(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
28 April 2022 (28.04.2022)

WIPO | PCT

(10) International Publication Number
WO 2022/082329 A1

(51) International Patent Classification:
C07C 255/54 (2006.01) *C07C 41/24* (2006.01)
C07C 253/30 (2006.01) *C07C 43/295* (2006.01)
C07C 29/143 (2006.01) *C07C 45/40* (2006.01)
C07C 35/37 (2006.01) *C07C 49/513* (2006.01)

(21) International Application Number:
PCT/CN2020/121745

(22) International Filing Date:
19 October 2020 (19.10.2020)

(25) Filing Language: English

(26) Publication Language: English

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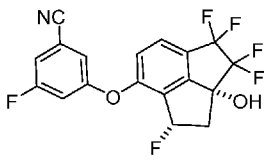
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, IT, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, WS, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2022/082329 A1

(54) Title: PROCESSES OF PREPARING 3-FLUORO-5- (((1S, 2AR) -1, 3, 3, 4, 4-PENTAFLUORO-2A-HYDROXY-2, 2A, 3, 4-TETRAHYDRO-1H-CYCLOPENTA [CD] INDEN-7-YL) OXY) -BENZONITRILE



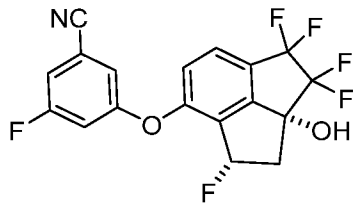
(I)

(57) Abstract: Disclosed herein are processes for preparing 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile (hereinafter as compound (I) having the following structure).

PROCESSES OF PREPARING 3-FLUORO-5-(((1S,2AR)-1,3,3,4,4-PENTAFLUORO-2A-HYDROXY-2,2A,3,4-TETRAHYDRO-1H-CYCLOPENTA[CD]INDEN-7-YL)OXY)-BENZONITRILE

Field of the disclosure

Disclosed herein are processes for preparing 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile (hereinafter Compound (I)) having the structure:



(I)

or a pharmaceutically acceptable salt thereof.

Background

Compound (I) is a hypoxia inducible factor -2α (HIF-2α) inhibitor and is being developed for treating diseases mediated by aberrant activity of HIF-2α including cancer, such as renal cancer, glioblastoma, neuroblastoma, pheochromocytomas and paragangliomas, somatostatinomas, hemangioblastomas, gastrointestinal stromal tumors (GIST), pituitary tumors, leiomyomas, leiomyosarcomas, polycythaemia, and retinal tumors and non-cancer diseases such as pulmonary artery hypertension (PAH), reflux esophagitis, hepatic steatosis, NASH, inflammatory disease such as inflammatory bowel disease, autoimmune disease such as Graft-versus-Host-Disease, and iron overload.

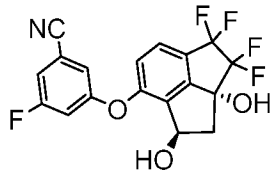
Synthesis of Compound (I) is disclosed in Example 5 of PCT Application No. PCT/US20/28579, filed on April 16, 2020.There is a need for alternative processes that allow for large scale synthesis of Compound (I) in a cost-effective manner. The processes disclosed herein fullfill this and related needs.

Summary

Provided herein is a process that make it feasible to produce Compound (I) in high purity, including enantiomeric purity, and yield in a cost-effective manner and that is suitable for use on a

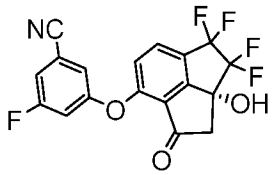
commercial scale. Also, provided are processes for preparing certain intermediates used in such process.

In one aspect, provided is a process of preparing compound (11)



(11)

comprising reducing the keto moiety of compound (10):



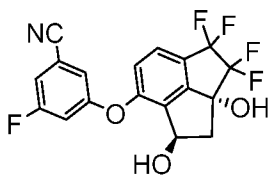
(10)

with:

(a) sodium borohydride in an organic solvent selected from a group consisting of (i) an alcohol containing acetic acid or trifluoroacetic acid, (ii) a cyclic ether, and (iii) a mixture of a cyclic ether and an alcohol wherein the cyclic ether of (ii) and the mixture of a cyclic ether and an alcohol of (iii) optionally contain acetic acid or trifluoroacetic acid; or

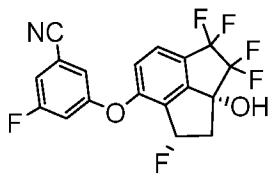
(b) lithium borohydride in a suitable organic solvent optionally containing acetic acid or trifluoroacetic acid.

In a second aspect, the process of the first aspect, further comprises converting compound (11):



(11)

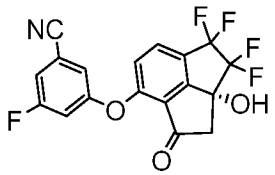
to Compound (I):



(I)

by reacting compound (11) with a deoxyfluorinating agent in the presence of an organic base in a suitable organic solvent.

In a third aspect, provided is a process of preparing compound (10):



(10)

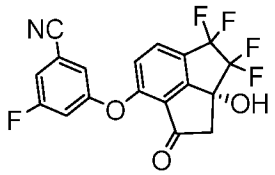
comprising reacting compound (9):



(9)

with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent other than dimethylformamide.

In a fourth aspect, the processes of the first and second aspects, further comprise preparing compound (10):



(10)

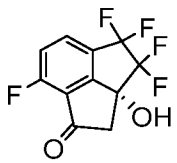
by reacting compound (9):



(9)

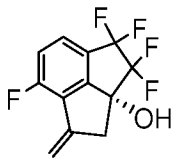
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent.

In a fifth aspect, provided is a process for preparing compound (9):



(9)

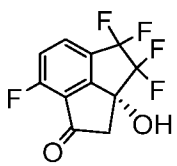
comprising carrying out oxidative cleavage of the vinylidene moiety of (8):



(8)

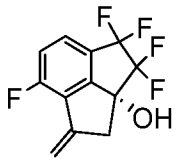
with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii) Oxone® in the presence of ruthenium chloride in a suitable organic solvent, or (iii) Ozone® in a suitable organic solvent.

In a sixth aspect, the processes of the third and fourth aspects, further comprise preparing compound (9):



(9)

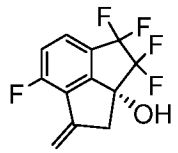
by carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

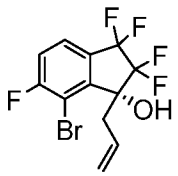
with a suitable oxidizing agent in a suitable organic or aqueous organic solvent.

In a seventh aspect, provided is a process for preparing compound (8):



(8)

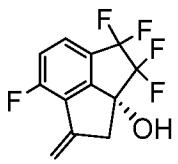
comprising performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

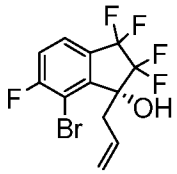
by treating compound (7) with a palladium catalyst in the presence of a base in a suitable organic solvent other than dimethylformamide.

In an eighth aspect, the processes of the fifth and sixth aspects, further comprise preparing compound (8):



(8)

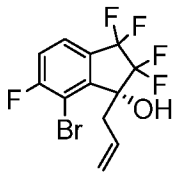
by performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

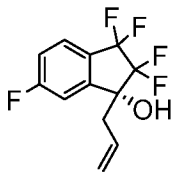
with a palladium catalyst in the presence of a base in a suitable organic solvent.

In a ninth aspect, provided is a process for preparing compound (7):



(7)

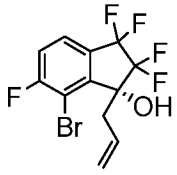
comprising brominating compound (6):



(6)

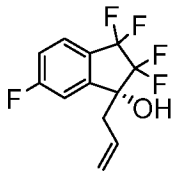
with 1,2-dibromo-1,1,2,2-tetrafluoroethane in the presence of a deprotonating agent in a suitable organic solvent.

