catalysts such as Raney nickel, palladium catalysts such as Pd/C, platinum catalysts such as PtO₂, or ruthenium catalysts such as RuCl₂(Ph₃P)₃ under H₂ atmosphere or in the presence of hydrogen sources such as hydrazine or formic acid. If desired, the reaction is carried out under acidic conditions, e.g., in the presence of HCl or HOAc.
- [0019] Carboxylic acids can be activated with agents such as EDC, DCC, benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate (BOP), bromo-tris-pyrrolidinophosphonium hexafluorophosphate (PyBrOP), or 2-fluoro-1-methylpyridinium *p*-toluenesulphonate (Mukaiyama's reagent with or without a base such NMM, TEA or DIPEA in an inert solvent such as dimethylformamide (DMF) or dichloromethane at temperatures between 0 °C and 60 °C. Acylation of amines (J. March, *supra* pp.417-425; H. G. Benz, *Synthesis of Amides and Related Compounds in Comprehensive Organic Synthesis*, E. Winterfeldt, ed., vol. 6, Pergamon Press, Oxford **1991** pp. 381-411; see R. C. Larock, *Comprehensive Organic Transformations – A Guide to Functional Group Preparations*, 1989, VCH Publishers Inc., New York; pp. 972-976) has been reviewed.
- [0020] In one embodiment of the invention there is provided a process for the preparation of **1** comprising the steps of (i) treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5**, Blackaby, W. et al., WO2014/048939) with an N-chlorosulfonamide (**18**; R¹ is nitrophenyl or *tert*-Bu) and a bromine source to afford the aziridine **19**; (ii) treating **19** with a

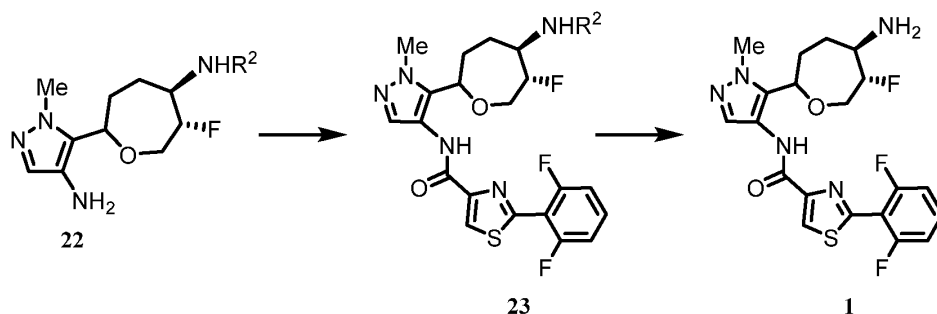
nucleophilic fluoride to afford **20a**; (iii) removing the amino protecting group (R^1) to afford **8**;
 (iv) introducing a second



amine protecting group to afford **21**; (v) reducing the nitro group of **21** to afford **22**;

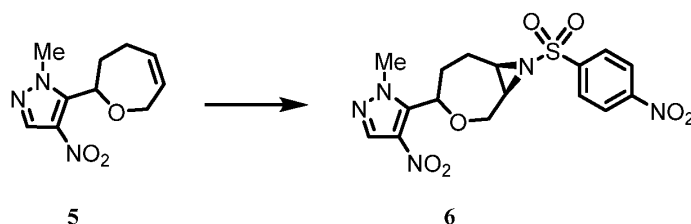


(vi) condensing **22** with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid in the presence of an

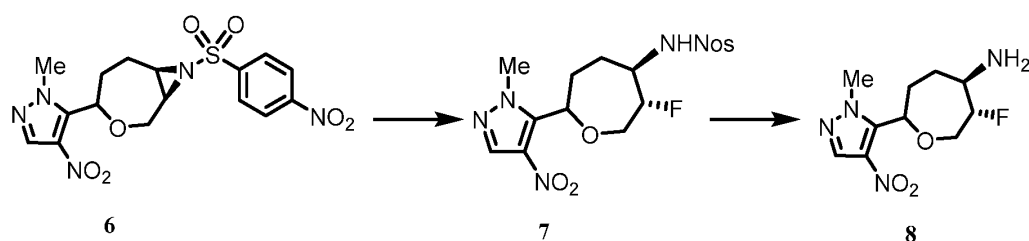


carboxylic acid activating agent; and, (vii) treating **23** with a second cleavage reagent to afford **1**.