In a tenth aspect, the processes of the seventh and eighth aspects, further comprise preparing compound (7):



(7)

by treating compound (6):



(6)

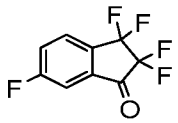
with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

In an eleventh aspect, the processes of the ninth and tenth aspects, further comprise preparing compound (6):



(6)

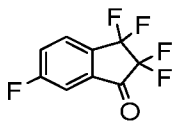
by treating compound (5):



(5)

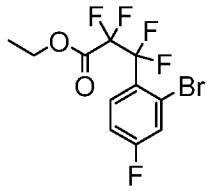
with 4,4,5,5-tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane in the presence of (S)-2-((3-(tert-butyl)-2-hydroxybenzyl)amino)-N,N,3-trimethylbutanamide and a base in a suitable organic solvent.

In a twelfth aspect, the process of eleventh aspect, further comprises preparing compound (5):



(5)

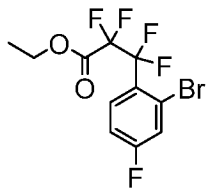
by treating compound (4):



(4)

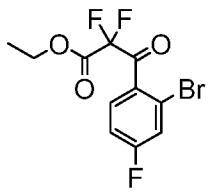
with an organolithium reagent in a suitable organic solvent.

In a thirteenth aspect, the process of twelfth aspect, further comprises preparing compound (4):



(4)

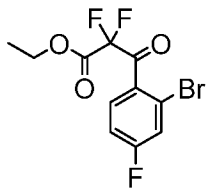
by treating compound (3):



(3)

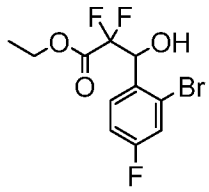
with a fluorinating agent in a suitable organic solvent.

In a fourteenth aspect, the process of thirteenth aspect, further comprises preparing compound (3):



(3)

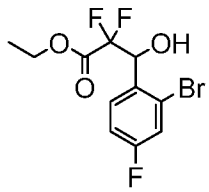
by treating compound (2):



(2)

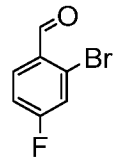
with an oxidizing agent in a suitable organic solvent.

In a fifteenth aspect, the process of fourteenth aspect, further comprises preparing compound (2):



(2)

by treating compound (1):



(1)

with ethyl bromodifluoroacetate in the presence of zinc metal, trimethylsilyl chloride, and 1,2-dibromoethane in a suitable organic solvent.

Detailed Description

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meaning:

As used herein, the term "reacting" or "treating" when describing a certain process is used as known in the art and generally refers to the bringing together of chemical reagents in such a manner so as to allow their interaction at the molecular level to achieve a chemical or physical transformation. The reacting steps of the processes described herein can be conducted for a time and under conditions suitable for preparing the identified product.

"Suitable organic solvent" refers to an organic solvent which, under the reaction conditions of the processes disclosed herein, does not enter into any appreciable reaction with either the reactants, intermediates an/or the products at the temperatures at which the reactions are carried out. A given reaction disclosed herein can be carried out in one organic solvent or a mixture of two or more organic solvents. Examples of suitable organic solvents that can be used in the reactions described herein include: halogenated solvents such as carbon tetrachloride, chloroform, dichloromethane, and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, l,3-dioxane, l,4-dioxane, diethyl ether, methyl t-butyl ether, and the like; alcohols such as methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, n-butyl alcohol, tert-butyl alcohol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, and the like; hydrocarbons such as benzene, toluene, xylene, cyclohexane, pentane, hexane, heptane, and the like. Additional organic solvents that can be used in the reactions described herein include polar organic solvents including, but not limited to, acetonitrile, dimethylformamide, ethyl acetate, alcohols, and the like. When polar organic solvents (e.g., alcohols, acetonitrile, DMF) contain water they are referred to herein as aqueous organic solvent. Depending on the reaction step, solvents that are suitable for the particular reaction step can be readily selected by a person skilled in the art.

For example, in the preparation of compound (2), besides, THF, the reaction was also carried out in MTBE, 2-methylTHF, or toluene solvent. In the preparation of compound (3), the reaction was also carried out in THFsolvent. In the preparation of compound (4), the reaction was also carried out in $CHCl_3$ solvent. In the preparation of compound (5), the reaction was also carried out in 2-methyl THF, n-heptane, or MTBE solvent. In the preparation of compound (8), the reaction was also carried out in DMF, 1,4-dioxane, THF, 2-methyl THF, toluene, oracetonitrile solvent. In the preparation of compound (9), the reaction was also carried out in a mixture of DCM/ACN/water. In the preparation of compound (10), the reaction was also carried out in DMF,

ACN, 2-methyl THF, or toluene solvent. In the preparation of compound (11), the reaction was also carried out in THF, CH_3OH, TFA/THF, or HOAc/THF solvent. In the preparation of compound (I), the reaction was also carried out in DCM, CH_3CN, 2-methyl THF, ethyl acetate, DMF, MTBE or toluene solvent.

In addition, the reactions were carried out at various temperatures. Reaction temperatures that were used in the preparation of compound (2) included 20 °C, 40 °C, 60 °C, and refluxing. Reaction temperatures that were used in the preparation of compound (3) included 0 – 15 °C and 15 – 25 °C. Reaction temperatures that were used in the preparation of compound (4) included 0 – 10 °C, 10 – 20 °C, 20 – 30 °C, and 30 – 40 °C. Reaction temperatures that were used in the preparation of compound (5) included -30 to -40 °C, -40 to -50 °C, -50 to -60 °C, and -60 to -70 °C. Reaction temperatures that were used in the preparation of compound (6) included 35 °C, 45 °C, and 60 °C. Reaction temperatures that were used in the preparation of compound (7) included -100 to -80 °C, -80 to -60 °C, and -60 to -40 °C. Reaction temperatures that were used in the preparation of compound (8) included 60 °C, 70 °C and refluxing. Reaction temperatures that were used in the preparation of compound (10) included 20 to 30 °C, and 40 °C. Reaction temperatures that were used in the preparation of compound (11) included 10 to 20 °C and -5 to 5 °C. And Reaction temperatures that were used in the preparation of compound (I) included 20 to 30 °C and -5 to 5 °C.

Additionally, bases that were used in the preparation of compound (8) included NaOAc, KOAc, and K_2CO_3;

brominating reagents that were used in the preparation of compound (7) included CBr_4 and CF_2BrCF_2Br;

catalysts that were used in the preparation of compound (8) included $Pd(dppf)Cl_2$, $Pd_2(dba)_3$/XPhos, $Pd(OAc)_2/PPh_3$, and $Pd(PPh_3)Cl_2$;

fluorinating reagents that were used in the preparation of compound (4) included DAST, 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride, and HF/SF_4;

fluorinating reagents that were used in the preparation of compound (I) included DAST, PyFluor, AlkylFluor and SulfoxFluor;

oxidizing agents that were used in the oxidation of compound (2) to (3) included 2-iodoxybenzoic acid (IBX), $RuCl_3/NaBrO_3$; TEMPO/NaClO, MnO_2, and TPAP/NMO.

oxidizing agents that were used in the oxidation of compound (8) to (9) included $RuCl_3/NaIO_4$, $RuCl_3$/Oxone® and O_3; and

reducing agents that were used in the reduction of compound (10) to (11) included $LiBH_4$ and $NaBH_4$.

The reactions of the processes described herein can be carried out in air or under an inert atmosphere. Typically, reactions containing reagents or products that are substantially reactive with air can be carried out using air-sensitive synthetic techniques that are well known to the skilled artisan.

The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry, or mass spectrometry; or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography. The compounds obtained by the reactions can be purified by any suitable method known in the art. For example, chromatography (medium pressure) on a suitable adsorbent (e.g., silica gel, alumina and the like), HPLC, or preparative thin layer chromatography; distillation; sublimation, trituration, or recrystallization. The purity of the compounds, in general, are determined by physical methods such as measuring the melting point (in case of a solid), obtaining an NMR spectrum, or performing a HPLC separation.

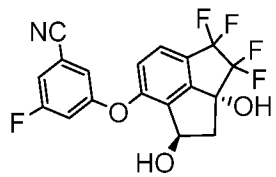
"Cyclic ether" refers to tetrahydrofuran, 2-methyltetrahydrofuran, or 1,4-dioxane.

"Alcohol" refers to an aliphatic hydrocarbon compound that carries a hydroxy group. Representative examples include, but are not limited to, methanol, ethanol, propanol, butanol, and the like.

"About" as used herein means ± 10%, preferably ± 5% of listed value. For example, a reaction carried out at about 10 °C includes 9 °C, 11 °C, and all temperatures contained in between 9 °C and 11 °C.

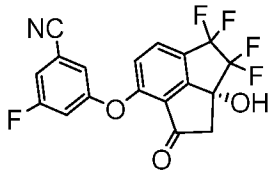
Embodiments:

1. In embodiment 1, provided is a process of preparing compound (11)



(11)

comprising reducing the keto moiety of compound (10):



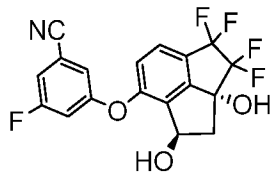
(10)

with:

(a) sodium borohydride in an organic solvent selected from a group consisting of (i) an alcohol containing acetic acid or trifluoroacetic acid, (ii) a cyclic ether, and (iii) a mixture of a cyclic ether and an alcohol; wherein the cyclic ether of (ii) and the mixture of a cyclic ether and an alcohol of (iii) optionally contain acetic acid or trifluoroacetic acid; or

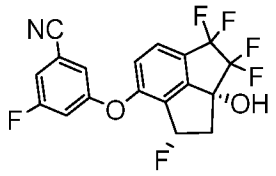
(b) lithium borohydride in a suitable organic solvent optionally containing acetic acid or trifluoroacetic acid.

2. In embodiment 2, the process of embodiment 1, further comprising converting compound (11):



(11)

to Compound (I):



(I)

by reacting compound (11) with a deoxyfluorinating agent in the presence of an organic base in a suitable organic solvent.

3. In embodiment 3, the process of embodiment 2, is wherein the deoxyfluorinating agent is diethylaminosulfur trifluoride, Phenofluor™, N-tosyl-4-chlorobenzene- sulfonimidoyl fluoride, pyridine-2-sulfonyl fluoride, or AlkylFluor.

4. In embodiment 4, the process of embodiment 2 or 3, is wherein the organic solvent is halogenated hydrocarbon, cyclic ethers, ethers, aromatic hydrocarbon, or a polar solvent. Preferably, the organic solvent is dichloromethane, acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, ethylacetate, dimethylformamide, methyl tert-butylether, or toluene.

5. In embodiment 5, the process of embodiment 2, is wherein the deoxyfluorinating agent is pyridine-2-sulfonyl fluoride and the base is 1,8-diazabicyclo-[5.4.0]undec-7-ene or 7-methyl-1,5,7-triaza-bicyclo[4.4.0]dec-1-ene.

6. In embodiment 6, the process of embodiment 1, is wherein the reduction of the keto group of compound (10) is carried out with sodium borohydride in tetrahydrofuran, 2-methyltetrahydrofuran, a mixture of tetrahydrofuran or 2-methyltetrahydrofuran and methanol, tetrahydrofuran containing acetic acid or trifluoroacetic acid, 2-methyltetrahydrofuran containing acetic acid or trifluoroacetic acid, or methanol containing acetic acid or trifluoroacetic acid.

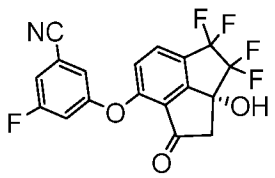
7. In embodiment 7, the process of embodiment 6, is wherein the organic solvent is a mixture of tetrahydrofuran and methanol and the reaction is carried out at about -5 °C to about 30°C.

8. In embodiment 8, the process of embodiment 6, is wherein the organic solvent is a mixture of tetrahydrofuran and methanol and the reaction is carried out at about -5 °C to about 5 °C.

9. In embodiment 9, the process of embodiment 5, is wherein the molar ratio of 1,8-diazabicyclo[5.4.0]-undec-7-ene to compound (11) is at least about 2 to about 1 and the organic solvent is tetrahydrofuran.

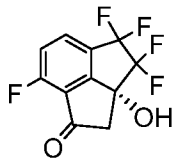
10. In embodiment 10, the process of embodiment 5 or 9, is wherein the reaction is carried out at 20 °C to about 30 °C

11. In embodiment 11, provided is process of preparing compound (10):



(10)

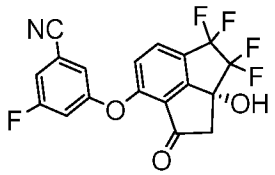
comprising reacting compound (9):



(9)

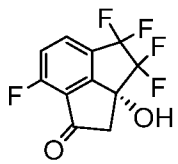
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent other than dimethylformamide.

12. In embodiment 12, the process of any one of embodiments 1 to 10, further comprising preparing compound (10):



(10)

by reacting compound (9):



(9)

with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent.

13. In embodiment 13, the process of embodiment 11 or 12, is wherein the base is an inorganic base.

14. In embodiment 14, the process of embodiment 13, is wherein the inorganic base is cesium carbonate or potassium carbonate.

15. In embodiment 15, the process of any one of embodiments 11 to 14, is wherein the organic solvent is tetrahydrofuran, 2-methyltetrahydrofuran, dimethylformamide, acetonitrile, or toluene.

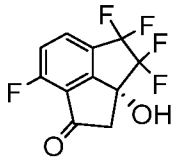
16. In embodiment 16, the process of embodiment 15, is wherein the organic solvent is tetrahydrofuran.

17. In embodiment 17, the process of any one of embodiments 11 to 16, is wherein the reaction is carried out at about 20 °C to about 40 °C.

18. In embodiment 17, the process of any one of embodiments 11 to 17, further comprising crystallizing compound (10) from a mixture of an ether and an alkane solvent.

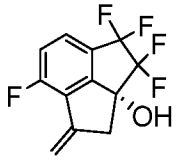
19. In embodiment 19, the process of embodiment 18 is wherein compound (10) is crystallized from a mixture of methyl tert-butyl ether and n-heptane.

20. In embodiment 20, provided is a process for preparing compound (9):



(9)

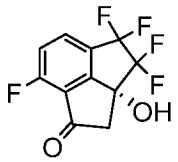
comprising carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii) Oxone® in the presence of ruthenium chloride in a suitable organic or aqueous organic solvent, or (iii) Ozone in a suitable organic or aqueous organic solvent.

21. In embodiment 21, the process of any one of embodiments 11 to 19, further comprising preparing compound (9):



(9)

by carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

with a suitable oxidizing agent agent in a suitable organic or aqueous organic solvent.

22. In embodiment 22, the process of embodiment 21, is wherein the oxidative cleavage of the vinylidene is carried out with (i) sodium periodate or Oxone® in the presence of ruthenium chloride or (ii) Ozone.

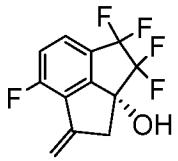
23. In embodiment 23, the process of embodiment 21, is wherein the solvent is a mixture of dichloromethane, acetonitrile and water or aqueous acetonitrile.

24. In embodiment 24, the process of any one of embodiments 20 to 23, is wherein the oxidative cleavage of the vinylidene is carried out with sodium periodate in the presence of catalytic amount of ruthenium chloride in aqueous acetonitrile.

24a. In embodiment 24a, the process of any one of embodiments 20 to 24, further comprising purification of compound (10) from a mixture of an ether and an alkane solvent.

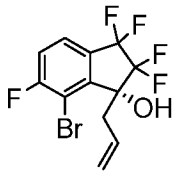
24b. In embodiment 24b, the process of embodiment 24a, is wherein purification of compound (10) is from a mixture of methyl tert-butyl ether and n-heptane.

25. In embodiment 25, provided is a process for preparing compound (8):



(8)

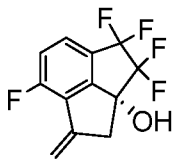
comprising performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

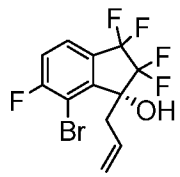
by treating compound (7) with a palladium catalyst in the presence of a base in a suitable organic solvent other than dimethylformamide.

26. In embodiment 26, the process of any one of embodiments 20 to 24, further comprising preparing compound (8):



(8)

by performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

with a palladium catalyst in the presence of a base in a suitable organic solvent.