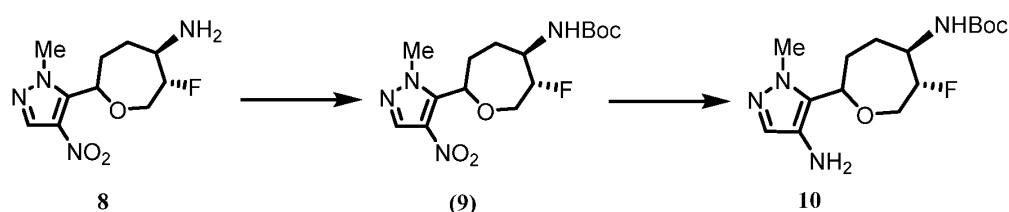
[0021] In another embodiment of the invention there is provided a process for the preparation of **1** comprising the steps of (i) treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1H-pyrazole (**5**) with sodium chloro((4-nitrophenyl)sulfonyl)amide and *N*-bromosuccinimide to afford the



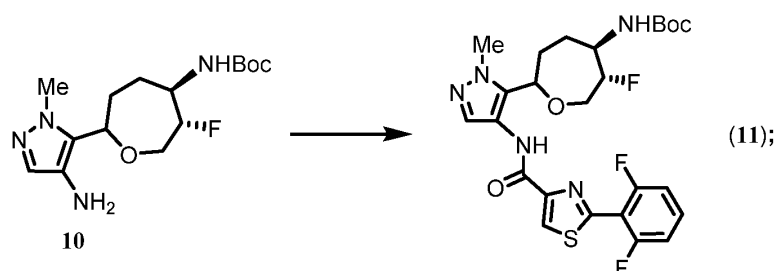
aziridine **6**; (ii) treating **6** with triethylamine trihydrofluoride to afford **7**; (iii) treating **7** with potassium-*tert*-butoxide and thioacetic acid to afford **8**; (iv) treating **8** with di-*tert*-butyl



pyrocarbonate to afford **9**; (v) reducing **9** with hydrogen and Nobllyst P8078 in ethanol to afford **10**;

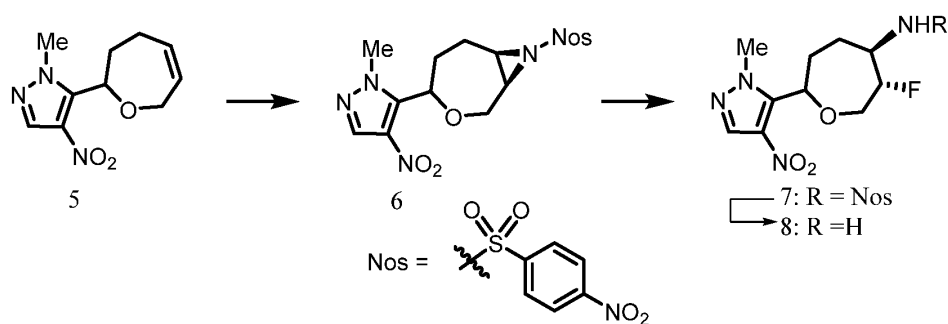


(vi) condensing **10** and 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid in the presence of

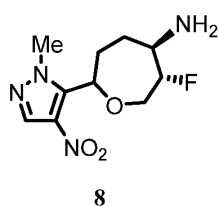


carbonyl diimidazole to afford **11**; and, (vii) removing the Boc protecting group from **10** to afford **1**.

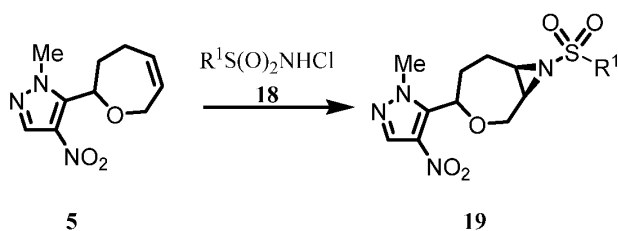
[0022] In another embodiment of the present invention there is provided a process for the preparation of **8** by introducing an aziridine into 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1H-pyrazole (**5**;) to afford (1R,7R)-4-(1-methyl-4-nitro-1H-pyrazol-5-yl)-8-((4-nitrophenyl)sulfonyl)-3-oxa-8-azabicyclo[5.1.0]octane (**6**). Contacting **6** with hydrogen fluoride- Et_3N results in ring opening to afford *N*-((3*S*,4*R*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-yl)-4-nitrobenzenesulfonamide (**7**). Reacting **7** with potassium *tert*-butoxide and thioacetic acid cleaves the Nos moiety and affords (3*S*,4*R*)-3-fluoro-7-(1-methyl-4-nitro-1H-pyrazol-5-yl)oxepan-4-amine (**8**). (T. Fukuyama *et al. Tetrahedron Lett.* **1995** 36:6373-6374; Maligres, P. M. *et al. Tetrahedron Lett* **1997** 38(30): 5253-5256; Cardullo, F. *et al Synlett* **2005** 19:2996-2998).