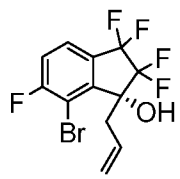
27. In embodiment 27, the process of embodiment 25 or 26, is wherein the palladium catalyst is $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_2(OAc)_2$, $Pd_2(dba)_3$/XPhos, or Pd(1,2-bis(diphenylphosphino)ethane)$(OAc)_2$ and the organic solvent is acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, 1,4-dioxane, or dimethylformamide.

28. In embodiment 28, the process of embodiment 27, is wherein the base is sodium acetate, potassium acetate, sodium carbonate, potassium carbonate or cesium carbonate.

29. In embodiment 29, the process of any one of embodiments 25, 26, or 28, is wherein the palladium catalyst is $Pd(PPh_3)_2Cl_2$, the base is potassium acetate and the solvent is acetonitrile.

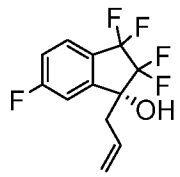
30. In embodiment 30, the process of embodimen 29, is wherein the reaction is carried out between about 60 °C to about 80 °C.

31. In embodiment 31, provided is a process for preparing compound (7):



(7)

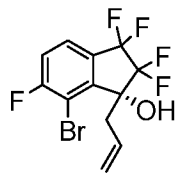
comprising brominating compound (6):



(6)

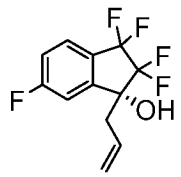
with 1,2-dibromo-1,1,2,2-tetrafluoroethane in the presence of a deprotonating agent in a suitable organic solvent.

32. In embodiment 32, the process of any one of embodiments 25 to 30, further comprising preparing compound (7):



(7)

by treating compound (6):



(6)

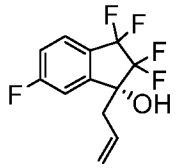
with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

33. In embodiment 33, the process of embodiment 32, wherein the brominating agent is carbon tetrabromide or 1,2-dibromo-1,1,2,2-tetrafluoroethane.

34. In embodiment 34, the process of embodiment 31 or 32, is wherein the brominating agent is 1,2-dibromo-1,1,2,2-tetrafluoroethane, the deprotonating agent is lithium diisopropylamide and the solvent is tetrahydrofuran.

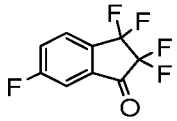
35. In embodiment 35, the process of embodiment 34, is wherein the reaction is carried at out at about -100 °C to about -20 °C.

36. In embodiment 36, the process of any one of embodiments 31 to 35, further comprising preparing compound (6):



(6)

by treating compound (5):

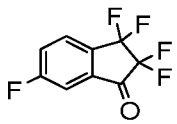


(5)

with 4,4,5,5-tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane in the presence of (S)-2-((3-(tert-butyl)-2-hydroxybenzyl)amino)-N,N,3-trimethylbutanamide and a base in a suitable organic solvent.

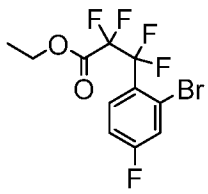
37. In embodiment 37, the process of embodiment 36, is wherein the base is sodium tert-butoxide and the organic solvent is a mixture of methanol and toluene.

38. In embodiment 38, the process of claim 36 or 37, further comprising preparing compound (5):



(5)

by treating compound (4):



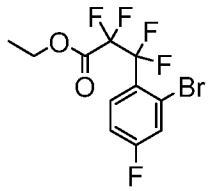
(4)

with an organolithium reagent in a suitable organic solvent.

39. In embodiment 39, the process of claim 38, is wherein the organolithium reagent is n-butyllithium and the organic solvent is tetrahydrofuran, 2-methyltetrahydrofuran, n-heptane and methyl ter-butylether.

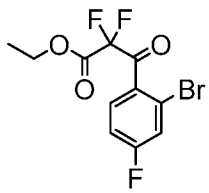
40. In embodiment 40, the process of embodiment 38 or 39, is wherein the solvent is tetrahydrofuran.

41. In embodiment 41, the process of any one of embodiments 38 to 40, further comprising preparing compound (4):



(4)

by treating compound (3):



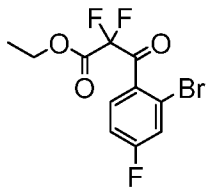
(3)

with a fluorinating agent in a suitable organic solvent.

42. In embodiment 42, the process of claim 41, is wherein the fluorinating agent is diethylaminosulfur trifluoride, 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride, or sulfur tetrafluoride and hydrofluoric acid.

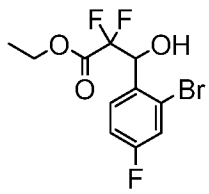
43. In embodiment 43, the process of embodiment 42, is wherein the fluorinating agent is sulfur tetrafluoride and hydrofluoric acid and the solvent is dichloromethane.

44. In embodiment 44, the process of any one of embodiments 41 to 43, further comprising preparing compound (3):



(3)

by treating compound (2):



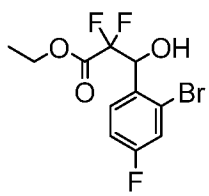
(2)

with an oxidizing agent in a suitable organic solvent.

45. In embodiment 45, the process of embodiment 44, is wherein the oxidizing agent is dimethyl sulfoxide/oxalyl chloride, 2-iodoxybenzoic acid, $RuCl_3/NaBrO_3$, MnO_2, $NaBrO_3/NaHSO_3$, or TPAP/NMO.

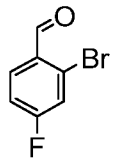
46. In embodiment 46, the process of embodiment 45, is wherein the oxidizing agent is is TPAP/NMO and reaction is carried in dichloromethane, acetonitrile or tetrahydrofuran, preferably dichloromethane.

47. In embodiment 47, the process of any one of embodiments 44 to 46, further comprising preparing compound (2):



(2)

by treating compound (1):



(1)

with ethyl bromodifluoroacetate in the presence of zinc metal, trimethylsilyl chloride, and 1,2-dibromoethane in a suitable organic solvent.

48. In embodiment 48, the process of embodiment 47, is wherein the organic solvent is tetrahydrofuran or 2-methyl tetrahydrofuran.

EXAMPLES

Abbreviations:

ACN: acetonitrile

AcOH or HOAc: acetic acid

AlkylFluor: CAS Registry No. 2043361-32-4

Cs_2CO_3: cesium carbonate

DAST: diethylaminosulfur trifluoride

DCM: dichloromethane

HF: hydrofluoric acid

HCl: hydrochloric acid

KOAc: potassium acetate

LDA: Lithium diisopropylamide

MTBE: methyl tert-butyl ether

NMO: N-Methylmorpholine N-oxide

MeOH: methanol

$NaBH_4$: sodium borohydride

$NaIO_4$: sodium perodiate

n-BuLi: n-butyllithium

$Pd(PPh_3)_2(OAc)_2$: bis(acetato)bis(triphenylphosphine)palladium(II)

$Pd(PPh_3)_2Cl_2$: bis(triphenylphosphine)palladium(II) dichloride

$Pd_2(dba)_3$: tris(dibenzylideneacetone)dipalladium(0)

PyFluor: 2-pyridinesulfonyl Fluoride

$RuCl_3•3H_2O$: ruthenium (III) chloride hydrate

SF_4: sulfur tetrafluoride

SulfoxFluor: [methyl(oxo){1-[6-(trifluoromethyl)-3-pyridyl]ethyl}-λ^6-sulfanylidene]cyanamide

TEMPO: (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl

TFA: trifluoroacetic acid

THF: tetrahydronfuran

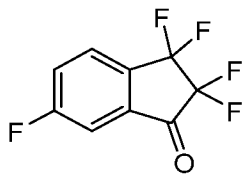
TPAP: tetrapropylammonium perruthenate

t-BuONa: sodium tert-butoxide

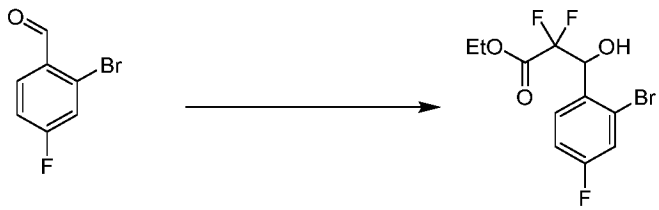
XPhos: 2-dicyclohexylphosphino-2 ,4 ,6 -triisopropylbiphenyl

Example 1

Synthesis of 2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-one



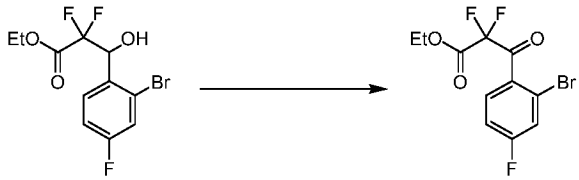
Step 1: ethyl 3-(2-bromo-4-fluorophenyl) -2,2-difluoro-3-hydroxypropanoate



To a mixture of zinc (211.36 g, 3.23 mol, 1.31 eq.) in THF (1.50 L) was added 1,2-dibromoethane (13.88 g, 73.89 mmol, 0.030 eq.) and TMSCl (53.52 g, 492.59 mmol, 0.20 eq.) in one portion. The mixture was stirred at 25 °C for 0.5 h, then a solution of 2-bromo-4-fluoro-benzaldehyde (500 g, 2.46 mol, 1.00 eq.) and ethyl 2-bromo-2,2-difluoro-acetate (549.93 g, 2.71 mol, 1.10 eq.) in THF (1.50 L) was added to the mixture dropwise over 1 h under refluxing, and the reaction mixture was stirred continually under refluxing for 1 h. The reaction mixture was cooled, then filtered, and the cake was washed with ethyl acetate. The filtrate was quenched with 1.0 M aqueous HCl (800 mL), then adjusted to pH = 5 – 6 and the mixture was extracted with

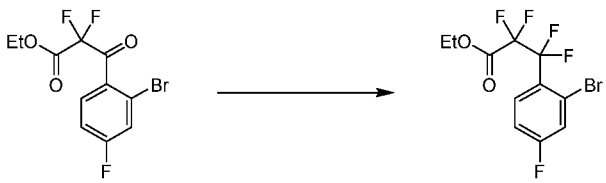
ethyl acetate. The combined organic phase was washed with 10% brine, dried with Na_2SO_4, concentrated in vacuum to give the title compound (857.0 g, , 88.8% assay purity, 94.5% assay yield) as a yellow oil, which was used for next step without further purification.

Step 2: ethyl 3-(2-bromo-4-fluorophenyl)-2,2-difluoro-3-oxopropanoate



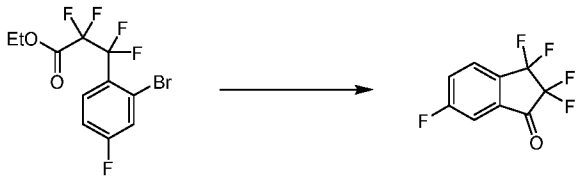
A mixture of NMO (297.86 g, 2.54 mol, 1.40 eq.), TPAP (15.96 g, 45.41 mmol, 0.025 eq.) and 4Å MS (94.0 g) in DCM (1000 mL) was degassed and purged with N_2 and a solution of ethyl 3-(2-bromo-4-fluorophenyl)- 2,2-difluoro-3-hydroxypropanoate (669.00 g, 1.82 mol, 88.8% assay, 1.00 eq.) in DCM (1000 mL) was added dropwise at 0-5 °C over 1.5 h. The resulting mixture was further stirred at 25 °C for 2 h under N_2 atmosphere, then was filtered through silica gel pad and the pad cake was washed with MTBE. The combined filtrate was washed with 1.0 M aqueous HCl. The combined aqueous phase was extracted with MTBE. The combined MTBE organic phase was washed with H_2O, filtered through a silica gel pad and the pad cake was washed with MTBE. The combined filtrate was concentrated to give the title compound (561.0 g, 95.1% yield) as a yellow oil, which was used for next step without further purification.

Step 3: ethyl 3-(2-bromo-4-fluorophenyl)-2,2,3,3-tetrafluoropropanoate



To an autoclave was charged ethyl 3-(2-bromo-4-fluorophenyl)-2,2-difluoro-3-oxopropanoate (550.00 g, 1.69 mol, 1.00 eq.) and DCM (55.5 mL). The mixture was cooled to -78 °C and HF (33.85 g, 1.69 mol, 1.00 eq.) was charged, followed by SF_4 (202.00 g, 1.87 mol, 1.11 eq.). The reaction mixture was warmed to room temperature and stirred at this temperature for 16 h. The reaction mixture was quenched by added slowly into saturated aqueous Na_2CO_3 (2.5 L) and then extracted with petroleum ether. The combined organic layer was washed with 10% brine, dried over Na_2SO_4, filtered and concentrated. The residue was further purified by vacuum distillation to afford the title compound (474.0 g, 81.1% yield) as yellow oil.

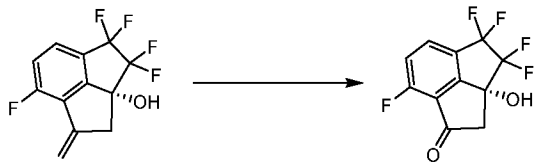
Step 4: 2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-one



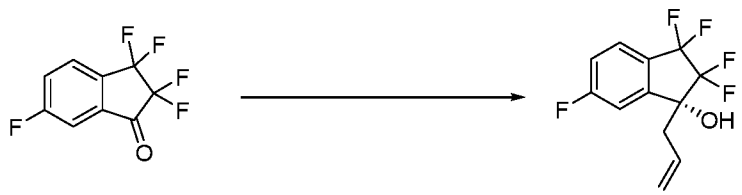
A stirred solution of ethyl 3-(2-bromo-4-fluorophenyl)-2,2,3,3-tetrafluoropropanoate (100.0. g, 288.11 mol, 1.00 eq.) in THF (1.0 L) was cooled to -65 °C, and n-BuLi (2.5 M, 138.0 mL, 345.0 mol, 1.20 eq.) was added dropwise at -60 to -70 °C over 1 h under nitrogen atmosphere. The resulting mixture was stirred further at -65 °C for 1 h, then was quenched with saturated aqueous NH_4Cl at -30 to -40 °C, followed by dilution with ethyl acetate and H_2O. After phase separation, the aqueous phase was extracted with ethyl acetate and the combined organic layer was washed with 10% brine, dried over Na_2SO_4, filtered and concentrated to give a residue. The residue was purified by vacuum distillation, and the distillate was triturated with petroleum ether at low temperature to give the title compound (41.0 g, 64.1% yield) as a white solid.

Example 2

Synthesis of (R)-3,3,4,4,7-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-1-one



Step 1: (R)-1-allyl-2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-ol



To a dry 3-neck flask were added 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (94.57 g, 562.78 mmol, 1.21 eq.), (S)-2-((3-(tert-butyl)-2-hydroxybenzyl)amino)-N,N,3-trimethyl-butanamide (36.51 g, 119.14 mmol, 0.26 eq.), t-BuONa (4.33 g, 45.06 mmol, 0.097 eq.), toluene

(900 mL) and MeOH (28.8 g, 898.88 mmol, 1.94 eq.). The mixture was stirred at 20 °C under nitrogen atmosphere until a clear solution formed. The reaction mixture was heated to 60 °C, and a solution of 2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-one (103.09 g, 464.14 mmol, 1.00 eq.) in toluene (100 mL) was added slowly over 2 h at 60 °C. The resulting mixture was stirred continually for 16 h at 60 °C, then cooled to room temperature, quenched with water, and extracted with MTBE. The organic layer was cooled to 0 °C andwashed with 1.0 M aqueous HCl, 0.5 M aqueous NaOH, water and 10% brine. The organic layer was concentrated to give the title compound (146.71g, 73.5% assay purity, 87.9% assay yield, 90.7% e.e.).