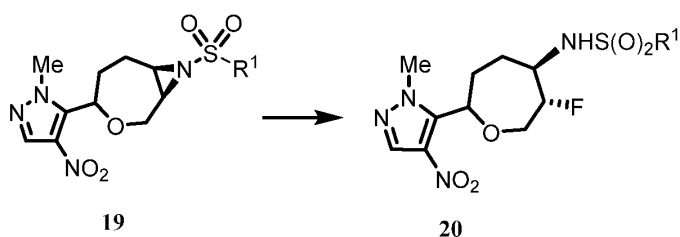
[0023] In another embodiment (3*S*,4*R*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-amine (**8**)



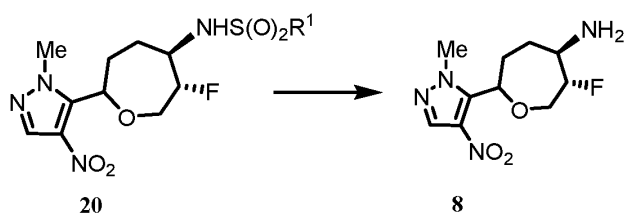
is prepared by the steps of: (i) treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5**) with an N-chlorosulfonamide (**18**) and bromine source to afford the aziridine **19**;



(ii) treating **19** with a nucleophilic fluoride source to afford **20**; (iii) contacting **20** with a reagent

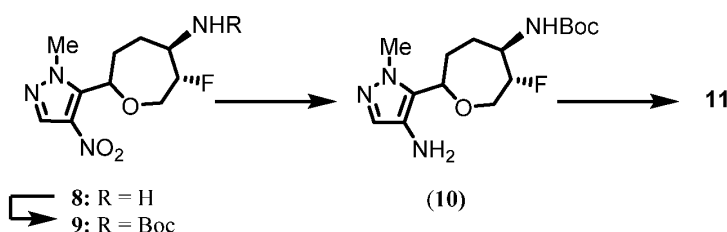


selected when R¹ is nitrophenyl from a thiol and a strong base or when R¹ is *tert*-butyl trifluoromethyl sulfonic acid to afford **8**.

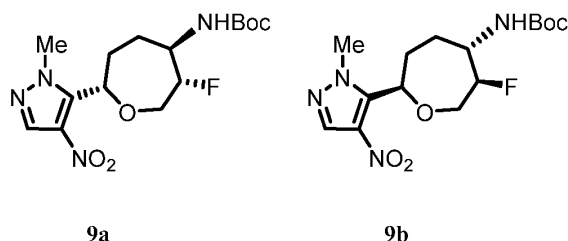


[0024] In another embodiment an N-chlorosulfonamide is sodium chloro((4-nitrophenyl)sulfonyl)amide, the bromine source is NBS, the fluoride source is triethylamine trihydrofluoride, the sulfonamide is cleaved with potassium-*tert*-butoxide and thioacetic acid.

[0025] In another embodiment of the invention the amino group of **8** is protected with Boc and then the nitro is reduced by catalytic hydrogenation to afford *tert*-butyl ((3*S*,4*R*)-7-(4-amino-1-methyl-1*H*-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (**10**). Acylation of **10** with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (**17**) and 1,1'-carbonyl diimidazole affords **11**.

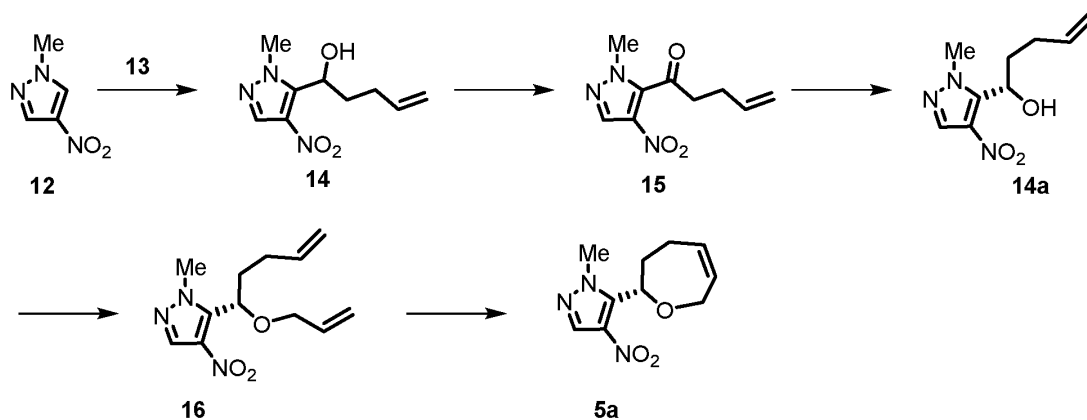


[0026] In another embodiment of the present invention **9** is resolved by chiral HPLC on CHIRALPAK AD-H to afford **9a** and **9b**. The enantiomer **9a** can then be transformed analogously to afford **1a**.