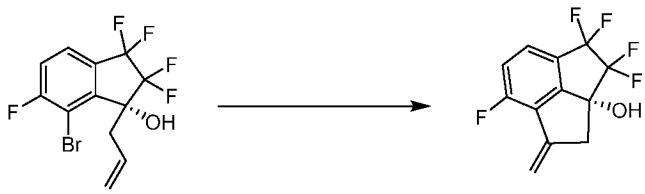
Step 2: (R)-1-allyl-7-bromo-2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-ol



To a dry 3-neck flask were added THF (500 mL) and LDA (356.82g, 25%, 832.76 mmol, 2.21 eq.) and then the solution was cooled to -50 °C under nitrogen atmosphere. A solution of (R)-1-allyl-2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-ol (100.00 g, 378.50 mmol, 1.00 eq.) in THF (200 mL) was added slowly at -50 °C. The resulting mixture was stirred at -50 °C for 1h, then cooled to -80 °C to form solution A.

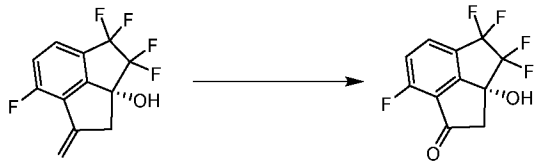
To another dry 3-neck flask were added dibromotetrafluoroethane (196.66 g, 756.91 mmol, 2.00 eq.) and THF (100 mL), and the solution was cooled to -80 °C. Solution A was slowly added with stirring and while maintaining the reaction temperature at about -80 °C. The mixture was stirred at -80 °C for additional 30 min and then slowly quenched by slowly adding a solution of AcOH (75.00 g, 1248.96 mmol, 3.30 eq.) in THF (75 mL) at temperature below -60 °C. The mixture was warmed slowly to room temperature anddiluted with water. The mixture was extracted with MTBE, and the combined organic layer was washed with water and 10% brine. The organic layer was concentrated to give the title compound as a solution in THF (204.40g, 50.4% assay purity, 79.3% assay yield).

Step 3: (R)-3,3,4,4,7-pentafluoro-1-methylene-1,2,3,4-tetrahydro-2aH-cyclopenta[cd]inden-2a-ol



Into a solution of (R)-1-allyl-7-bromo-2,2,3,3,6-pentafluoro-2,3-dihydro-1H-inden-1-ol (100.00 g, 291.47 mmol, 1.00 eq.) in acetonitrile (1.50 L) were added KOAc (86.50g, 881.39 mmol, 3.03 eq.) and $Pd(PPh_3)_2Cl_2$ (10.30 g, 14.67 mmol, 0.050 eq.) under N_2 atmosphere. The mixture was stirred for 4 h at 80 °C and then concentrated under vacuum to about 1/3 volume. The residue was diluted with MTBE and washed with water. The organic layer was diluted with n-heptane and passed through a silica gel pad (200 g). The pad was rinsed with MTBE/n-heptane=1/3 to wash out the product. The eluent was concentrated and exchange the solvent into acetonitrile to give the title compound as a solution in acetonitrile (120.15g, 51.7% assay purity, 81.3% assay yield, 90.6% e.e.).

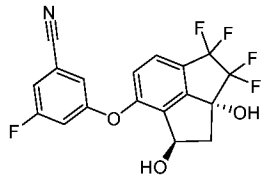
Step 4: (R)-3,3,4,4,7-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-1-one



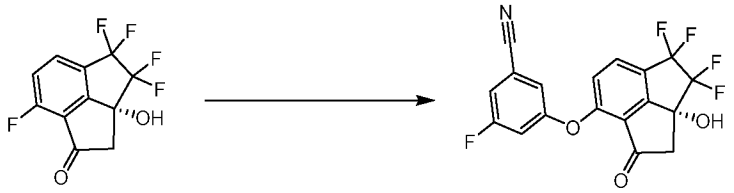
To a stirred mixture of (R)-3,3,4,4,7-pentafluoro-1-methylene-1,2,3,4-tetrahydro-2aH-cyclopenta[cd]inden-2a-ol (80.00 g, 305.13 mmol, 1.00 eq.) in ACN (1200 mL) and H_2O (3200 mL) was added $RuCl_3 \cdot 3H_2O$ (4.00 g, 15.30 mmol, 0.050 eq.), followed by $NaIO_4$ (456.87 g, 2.14 mol, 7.01 eq.) in portions while maintaining the reaction temperature at 10 to20 °C. After stirring further at 10 to 20 °C for 1 h, MTBE (800 mL) was added to the mixture and the mixture was filtered through a Celite layer. The Celite solid cake was washed with MTBE. The organic layer was separated from the combined filtrate, and the aqueous layer was extracted with MTBE. The combined organic layer was washed with 5% aqueous Na_2SO_3 and 10% aqueous Na_2SO_4. The organic layer was concentrated, and the residue was dissolved in MTBE and n-heptane. The solution was filtered through a silica gel pad (200 g) and the pad solid cake was rinsed with MTBE/n-heptane=1/3. The combined eluent was concentrated to about 3V to precipitate out the product which was filtered and dried to give the title compound as a white solid (70.62 g, 88.4% assay purity, 77.5% assay yield, ~ 91.7% e.e.).

Example 3

Synthesis of 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy- 2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile

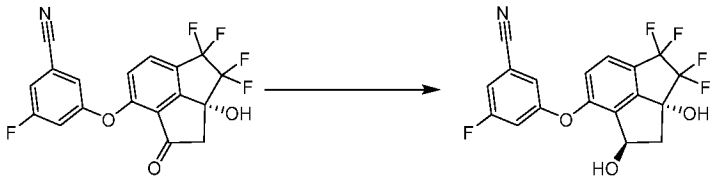


Step 1: (R)-3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-oxo-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile



To a stirred mixture of (R)-3,3,4,4,7-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden -1-one (100.00 g, after assay adjustment, 378.57 mmol, 1.00 eq.) in THF (500 mL) were added 3-fluoro-5-hydroxybenzonitrile (57.10 g, 416.45 mmol, 1.10 eq.) and Cs_2CO_3 (74.01 g, 227.15 mmol, 0.60 eq.) at room temperature. The resulting mixture was stirred at 40 °C for 20 h. The mixture was cooled to room temperature and MTBE was added, followed by water. After layer separation, the aqueous layer was extracted with MTBE and the combined organic layer was washed with 5% aqueous Na_2CO_3 and then 10% brine. The organic layer was concentrated and the residue was recrystallized from MTBE/n-heptane = 3/20 to give the title compound as a yellow solid (145.78 g, 84.4% assay purity, 85.2% assay yield, 98.4% e.e.).

Step 2: 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy- 2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile

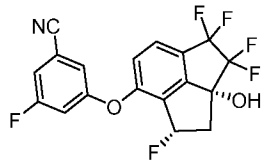


To a stirred solution of (R)-3-fluoro-5-((3,3,4,4-tetrafluoro-2a-hydroxy-1-oxo-2,2a,3,4-tetrahydro-1H- cyclopenta[cd]inden-7-yl)oxy)benzonitrile (50.00 g, after assay adjustment, 131.14 mmol, 1.00 eq.) in MeOH (53.0 mL, 1.31 mol, 10.00 eq.) and THF (500 mL) was added $NaBH_4$ (1.84 g, 48.64 mmol, 0.37 eq.) in portions at -5 to 0 °C. The reaction mixture was stirred at -5 to 0 °C for an additional hour, then quenched with 2.0 M aqueous HCl (about 30.0 g) below 5 °C to pH = 5 – 7 and diluted with water. The mixture was extracted with MTBE, and the combined organic layer was washed with water and 10% brine. The organic layer is concentrated and the

solvent was exchanged to THF to obtain a THF solution of the title compound (286.66 g, 16.6% assay purity, 94.7% assay yield, 97.7% e.e.). ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.55 (d, 1H), 7.18 - 7.16 (m, 2H), 7.13 (d, 1H), 7.08 (d, 1H), 5.89 – 5.84 (m, 1H), 3.06 (s, 1H), 2.83 – 2.78 (m, 1H), 2.47 – 2.42 (m, 1H), 2.35 (d, 1H).