[0027] In yet another embodiment of the invention (*S*)-1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5a**) is prepared deprotonation *N*-methyl 4-nitro-1*H*-pyrazole (**12**) with strong base to afford (1-methyl-4-nitro-1*H*-pyrazol-5-yl) lithium which is condensed with pent-4-enal (**13**) to afford **14**. Oxidation of **14** to affords the corresponding ketone **15** which is subjected to asymmetric hydrogenation with chloro{*N*-[(1*S*,2*S*)-2-[(*R*)-[2-[[1,2,3,4,5,6-η)-4-methylphenyl]methoxy]ethyl]amino]-1,2-diphenylethylmethanesulfonamido}ruthenium(II) to afford **14a** in 98% yield and 94% ee. The chiral alcohol is alkylated with allyl bromide to afford (*S*)-1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)pent-4-en-1-ol (**16**) which is converted to (*S*) 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-

yl)-1*H*-pyrazole (**5a**) by olefin metathesis (for reviews of the olefin metathesis reaction see, for example, K.C. Nicolaou *et al.*, *Angew. Chem. Int. Ed.* **2005** 44:4490; A. Michrowska and K. Grela, *Pure Appl. Chem.* **2008** 80(1):31).



Example 1

(1*R*,7*R*)-4-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-8-((4-nitrophenyl)sulfonyl)-3-oxa-8-azabicyclo[5.1.0]octane (**6**)

[0028] A 500 L reactor was charged with acetonitrile (200 kg). The reactor was then charged with 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (25 kg, 112 mol) and *N*-bromosuccinimide (4 kg, 22.5 mol) and the resulting suspension was stirred until the solution was homogenous. The reactor was purged with N₂ and the reaction mixture was maintained between 20 and 30 °C. To the solution was added in 4 batches sodium chloro((4-nitrophenyl)sulfonyl)amide (43.4 kg 168 mol) while maintaining a positive N₂ pressure to maintain an inert atmosphere. The reaction was stirred for 13 h and then H₂O (1000 L) was charged. The resulting mixture was stirred for 1 h and the resulting slurry was collected by filtration. The solid was slurried with EtOH (250 kg) filtered and centrifuged to afford (1*R*,7*R*)-4-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-8-((4-nitrophenyl)sulfonyl)-3-oxa-8-azabicyclo[5.1.0]octane (**6**) as a white solid. The solid was dried *in vacuo* to afford 42 kg, 88.6% isolated yield as a white powder.

Example 2

N-((3*S*,4*R*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-yl)-4-nitrobenzenesulfonamide (**7**)

[0029] To a 1000 L reactor was charged with MeCN (168 kg) and THF (168 kg) was added with stirring (1*R*,7*R*)-4-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)-8-((4-nitrophenyl)sulfonyl)-3-oxa-8-azabicyclo[5.1.0]octane (**6**; 42 kg, 99.3 mol) and Et₃N·(HF)₃ (31.9 kg, 267.9 mol). The reactor was maintained at 20 to 30 °C and DBU (45.2 kg, 297.9 mol) was added dropwise. The reactor was purged with N₂ and the reaction heated to 65-70 °C for 20 h under positive N₂ pressure. The

reaction mixture was cooled to 20-30 °C and the reaction quenched with 1M HCl (47.0 kg). The solvents were removed by vacuum distillation (internal temperature < 50°C) and the resulting solid was filtered sequentially slurried with H₂O (RT), DCM (RT) and thrice with MeCN (80 °C). The solid was filtered and dried *in vacuo* at 45 °C to afford **7** (17 kg, 38.6% isolated) as an off white solid.

Example 3

(3*S*,4*R*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-amine (**8**)

[0030] A 500 L reactor was charged with MeOH (250 kg) and maintained under a N₂ atmosphere. Potassium *tert*-butoxide (24.3 kg, 36.1 mol) was added portionwise at 20 to 30° C. To the resulting solution was added dropwise HSCH₂CO₂H (12.5 kg, 135.9 mol) while maintaining the solution at 20 to 30 °C. The resulting solution was stirred for at RT for 1h then **7** (16 kg, 36.1 mol) was added. The reaction mixture was heated at 45-60° C for about 4 h. The reaction mixture was quenched with H₂O (320 kg) and the MeOH distilled under reduced pressure (internal temperature < 50° C). The aqueous phase was extracted with DCM (2 x 200 kg) and the combined DCM extracts washed sequentially with 0.1 M NaOH (2 x 100 kg) and H₂O (100 kg) then dried (Na₂SO₄), filtered and the DCM was replaced with petroleum ether (10 L). The resulting precipitate was filtered and air-dried to afford **8** (8.4 kg, 90%) as a white crystalline solid.