Example 4

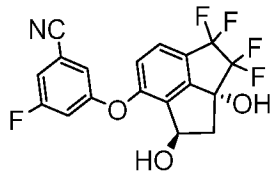
Synthesis of 3-fluoro-5-(((1S,2aR)-1,3,3,4,4-pentafluoro-2a-hydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile



To a stirred solution of 3-fluoro-5-(((1R,2aR)-3,3,4,4-tetrafluoro-1,2a-dihydroxy-2,2a,3,4-tetrahydro-1H-cyclopenta[cd]inden-7-yl)oxy)benzonitrile (54.30 g, 141.68 mmol, 1.00 eq.) and DBU (43.14 g, 283.37 mmol, 2.00 eq.) in THF (1200 mL) was added a solution of pyridine-2-sulfonyl fluoride (32.00 g, 198.57 mmol, 1.40 eq.) in THF (200 mL) dropwise at 20-30 °C over 2 h under nitrogen atmosphere. The resulting mixture was stirred further for 20 h at 20-30 °C, quenched with 0.5N aqueous NaOH (600 mL). After stirring at 20-30 °C for 30 min, the layers were separated. The aqueous layer was extracted with MTBE. The combined organic layers were concentrated, and the residue was dissolved in MTBE. The organic layer was washed with water, 0.5 N aqueous HCl, water and 10% brine. The organic layer is concentrated and the residue was purified with a silica gel column, eluted with n-heptane/ethyl acetate=4/1, to obtain crude product (49.0g), which was further recrystallized from MTBE/n-heptane=1/9 to give the title product (42.0g, 76.9% yield). ^{1}H NMR (400MHz, $CDCl_3$) δ = 7.71 - 7.67 (m, 1H), 7.29 - 7.26 (m, 2H), 7.25 - 7.09 (m, 2H), 6.60 - 5.80 (ddd, 1H), 2.87 (s, 1H), 2.91 - 2.57 (m, 2H).

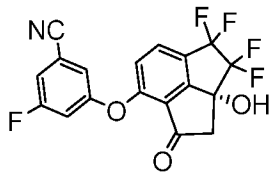
What is Claimed:

1. A process of preparing compound (11)



(11)

comprising reducing the keto moiety of compound (10):



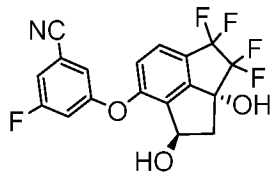
(10)

with:

(a) sodium borohydride in an organic solvent selected from a group consisting of (i) an alcohol containing acetic acid or trifluoroacetic acid, (ii) a cyclic ether, and (iii) a mixture of a cyclic ether and an alcohol; wherein the cyclic ether of (ii) and the mixture of a cyclic ether and an alcohol of (iii) optionally contain acetic acid or trifluoroacetic acid; or

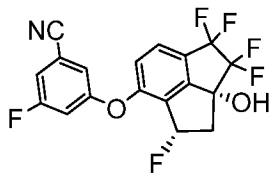
(b) lithium borohydride in a suitable organic solvent optionally containing acetic acid or trifluoroacetic acid.

2. The process of claim 1, further comprising converting compound (11):



(11)

to Compound (I):



(I)

by reacting compound (11) with a deoxyfluorinating agent in the presence of an organic base in a suitable organic solvent.

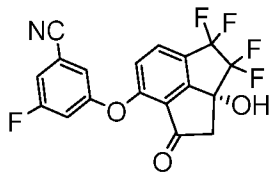
3. The process of claim 2, wherein the deoxyfluorinating agent is pyridine-2-sulfonyl fluoride and the base is 1,8-diazabicyclo-[5.4.0]undec-7-ene or 7-methyl-1,5,7-triaza-bicyclo-[4.4.0]dec-1-ene.

4. The process of claim 1, wherein the reduction of the keto group of compound (10) is carried out with sodium borohydride in tetrahydrofuran, 2-methyltetrahydrofuran, a mixture of tetrahydrofuran or 2-methyltetrahydrofuran and methanol, tetrahydrofuran containing acetic acid or trifluoroacetic acid, 2-methyltetrahydrofuran containing acetic acid or trifluoroacetic acid, or methanol containing acetic acid or trifluoroacetic acid.

5. The process of claim 4, wherein the organic solvent is a mixture of tetrahydrofuran and methanol and the reaction is carried out at about -5 °C to about 30 °C.

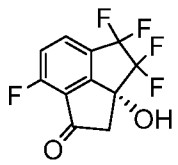
6. The process of claim 3, wherein the molar ratio of 1,8-diazabicyclo[5.4.0]-undec-7-ene to compound (11) is at least about 2 to about 1 and the organic solvent is tetrahydrofuran.

7. A process of preparing compound (10):



(10)

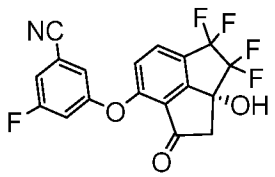
comprising reacting compound (9):



(9)

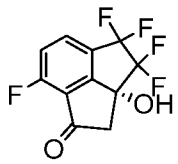
with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent other than dimethylformamide.

8. The process of any one of claims 1 to 6, further comprising preparing compound (10):



(10)

by reacting compound (9):



(9)

with 3-fluoro-5-hydroxybenzonitrile in the presence of a base in a suitable organic solvent.

9. The process of claim 7 or 8, wherein the base is an inorganic base.

10. The process of claim 9, wherein the inorganic base is cesium carbonate or potassium carbonate

11. The process of claim 7 to 10, wherein the organic solvent is tetrahydrofuran.

12. The process of any one of claims 7 to 11, further comprising crystallizing compound (10) from a mixture of an ether and an alkane solvent.

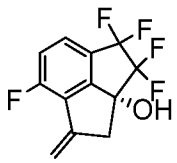
13. The process of claim 12, wherein compound (10) is crystallized from a mixture of methyl tert-butyl ether and n-heptane.

14. A process for preparing compound (9):



(9)

comprising carrying out oxidative cleavage of the vinylidene moiety of compound (8):



(8)

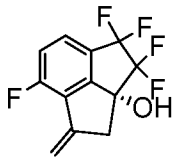
with (i) sodium periodate in the presence of ruthenium chloride in aqueous acetonitrile, (ii) Oxone® in the presence of ruthenium chloride in a suitable organic or aqueous organic solvent, or (iii) Ozone in a suitable organic or aqueous organic solvent.

15. The process of any one of claims 7 to 13, further comprising preparing compound (9):



(9)

by carrying out oxidative cleavage of the vinylidene moiety of compound (8):

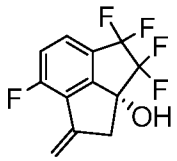


(8)

with a suitable oxidizing agent in a suitable organic or aqueous organic solvent.

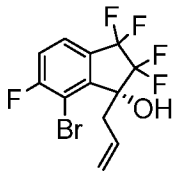
16. The process of claim 14 or 15, wherein the oxidative cleavage of the vinylidene is carried out with sodium periodate in the presence of catalytic amount of ruthenium chloride in aqueous acetonitrile.

17. A process for preparing compound (8):



(8)

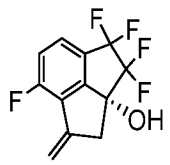
comprising performing intramolecular cyclization between the alkene and bromo groups in compound (7):



(7)

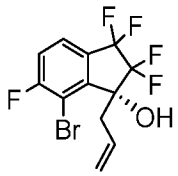
by treating compound (7) with a palladium catalyst in the presence of a base in a suitable organic solvent other than dimethylformamide.

18. The process of any one of claims 14 to 16, further comprising preparing compound (8):



(8)

by performing intramolecular cyclization between the alkene and bromo groups in compound (7):



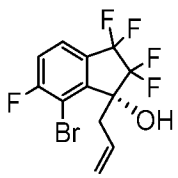
(7)

with a palladium catalyst in the presence of a base in a suitable organic solvent.

19. The process of claim 16 or 17, wherein the palladium catalyst is $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_2(OAc)_2$, $Pd_2(dba)_3$/XPhos, or Pd(1,2-bis(diphenylphosphino)-ethane)$(OAc)_2$ and the organic solvent is acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, toluene, 1,4-dioxane, or dimethylformamide.

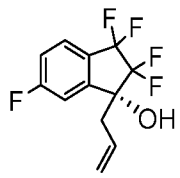
20. The process of claim 19, wherein the palladium catalyst is $Pd(PPh_3)_2Cl_2$, the base is potassium acetate, and the solvent is acetonitrile.