Example 4

tert-butyl ((3*S*,4*R*)-7-(4-amino-1-methyl-1*H*-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (**9**)

[0031] A 20 L reactor was charged with **8** (800 g, 3.10 mol), 2-Me-THF (5 L) and 1M K₃PO₄ (9.3 L, 9.3 mol). To the solution was added dropwise at 20 – 30° C a solution of (Boc)₂O (706 g, 3.25 mol) and 2-Me-THF (1 L). The resulting mixture was stirred at RT for 2 h. After the reaction was complete the organic phase was separated and the aqueous phase was extracted with DCM (3 L). The organic phase was dried (Na₂SO₄), filtered and concentrated. Eight identical batches were combined and concentrated to *ca.* 10 L and petroleum ether (10 L) was added and the resulting mixture stirred for 20 min. The resulting precipitate was collected and air-dried to afford 8 kg of **9** as a white solid.

[0032] The 7.5 kg of racemate was resolved by chiral HPLC on a 0.46 cm ID x 15 cm CHIRALPAK AD-H column to afford 3.4 kg of *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-yl)carbamate (**9a**) and 3.6 kg of *tert*-butyl ((3*R*,4*S*,7*R*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-yl)carbamate (**9b**).

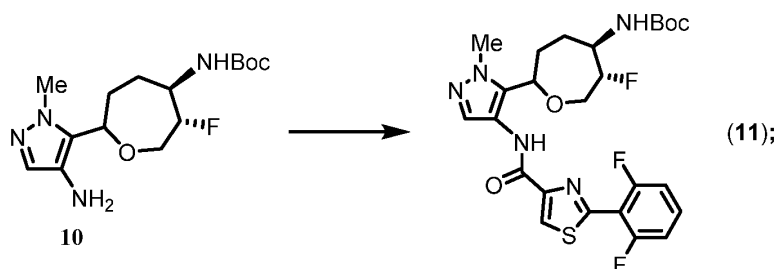
Example 5

tert-butyl ((3*S*,4*R*)-7-(4-amino-1-methyl-1*H*-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (**10**)

[0033] A 10L autoclave equipped with a mechanical stirrer and thermometer was charged with EtOH (7 L), *tert*-butyl ((3*S*,4*R*,7*S*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-yl)carbamate (**9a**, 750 g, 2.09 mol) and Noblyst P8078 catalyst (37.5 g). The autoclave was closed, thrice purged with N₂ the thrice purged with H₂. The mixture was stirred at 50° C under 2 MPa of H₂ pressure. The mixture was filtered through CELITE® and washed with MeOH (4 L). The filtrate was concentrated under reduced pressure to about 1 L. Four 750 g batches were combined and deionized H₂O (9 L) at 50 °C for 1 h then cooled to RT. The mixture was filtered and cake washed with deionized water. The resulting solid was slurried with petroleum ether. The resulting solid was filtered and dried *in vacuo* at 50° C to afford **10** (93%) as a white solid.

Example 6

tert-butyl ((3*S*,4*R*)-7-(4-(2-(2,6-difluorophenyl)thiazole-4-carboxamido)-1-methyl-1*H*-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate



[0034] A 100 L reactor was charged with 2-(2,6-difluorophenyl)thiazole-4-carboxylic acid (**17**, 2.921 kg, 1.19 equiv) and THF (11.05 kg, 4.41 vol). A 20 L reactor was charged with 1,1'-carbonyldiimidazole (CDI, 1.490 kg, 1.20 equiv) and THF (13.40 kg, 5.34 vol). The contents of the 20 L reactor were transferred to the 100 L reactor over ≥ 15 min. The 20 L reactor was rinsed with additional THF (3.25 kg, 1.30 vol) and transferred to the 100 L reactor. The mixture was aged for about 30 min. The 20 L reactor was then charged with *tert*-butyl ((3*S*,4*R*)-7-(4-amino-1-methyl-1*H*-pyrazol-5-yl)-3-fluorooxepan-4-yl)carbamate (2.508 kg, 1.00 equiv) and THF (13.35 kg, 5.32 vol). The 20 L reactor was rinsed with THF (3.30 kg) and the solution transferred to the 100 L reactor and aged for approximately 30 min. The contents were distilled while maintaining the batch temperature ≤ 55 °C until approximately 20 L remained. A 50 L reactor was charged with purified water (40 kg) and NaOH (50 wt%, aq, 0.824 kg, 1.35 equiv). The contents of the 50 L reactor were transferred to the 100 L reactor over about 5 min. The contents were heated to 50 °C, maintained at that temperature for at least 30 min, and then cooled to 20 °C over at least 2 h. The mixture was held for ≥ 60 min. The mixture was filtered through a filter dryer. The 50L reactor was charged with purified water (9.85 kg, 3.93 vol) and NaOH (50 wt%, aq, 0.211 kg, 0.35equiv), and the contents were transferred to the 100 L reactor, then filtered through the filter Dryer. The cake was washed with purified water until the filtrate pH was ≤ 7 (32.95 kg, 13.14 vol followed by 15.35 kg, 6.12 vol). After no more filtrate could be collected

from the filter, the cake was dried in the filter dryer at 60 °C (jacket temperature) under house vacuum with a nitrogen purge. Drying was continued for about 3 h to afford 3.797 kg **11** (90% yield; >99.9 area% by HPLC) as an off-white solid.