21. A process for preparing compound (7):



(7)

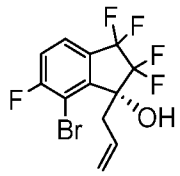
comprising brominating compound (6):



(6)

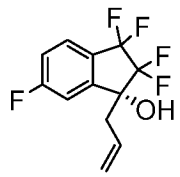
with 1,2-dibromo-1,1,2,2-tetrafluoroethane in the presence of a deprotonating agent in a suitable organic solvent.

22. The process of any one of claims 17 to 20, further comprising preparing compound (7):



(7)

by treating compound (6):



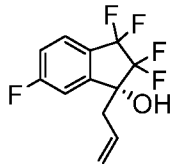
(6)

with a brominating agent in the presence of a deprotonating agent in a suitable organic solvent.

23. The process of claim 21 or 22, wherein the deprotenating agent is lithium diisopropylamide.

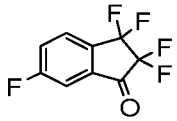
24. The process of claim 21 or 22, wherein the brominating agent is 1,2-dibromo-1,1,2,2-tetrafluoroethane, the deprotenating agent is lithium diisopropylamide and the solvent is tetrahydrofuran.

25. The process of any one of claims 21 to 24, further comprising preparing compound (6):



(6)

by treating compound (5):

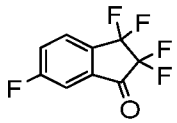


(5)

with 4,4,5,5-tetramethyl-2-(prop-2-en-1-yl)-1,3,2-dioxaborolane in the presence of (S)-2-((3-(tert-butyl)-2-hydroxybenzyl)amino)-N,N,3-trimethylbutanamide and a base in a suitable organic solvent.

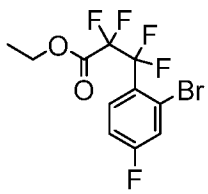
26. The process of claim 25, wherein the base is sodium tert-butoxide and the organic solvent is a mixture of methanol and toluene.

27. The process of claim 25 or 26, further comprising preparing compound (5):



(5)

by treating compound (4):

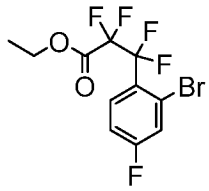


(4)

with an organolithium reagent in a suitable organic solvent.

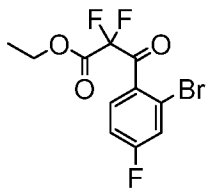
28. The process of claim 27, wherein the organolithium reagent is n-butyllithium and the organic solvent is tetrahydrofuran.

29. The process of claim 27 or 28, further comprising preparing compound (4):



(4)

by treating compound (3):



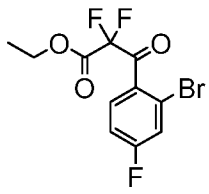
(3)

with a fluorinating agent in a suitable organic solvent.

30. The process of claim 29, wherein the fluorinating agent is diethylaminosulfur trifluoride, 4-tert-butyl-2,6-dimethylphenylsulfur trifluoride, or sulfur tetrafluoride and hydrofluoric acid.

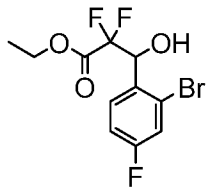
31. The process of claim 30, wherein the fluorinating agent is sulfur tetrafluoride and hydrofluoric acid and the solvent is dichloromethane.

32. The process of claim 29, 30, or 31, further comprising preparing compound (3):



(3)

by treating compound (2):



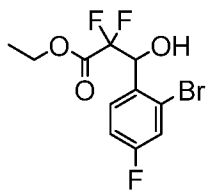
(2)

with an oxidizing agent in a suitable organic solvent.

33. The process of claim 32, wherein the oxidizing agent is DMSO/oxalyl chloride, 2-iodoxybenzoic acid, $RuCl_3/NaBrO_3$, MnO_2, $NaBrO_3/NaHSO_3$ or TPAP/NMO.

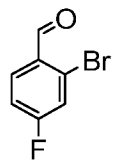
34. The process of claim 33, wherein the oxidizing agent is is TPAP/NMO and reaction is carried in dichloromethane.

35. The process of any one of claims 32 to 34, further comprising preparing compound (2):



(2)

by treating compound (1):



(1)

with ethyl bromodifluoroacetate in the presence of zinc metal, trimethylsilyl chloride, and 1,2-dibromoethane in a suitable organic solvent.

36. The process of claim 35, wherein the organic solvent is tetrahydrofuran.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2020/121745

A. CLASSIFICATION OF SUBJECT MATTER

C07C 255/54(2006.01)i; C07C 253/30(2006.01)i; C07C 29/143(2006.01)i; C07C 35/37(2006.01)i; C07C 41/24(2006.01)i; C07C 43/295(2006.01)i; C07C 45/40(2006.01)i; C07C 49/513(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPODOC,WPI,CNPAT,STN(REGISTRY,CAPLUS,CASREACT):hypoxia inducible factor, HIF, +indene+, indane, structure search, reaction research

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2020081695 A1 (NIKANG THERAPEUTICS, INC.) 23 April 2020 (2020-04-23) Claims 1 and 33; Table 1, and exampls 1, 4, 11, 14-15, 20	1-36
A	WO 2018031680 A1 (FRONTHERA U. S. PHARMACEUTICALS LLC) 15 February 2018 (2018-02-15) Paragraphs [0004]-[0005] and [00173], and examples 1-5, 8-11, 15, 20-21	1-36
A	CN 105530923 A (PELOTON THERAPEUTICS, INC.) 27 April 2016 (2016-04-27) Paragraphs [0006]-[0010] and [0202], Schemes 3-4 in page 53, and Schemes 10-11 in page 56	1-36
A	WO 2016057242 A1 (THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM) 14 April 2016 (2016-04-14) Paragraphs [019]-[021], Schemes 1-4 in pages 29-32, and Scheme 12 in page 37	1-36
A	US 2016362390 A1 (PELOTON THERAPEUTICS, INC.) 15 December 2016 (2016-12-15) Paragraphs [0004]-[0018] and [0284], Scheme 1 in page 24, Table 1, and examples 4-6	1-36
A	WO 2016145032 A1 (PELOTON THERAPEUTICS, INC.) 15 September 2016 (2016-09-15) Paragraphs [0006] and [0022], Schemes 1-4 in pages 80-83, Scheme 8 in page 85, Scheme 12 in page 87, Table 2, and examples 1-2	1-36

☑ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
05 July 2021	**15 July 2021**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **WANG,Limin** Telephone No. **86-(10)-53960198**

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2016168510 A1 (PELOTON THERAPEUTICS, INC.) 20 October 2016 (2016-10-20) Paragraphs [0011], [0018] and [0027], Schemes 2-6 in pages 92-95, Schemes 11-12 in pages 97-98, Scheme 27 in pages 107-108, Table 1, and examples 1-2	1-36
A	WO 2019191227 A1 (PELOTON THERAPEUTICS, INC.) 03 October 2019 (2019-10-03) Paragraphs [007], [024], Schemes 2-4 in pages 80-83, Table 1, and examples 1-3	1-36
A	WO 2017053192 A1 (THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM) 30 March 2017 (2017-03-30) Paragraph [016], Schemes 1-17 in pages 103-115, Table 1, and examples 1-3	1-36

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2020/121745

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WO 2018031680 A1	15 February 2018	None	
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		EP 3043784 B9	20 November 2019
		EP 3417852 A1	26 December 2018

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2020/121745

Patent document cited in search report			Publication date (day/month/year)	Patent family member(s)			Publication date (day/month/year)
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WO	2016057242	A1	14 April 2016	EP	3203991	A4	20 June 2018
				US	2017304300	A1	26 October 2017
				US	10098878	B2	16 October 2018
				EP	3203991	A1	16 August 2017
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WO	2016145032	A1	15 September 2016	EP	3267792	A4	26 September 2018
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				EP	3267792	A1	17 January 2018
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				US	10278942	B2	07 May 2019
WO	2016168510	A1	20 October 2016	US	10786480	B2	29 September 2020
				US	2019282535	A1	19 September 2019
				US	2018140569	A1	24 May 2018
				US	10335388	B2	02 July 2019
WO	2019191227	A1	03 October 2019	US	2021015764	A1	21 January 2021
				TW	202003430	A	16 January 2020
				EP	3774709	A1	17 February 2021
WO	2017053192	A1	30 March 2017	US	2019048421	A1	14 February 2019