Example 7

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 (**I**)

[0035] A 50 L reactor was charged with purified water (12.15 kg, 3.24 vol) and cooled to 10 °C. Sulfuric acid (95-98 wt%, aq, 5.95 kg, 8.76 equiv) was added while maintaining the temperature less 50 °C. A 100 L reactor was charged with **11** (3.747 kg, 1.00 equiv) and anisole (18.15 kg, 4.84 vol). The contents of the 50 L reactor were transferred to the 100 L reactor while maintaining the temperature less than 55 °C. The contents of the 100 L reactor were heated to 55 °C and then held at that temperature for at least 60 min. The contents were cooled to 20 °C and the layers were drained into separate carboys. The aqueous layer was charged to the 100 L reactor, cooled to 10 °C, and then NaOH (50 wt.%, aq, 10.10 kg, 18.6 equiv) was added while maintaining the temperature below 40 °C. Anisole (17.95 kg, 4.79 vol) was charged to the 100 L reactor, and the contents were heated to 55 °C. The lower aqueous layer was drained at this temperature. Purified water (14.90 kg, 3.98 vol) was added to the 100 L reactor, the contents were heated to 55 °C, and then the lower organic layer was transferred to the 50 L reactor.

[0036] Anisole (5.30 kg, 1.41 vol) was charged to the 50 L reactor and the contents were distilled until 17 L remained, while maintaining the batch temperature less below 90 °C. The contents were then cooled to 55 °C.

[0037] The contents were heated to 85 °C, and then transferred to a new 100 L reactor through an in-line filter. The 50 L reactor was charged with anisole (3.05 kg, 0.81 vol), which was then transferred to the new 100 L reactor through the in-line filter. Heptane (4.95 kg, 1.32 vol) was charged to the new 100 L reactor through an in-line filter, and the contents were heated to 90 °C. The contents were agitated for at least 10 min (until a solution was obtained) and then cooled to 75 °C. A slurry of **1** seeds (0.0218 kg) in anisole (0.1856 kg, 0.50 vol) were charged to reactor 3. The contents were held at 75 °C for at least 60 min, cooled to 10 °C over ≥ 5 h, then held at that temperature for ≥ 3 h. The contents were filtered through a filter dryer. Anisole (3.20 kg, 0.85 vol) and heptane (1.07 kg, 0.29 vol) were charged through an in-line filter to reactor 3, and then filtered through the filter dryer. The cake was washed with heptane (5.70 kg, 1.52 vol) and then dried in the filter dryer at 70 ± 5 °C (jacket temperature) under house vacuum with a nitrogen purge. Drying was continued for ≥ 6 h. The process afforded 2.706 kg of **1** (88% yield; 99.9 area% by HPLC) as an off-white solid.

[0038] The features disclosed in the foregoing description, or the following claims, expressed in their specific forms or in terms of a means for performing the disclosed function, or a method or

process for attaining the disclosed result, as appropriate, may, separately, or in any combination of such features, be utilized for realizing the invention in diverse forms thereof.

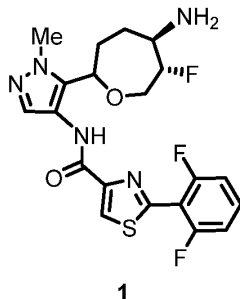
[0039] The foregoing invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding. It will be obvious to one of skill in the art that changes and modifications may be practiced within the scope of the appended claims. Therefore, it is to be understood that the above description is intended to be illustrative and not restrictive. The scope of the invention should, therefore, be determined not with reference to the above description, but should instead be determined with reference to the following appended claims, along with the full scope of equivalents to which such claims are entitled.

[0040] The patents, published applications, and scientific literature referred to herein establish the knowledge of those skilled in the art and are hereby incorporated by reference in their entirety to the same extent as if each was specifically and individually indicated to be incorporated by reference. Any conflict between any reference cited herein and the specific teachings of this specifications shall be resolved in favor of the latter. Likewise, any conflict between an art-understood definition of a word or phrase and a definition of the word or phrase as specifically taught in this specification shall be resolved in favor of the latter.

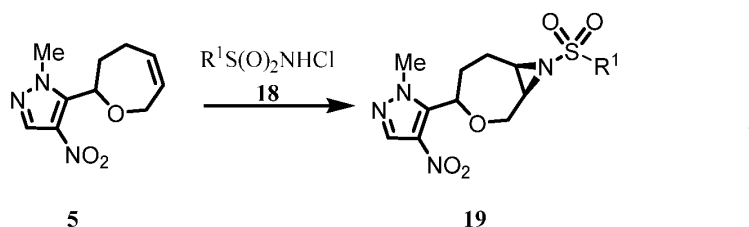
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We claim:

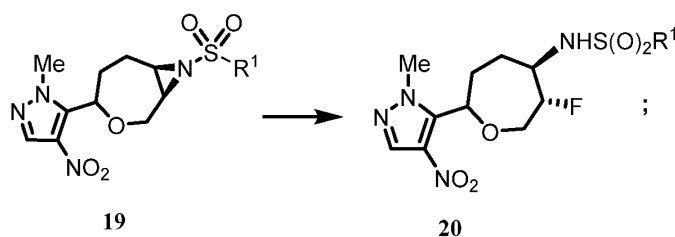
1. A process for the preparation of N-(5-((5*R*,6*S*)-5-amino-6-fluorooxepan-2-yl)-1-methyl-1*H*-pyrazol-4-yl)-2-(2,6-difluorophenyl)thiazole-4-carboxamide (1) comprising the steps of:



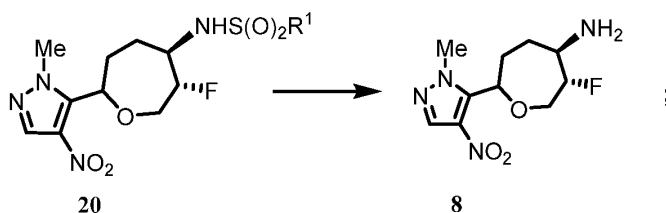
(i). treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5**) with an N-chlorosulfonamide (**18**) and a bromine source to afford the aziridine **19**



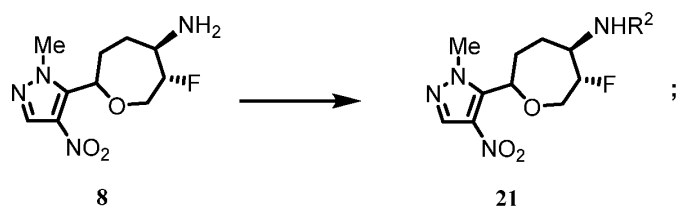
(ii) treating **19** with a nucleophilic fluoride source to afford **20**



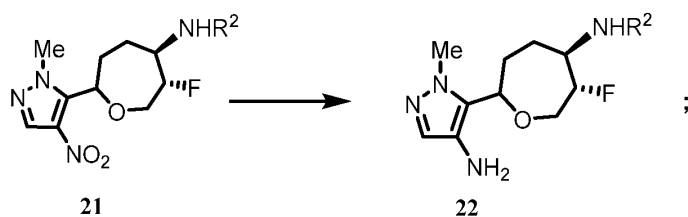
(iii) contacting **20** with a first cleavage reagent selected from a thiol and strong base or trifluoromethyl sulfonic acid to afford **8**



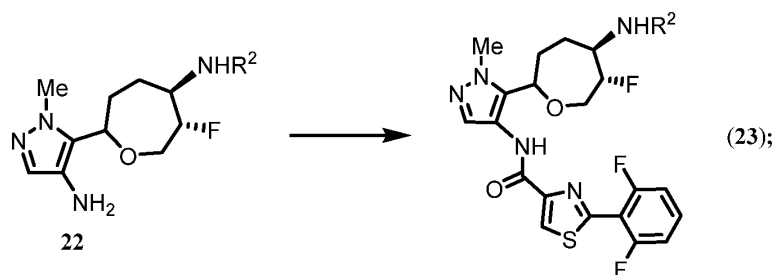
(iv) introducing a amine protecting group to afford **21**



(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**.

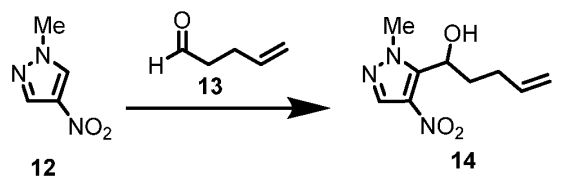
2. The process of claim 1 wherein;

- (a) R¹ is nitrophenyl or *tert*-butyl;
- (b) the bromine source is N-bromosuccinimide;
- (c) the nucleophilic fluoride source is triethylamine trihydrofluoride
- (d) R² is selected from the group consisting of Boc, Fmoc and Cbz;
- (e) the first cleavage reagent is thioacetic acid and potassium *tert*-butoxide when R¹ is nitrophenyl and trifluoromethyl sulfonic acid when R¹ is *tert*-butyl;
- (f) the nitro reducing agent is hydrogen and Noblyst P8078;
- (g) the second cleavage agent is trifluoroacetic acid, piperidine or catalytic hydrogenation.

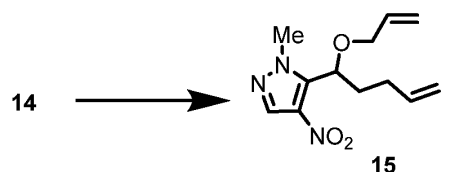
3. The process of claim 2 wherein:

- (a) R¹ is *p*-nitrophenyl or *o*-nitrophenyl;

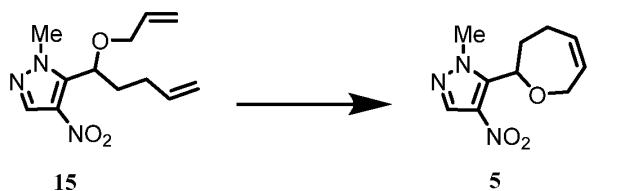
- (b) R² is Boc;
- (c) the first cleavage reagent is thioacetic acid and potassium *tert*-butoxide;
- (e) the second cleavage agent is trifluoroacetic.
4. The process of claim 3 wherein R¹ is *p*-nitrophenyl.
5. The process of claim 1 which process further comprises the steps of
- (i) deprotonating N-methyl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



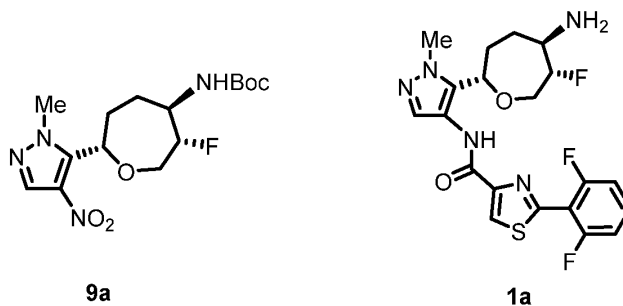
- (ii) alkylating the hydroxyl moiety with allyl bromide to afford **15**



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

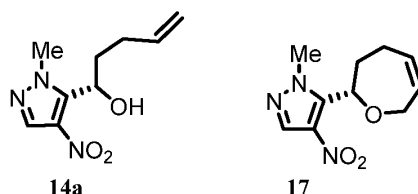


6. The process of claim 3 said process further comprising resolution of compound **9a** by chiral HPLC



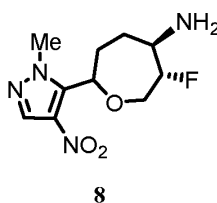
chromatography to afford **9a** that is further converted into **1a** as described in claim 1.

7. The process of claim 1 said process further comprising the chiral synthesis of **17** by oxidation of

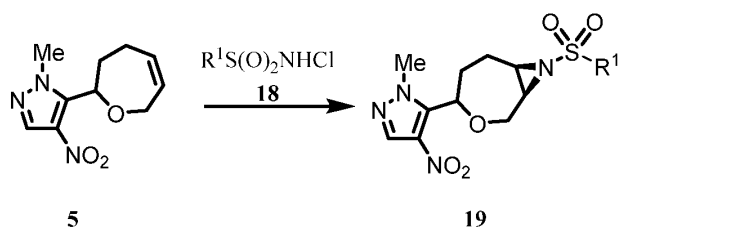


14 to afford 1-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)pent-4-en-1-one (**16**) with the Dees-Martin reagent and chiral catalytic hydrogenation with chloro[*N*-[(1*R*,2*R*)-1,2-diphenyl-2-[[3-(η^6 -phenyl)propyl]amino- κN][ethyl]-4-methylbenzenesulfonamido- κN]-ruthenium to afford (*S*)-1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole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

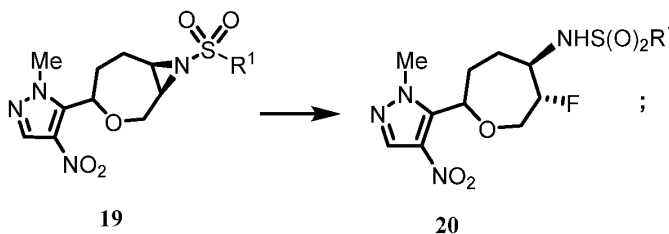
8. A process for the preparation of (3*S*,4*R*)-3-fluoro-7-(1-methyl-4-nitro-1*H*-pyrazol-5-yl)oxepan-4-amine (**8**) comprising the steps:



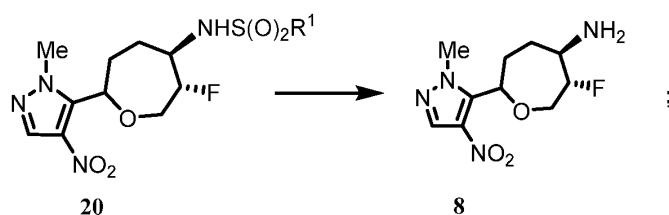
(i) treating 1-methyl-4-nitro-5-(2,3,4,7-tetrahydrooxepin-2-yl)-1*H*-pyrazole (**5**) with an *N*-chlorosulfonamide (**18**) and bromine source to afford the aziridine **19**



(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 of claim 6 wherein the N-chlorosulfonamide is sodium chloro(*tert*-butylsulfonyl)amide and the cleavage reagent trifluoromethylsulfonic acid.

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